Adolescent Development

Chapter 110

Adolescent Physical and Social Development

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During the preteen, teenage, and young adult years, young people undergo not only dramatic changes in physical appearance, but also rapid changes in physiologic, psychological, and social functioning. Hormonally driven physiologic changes and ongoing neurologic development occur in the setting of social structures that foster the transition from childhood to adulthood. This period of development comprises adolescence, which is divided into 3 phases—early, middle, and late adolescence—each marked by a characteristic set of biologic, cognitive, and psychosocial milestones (Table 110-1). Although individual variations in the timing and pace of development undoubtedly exist, these changes follow a fairly predictable pattern of occurrence. Gender and culture profoundly affect the developmental course, as do physical, social, and environmental influences. Given the interaction of these domains, a biopsychosocial approach is best suited to approach the healthcare of the adolescent.

PHYSICAL DEVELOPMENT

Puberty is the biologic transition from childhood to adulthood. Pubertal changes include the appearance of the secondary sexual characteristics, increase in height, change in body composition, and development of reproductive capacity. Adrenal production of androgen (chiefly dehydroepiandrosterone sulfate [DHEAS]) may occur as early as 6 yr of age, with development of underarm odor and faint genital hair (adrenarche). Maturation of the gonadotropin-releasing hormone pulse generator is among the earliest neuroendocrine changes associated with the onset of puberty. Under the influence of gonadotropin-releasing hormone, the pituitary gland secretes luteinizing hormone and follicle-stimulating hormone; initially this occurs in a pulsatile fashion primarily during sleep, but this diurnal variation diminishes throughout puberty. Luteinizing hormone and follicle-stimulating hormone stimulate corresponding increases in gonadal androgens and estrogens. The triggers for these changes are incompletely understood, but may involve the hormone leptin, high concentrations of which are associated with increased body fat and earlier onset of puberty.

Sexual Development

The progression of the development of the secondary sex characteristics may be described using the sexual maturity rating (SMR) scale (ranging from 1, preadolescence, to 5, sexual maturity), or Tanner stages. Figures 110-1 and 110-2 depict the physical findings of breast and pubic hair maturation at each SMR. Figures 110-3 and 110-4 depict the typical sequence of pubertal changes in males and females, respectively. The range of normal progress through sexual maturation is wide, and is affected by genetics, the psychosocial environment, nutrition, and overall health status. Environmental exposures may play a role as well.

In males, the first visible sign of puberty and the hallmark of SMR 2 is testicular enlargement, beginning as early as 9.5 yr, followed by the development of pubic hair. This is followed by penile growth during SMR 3. Peak growth occurs when testis volumes reach approximately 9-10 cm³ during SMR 4. Under the influence of luteinizing hormone and testosterone, the seminiferous tubules, epididymis, seminal vesicles, and prostate enlarge. Sperm may be found in the urine by SMR 3; nocturnal emissions may be noted at this time as well. Some degree of breast tissue growth, typically bilateral, occurs in 40-65% of males during SMR 2-3 as a consequence of a relative excess of estrogen stimulation. This generally resolves with ongoing maturation.

In females, typically the first visible sign of puberty and the hallmark of SMR 2 is the appearance of breast buds (thelarche), between 8 and 12 yr of age. A significant minority of females develops pubic hair (pubarche) prior to thelarche. Less visible changes include enlargement of the ovaries, uterus, labia, and clitoris, and thickening of the endometrium and vaginal mucosa. A clear vaginal discharge may be present prior to menarche (physiologic leukorrhea). Menses typically begins 2.5 yr after the onset of puberty, during SMR 3-4 (average age: 12.5 yr; normal range: 9-15 yr) (see Fig. 110-4). The timing of menarche is determined largely by genetics; contributing factors likely include adiposity, chronic illness, nutritional status, and the psychosocial environment. Early menstrual cycles often are anovulatory, and therefore somewhat irregular, but typically occur every 21-45 days and include 3-7 days of bleeding.

The onset of puberty and menarche appear to be occurring at earlier ages than previously reported in the United States. Several studies from 1948-1981 identified the average age for the onset of breast development as ranging from 10.6-11.2 yr of age. Multiple reports since 1997 suggest a significantly earlier average age of onset, ranging from 8.9-9.5 yr in African-American females and 10.0-10.4 yr in white females. Nearly 25% of African-American females and 10% of white females initiate breast development by 7 yr of age. There also appears to be a trend toward decreasing ages for the onset of pubic hair development and menarche. Data from the National Health and Nutrition Examination Survey, a nationally representative, longitudinal survey in the United States, show a decline in the average age of menarche of 4.9 mo between the 1960s and 2002. Changes in the timing of menarche within ethnic groups, however, were significantly smaller. The larger change seen in the population as a whole may be partially explained by changes in the ethnic makeup of the sample. The reasons for the larger decrease in age for breast development have been postulated to include the epidemic of childhood obesity as well as exposure to estrogen-like environmental toxins (endocrine disruptors), but further research in this area is needed.

Although fewer data are available on changes in the timing of puberty in males, they may be experiencing a similar trend. Although the method of assessing the onset of puberty (i.e., inspection vs. palpation of the testes) varies between studies, it appears that the average age for the onset of genital and pubic hair development may have decreased by 1-2 yr over the past several decades in many industrialized countries. An association of obesity with later onset of puberty in males has been theorized, but has not been consistently demonstrated.

Somatic Growth (See Also Fig. 13-1)

Linear growth acceleration begins in early adolescence for both genders, with 15-20% of adult height accrued during puberty. Females attain a peak height velocity (PHV) of 8.9 cm/yr at SMR 2-3, approximately 6 mo before menarche. Males typically begin their growth
acceleration at a later SMR stage, achieve a PHV of 9–10 cm/yr later in the course of puberty (SMR 3–4), and continue their linear growth for approximately 2–3 yr after females have stopped growing (Fig. 110-5). The growth spurt begins distally, with enlargement of the hands and feet, followed by the arms and legs, and finally, the trunk and chest. This growth pattern imparts a characteristic “awkward” appearance to some early adolescents. Body composition changes as well, following the attainment of PHV. Males undergo an increase in lean body mass (sometimes referred to as the “strength spurt”), whereas females develop a higher proportion of body fat. Scoliosis, if present, may lead to changes in vocal quality in males, typically preceded by vocal instability (voice cracking). Elongation of the optic globe often results in myopia (see Chapter 620). Dental changes include jaw growth, loss of the final deciduous teeth, and eruption of the permanent cuspids, premolars, and finally, molars (see Chapter 307). Orthodontic appliances may be needed, secondary to growth exacerbations of bite disturbances. Physiologic changes in sleep patterns and increased sleep requirements occur, causing many adolescents to delay sleep onset at night, with subsequent difficulty awakening for early school start times in the morning (see Chapter 19).

**NEUROLOGIC, COGNITIVE, AND MORAL DEVELOPMENT**

Cognitive development correlates more closely with chronologic age than pubertal maturation. As children progress through adolescence, they develop and refine their ability to use formal operational thought processes. Abstract, symbolic, and hypothetical thinking replaces the need to manipulate concrete objects. Middle and late adolescents develop the ability to consider multiple options and to assess the long-term consequences of their actions. The capacity for verbal expression is enhanced. Since adolescents’ decision-making and subsequent behaviors are the largest determinants of their mortality and morbidity, understanding these cognitive processes is of critical importance.

The belief that major structural brain development is completed in childhood is outdated. It is now clear that neuromaturation continues into the third decade. This maturation is characterized by decreases in gray matter, increases in white matter, and an apparent increase in the efficiency of communication and connectivity between different brain regions. Gray matter volume peaks in the frontal lobes in preadolescence, then decreases. This decrease is a consequence of selective “pruning” of rarely used synaptic connections. Increased white matter volume is believed to reflect increasing myelination and subsequent

### Table 110-1 Milestones in Early, Middle, and Late Adolescent Development

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>EARLY ADOLESCENCE</th>
<th>MIDDLE ADOLESCENCE</th>
<th>LATE ADOLESCENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Approximate age range</td>
<td>10-13 yr</td>
<td>14-17 yr</td>
<td>18-21 yr</td>
</tr>
<tr>
<td>Sexual maturity rating*</td>
<td>1-2</td>
<td>3-5</td>
<td>5</td>
</tr>
<tr>
<td>Physical</td>
<td>Females: Secondary sex characteristics (breast, pubic, axillary hair, start of growth spurt)</td>
<td>Females: peak growth velocity, menarche (if not already attained)</td>
<td>Physical maturation slows</td>
</tr>
<tr>
<td></td>
<td>Males: testicular enlargement, start of genital growth</td>
<td>Males: growth spurt, secondary sex characteristics, nocturnal emissions, facial and body hair, voice changes</td>
<td>Increased lean muscle mass in males</td>
</tr>
<tr>
<td>Cognitive and moral</td>
<td>Concrete operations</td>
<td>Emergence of abstract thought (formal operations)</td>
<td>Future-oriented with sense of perspective</td>
</tr>
<tr>
<td></td>
<td>Egocentricity</td>
<td>May perceive future implications, but may not apply in decision making</td>
<td>Able to think things through independently</td>
</tr>
<tr>
<td></td>
<td>Unable to perceive long-term outcome of current decisions</td>
<td>Strong emotions may drive decision making</td>
<td>Improved impulse control</td>
</tr>
<tr>
<td></td>
<td>Follow rules to avoid punishment</td>
<td>Sense of invulnerability</td>
<td>Improved assessment of risk vs. reward</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Growing ability to see others’ perspectives</td>
<td>Able to distinguish law from morality</td>
</tr>
<tr>
<td>Self-concept/identity formation</td>
<td>Preoccupied with changing body</td>
<td>Concern with attractiveness</td>
<td>More stable body image</td>
</tr>
<tr>
<td></td>
<td>Self-consciousness about appearance and attractiveness</td>
<td>Increasing introspection</td>
<td>Attractiveness may still be of concern</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Consolidation of identity</td>
</tr>
<tr>
<td>Family</td>
<td>Increased need for privacy</td>
<td>Conflicts over control and independence</td>
<td>Emotional and physical separation from family</td>
</tr>
<tr>
<td></td>
<td>Exploration of dependence/independence boundaries</td>
<td>Struggle for greater autonomy</td>
<td>Increased autonomy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Increased separation from the parents</td>
<td>Reestablishment of “adult” relationship with parents</td>
</tr>
<tr>
<td>Peers</td>
<td>Same-sex peer affiliations</td>
<td>Intense peer group involvement</td>
<td>Peer group and values recede in importance</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Preoccupation with peer culture</td>
<td></td>
</tr>
<tr>
<td>Sexual</td>
<td>Increased interest in sexual anatomy</td>
<td>Testing ability to attract partner</td>
<td>Consolidation of sexual identity</td>
</tr>
<tr>
<td></td>
<td>Anxieties and questions about pubertal changes</td>
<td>Initiation of relationships and sexual activity</td>
<td>Focus on intimacy and formation of stable relationships</td>
</tr>
<tr>
<td></td>
<td>Limited capacity for intimacy</td>
<td>Questions of sexual orientation</td>
<td>Planning for future and commitment</td>
</tr>
</tbody>
</table>

*See text and Figures 110-1 and 110-2.

*Table 110-1 Milestones in Early, Middle, and Late Adolescent Development*
facilitation of integrated brain activity and more efficient transmission of information between different regions of the brain. These changes are first seen in the posterior cortex (sensory and motor regions), and progress anteriorly (Fig. 110-6). The frontal lobes are among the last areas of the brain to mature, including the prefrontal cortex, the region of the brain associated with executive function: the coordination of complex cognitive processes including impulse control, working memory, the consideration of multiple options and their possible consequences, and the evaluation of risk and reward, among others. (see Chapter 7).

The behavioral correlates of these anatomical changes are speculative; adolescent behaviors may in part be biologically driven and reflect the relative immaturity of the prefrontal cortex and its communication with other regions of the brain. The earlier maturation of the amygdala and other limbic structures, which are involved in the experience of fear and emotion, relative to the frontal executive function systems, which facilitate the regulation and interpretation of those emotional experiences, could explain why adolescents are more likely to make poor decisions in highly emotionally charged situations, relative to mature adults. These so-called “hot cognition” processes may result in the adolescent making a different decision in the context of a strong affective experience than he or she would in a less emotional state (“cool cognition”). These 2 types of cognitive processes may not develop at the same rate; the adolescent may be able to use higher brain structures and functions more effectively when in states of lower
emotional arousal. Adolescents’ risk taking, desire for immediate gratification, and increased sensation and novelty seeking are similarly believed to result, in part, from this asynchronous brain maturation.

Early adolescents often continue to employ the concrete operational cognitive processes of childhood. Although formal operational cognition is developing, it may be applied inconsistently across different domains. A young adolescent may be able to use abstract thought when completing schoolwork, but not when working through a personal dilemma. Early adolescence also is characterized by egocentricity, the adolescent’s belief that they are the center of everyone’s attention. Despite being largely imagined, this perception of always being “on stage” can be stressful to the adolescent, who may feel that others are constantly judging or evaluating the adolescent. Early adolescents express a greater need for privacy than they did in childhood, and begin to appreciate the privacy of their own thoughts. With ongoing cognitive development, middle adolescents are more able to consider the needs and feelings of other people. Their creativity and intellectual abilities are enhanced. Perhaps as a result of their increased capacity for abstract thought in combination with a persistent perception of uniqueness, middle adolescents may feel a sense of immortality and immunity to the consequences of risky behaviors. Late adolescents are more future-oriented and able to delay gratification. They can think more independently, consider others’ views, and compromise. They have a stronger sense of self, and more stable interests. Under times of

**Table 110-2** Sexual Maturity Rating Stages in Females

<table>
<thead>
<tr>
<th>SMR STAGE</th>
<th>PUBIC HAIR</th>
<th>BREASTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Preadolescent</td>
<td>Preadolescent</td>
</tr>
<tr>
<td>2</td>
<td>Sparse, lightly pigmented, straight, medial border of labia</td>
<td>Breast and papilla elevated as small mound; diameter of areola increased</td>
</tr>
<tr>
<td>3</td>
<td>Darker, beginning to curl, increased amount</td>
<td>Breast and areola enlarged, no contour separation</td>
</tr>
<tr>
<td>4</td>
<td>Coarse, curly, abundant, but less than in adult</td>
<td>Areola and papilla form secondary mound</td>
</tr>
<tr>
<td>5</td>
<td>Adult feminine triangle, spread to medial surface of thighs</td>
<td>Mature, nipple projects, areola part of general breast contour</td>
</tr>
</tbody>
</table>


**Table 110-3** Sexual Maturity Rating Stages in Males

<table>
<thead>
<tr>
<th>SMR STAGE</th>
<th>PUBIC HAIR</th>
<th>PENIS</th>
<th>TESTES</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>None</td>
<td>Preadolescent</td>
<td>Preadolescent</td>
</tr>
<tr>
<td>2</td>
<td>Scanty, long, slightly pigmented</td>
<td>Minimal change/enlargement</td>
<td>Enlarged scrotum, pink, texture altered</td>
</tr>
<tr>
<td>3</td>
<td>Darker, starting to curl, small amount</td>
<td>Lengthens</td>
<td>Larger</td>
</tr>
<tr>
<td>4</td>
<td>Resembles adult type, but less quantity; coarse, curly</td>
<td>Larger; glans and breadth increase in size</td>
<td>Larger; scrotum dark</td>
</tr>
<tr>
<td>5</td>
<td>Adult distribution, spread to medial surface of thighs</td>
<td>Adult size</td>
<td>Adult size</td>
</tr>
</tbody>
</table>


**Figure 110-4** Sequence of pubertal events in females. PHV, peak height velocity. (From Root AW: Endocrinology of puberty, J Pediatr 83:1, 1973.)

**Figure 110-5** Height velocity curves for American males (solid line) and females (dashed line) who have their peak height velocity at the average age (i.e., average growth tempo). (From Tanner JM, Davies PSW: Clinical longitudinal standards for height and height velocity for North American children, J Pediatr 107:317, 1985.)
of their dependence on, and independence from, their parents. With evolving cognitive skills, an adolescent has the ability to conceive of an ideal parent, and contrast this ideal with his or her own parents. Adolescents may seek out alternative adult role models, such as teachers, coaches, or parents of friends. Parent–child conflict often peaks during middle adolescence, with disagreements over privileges, independence, and other limits set by the parents. Adolescents may appear intermittently to seek and reject parental acceptance. It is theorized that perhaps the adolescent needs to conceive of the parents as “wrong” in order to ameliorate the pain of separating from them. Throughout this time, however, the parents remain a critical source of nurturing and support for the adolescent, and continue to exert significant influence over the adolescent’s decision making. Paradoxically, frequent arguments and conflict may coexist with strong emotional bonds and closeness. The late adolescent may reestablish a more “adult–adult” type of relationship with the parents, once again seeking out and considering parental advice and guidance as they enter adulthood.

Increasing importance of the peer group also may buffer the emotional trauma of separating from the parents. Early adolescents tend to socialize largely with same sex peers, both in their individual friendships and larger groups. Females’ peer groups tend to be more relationship oriented, whereas males’ peer groups are more likely to be centered around a particular activity. In both cases, group cohesion and a sense of belonging become important. Peers become increasingly important in middle adolescence, during which time the adolescent may experiment with being a part of different groups and “try on” different identities. These groups may include both genders. Peer groups may arise from organized activities, such as sports or clubs, or may simply be friendship based. Gang membership is another form of peer acceptance. Conformity with the peers in manners of dress, speech, and behavior is a normal part of this process, and should not necessarily be viewed negatively. Similarly, peer pressure may exist, but its influence over the adolescent’s decision making may be positive, negative, or negligible. Acceptance and successful navigation of peer groups during adolescence may give the individual more confidence to move into and out of various social, academic, and professional groups in the future. Late adolescents are less vulnerable to peer group influence, having moved closer to establishing their own stable identity. Their cognitive skills allow them to choose selectively among different peer groups, endorsing and adopting individual values and behaviors that best reflect who they are becoming.

Early adolescents have increased sexual awareness and interest, which may manifest as sexual talk and gossip, and often is focused on sexual anatomy. Masturbation and other sexual exploration, sometimes with same-sex peers, are common. The prevalence of other forms of sexual behavior varies by culture; in general, these behaviors are less common in early adolescents. Romantic relationships, if they exist at all, lack emotional depth. Sexual curiosity, experimentation, and activity become more common among middle adolescents. Same-sex attraction is common; sexual orientation may become clear to some adolescents, but still may be evolving in others during this time. Dating behaviors may be seen, but this is culture dependent and may not be a popular construct for all adolescents. Individual relationships often continue to emphasize sexual attraction over emotional intimacy, the latter of which may not be seen until late adolescence. At this time, relationships increasingly involve love and commitment, and demonstrate greater stability.

Body image may affect (and be affected by) adolescents’ psychosocial development as well. Early and middle adolescence are commonly the ages at which poor or distorted body image and eating disorders develop. Early adolescents undergo rapid physical changes and may experience uncertainty about whether all of these anatomic and physiological changes are progressing normally. Reassurance from adults, including their healthcare providers, may be comforting. As puberty comes to an end and these changes slow, the middle adolescent’s preoccupation may shift to whether the adolescent is attractive to others. A strong emphasis on physical appearance during this time is normal. Although this focus on physical appearance may continue into adulthood, late adolescence generally is characterized by a shifting balance.
toward introspection, with somewhat less emphasis placed on external characteristics.

The \textit{timing of pubertal changes} also can affect psychosocial development and well-being. The progression of pubertal changes in males is generally associated with a positive self-image. Females may initially perceive these changes in their physical appearance more negatively. This appears to be especially true for early-maturing females, some of whom experience greater decreases in self-esteem, engage in more disruptive behaviors, and have more conflict with their parents than do on-time or late-maturing females. Perhaps because they are more comfortable associating with older peers, they are vulnerable to making poor decisions when exposed to high-risk situations, still lacking the cognitive skills to effectively navigate these situations. Early-maturing males tend to have greater self-confidence, social, and academic success, while later-maturing males are at risk for more internalizing behaviors and diminished self-esteem. Many other factors influence how adolescents experience puberty, and supportive peers and adults can have a positive impact on psychosocial development. With successful navigation of these domains, the emerging adult moves into the world with a strong sense of personal identity and their place in society. They are able to work toward a vocation and financial independence, and to manage the responsibilities of adulthood.

\section*{IMPLICATIONS FOR PROVIDERS AND PARENTS}

Providers can help parents approach their child's adolescent years by reframing some of the "challenges" of adolescence as normal developmental milestones that should be anticipated and accepted. Puberty and emerging sexuality should be approached as positive and health-affirming life changes, rather than focusing discussions only on the negative reproductive risks and outcomes. Even good-natured teasing about bodily changes can be detrimental to the adolescent's self-image. Early-maturing females and late-maturing males should be supported, recognizing their potential increased risk for psychosocial challenges. Emerging positive coping strategies should be promoted in all youth, particularly those with chronic illness or other challenges. Providers need to determine the young adolescents' cognitive development and capacity for abstract thought, and to tailor their communication and counseling style accordingly. Physical examinations should be performed in private with the parent outside the exam room (provided the adolescent is comfortable with this), which also affords the adolescent and provider an opportunity to discuss confidential issues. Reassurance of normal development should be provided.

As adolescents develop more independence and parent–child conflict peaks, providers should remind parents that this is typical, and that arguing does not mean the adolescent does not value the parents' input and perspectives. Although some may rebel initially, most adolescents ultimately adopt a value system very similar to that of their parents. Even if discussions feel ineffective to parents, they should continue to demonstrate and model these values to their child. Similarly, rather than categorically dismissing their child's "negative" interests, such as playing a violent video game, parents should be encouraged to use these opportunities to model critical thinking about the impact of such an activity. Potentially negative peer groups may be approached the same way, while fostering the development of positive peer networks. Authoritative parenting, in which clear and appropriate negotiated limits are set in the context of a caring and mutually respectful parent–child relationship, is most strongly associated with positive psychosocial development. Parental connectedness and close supervision or monitoring of the youth's activities and peer group can be protective against early onset of sexual activity and involvement in other risk-taking behaviors, and can foster positive youth development. Parents should also assume an active role in their adolescent's transition to adulthood to ensure that their child receives appropriate preventive health services.

Parents and providers may each work with adolescents to foster good decision making. In addition to providing adolescents with accurate and complete health information, the adolescent's cognitive ability to use this information in various contexts must be considered. Adolescents may find themselves needing to make important decisions in highly affectively charged situations, in which they may be unable to effectively manage their emotions and use their higher cognitive functions to think through the consequences of their decision. For example, if a romantic couple gets "carried away" in a sexual situation with high emotional arousal, they may make the decision to proceed with unprotected intercourse. By anticipating this situation ahead of time, under conditions of lower emotional arousal, and making a plan for how they will deal with this should it occur, it is possible they may make a different decision (e.g., stick with their prior decision never to have sex without protection), when the time comes. Parents and healthcare providers are in a position to encourage and foster this anticipation and planning under conditions of "cool cognition."

Providers may need to help parents distinguish normal adolescent development and risk-taking behaviors from possible signs of a more serious mental health or conduct problem. Bids for autonomy, such as avoiding family activities, demanding privacy, and increasing argumentativeness, are normal; extreme withdrawal or antagonism may be dysfunctional. Bewilderment and dysphoria at the start of middle school are normal; continued failure to adapt several months later suggests a more serious problem. Although some degree of risk-taking is normal, progressive escalation of risk-taking behaviors is problematic. In general, when the adolescent's behaviors cause significant dysfunction in the domains of home life, academics, or peer relationships, they should be addressed by the parents and healthcare provider, and referral to a mental health provider may be considered. In most cases, parents can be reassured that although adolescence can pose unique challenges, their adolescent, like most adolescents, will come through it to become a successful and happy adult.

\textit{Bibliography is available at Expert Consult.}

\section*{110.2 Sexual Identity Development}

\textit{Walter O. Bockting}

\section*{TERMS AND DEFINITIONS}

\textbf{Sex and Sexual Identity}

Sex is multifaceted, with at least 9 components: chromosomal sex, gonadal sex, fetal hormonal sex (prenatal hormones produced by the gonads), internal morphologic sex (internal genitalia), external morphologic sex (external genitalia), hypothalamic sex (sex of the brain), sex of assignment and rearing, pubertal hormonal sex, and gender identity and role. \textit{Sexual identity} is a self-perceived identification distilled from any or all aspects of sexuality, and has at least 4 components: sex assigned at birth, gender identity, social sex role, and sexual orientation.

\textbf{Sex Assigned at Birth}

A newborn is assigned a sex before (typically through ultrasound) or at the time of birth based on the external genitalia (natal sex). In case of a \textit{disorder of sex development}, these genitalia may appear ambiguous, and additional components of sex (e.g., chromosomal, gonadal, hormonal sex) are assessed. In consultation with specialists, parents assign the child a sex that they believe is most likely to be consistent with gender identity, which cannot be assessed until later in life (see Chapter 588).

\textbf{Gender Identity, Gender Role, and Social Sex Role}

\textit{Gender identity} refers to a person's basic sense of being a boy/man, girl/woman, or other gender (e.g., transgender). \textit{Gender role} refers to one's role in society, typically either the male or female role. Gender identity needs to be distinguished from \textit{social sex role} (also referred to as gender expression), which refers to characteristics in personality, appearance, and behavior that are, in a given culture and time, considered masculine or feminine. Gender role is about one's presentation as a boy/man or girl/woman, whereas social sex role is about the masculine and/or
Bibliography


feminine characteristics one exhibits in a given gender role. Both boys/men, girls/women, and transgender persons can be masculine and/or feminine to varying degrees; gender identity and social sex role are not necessarily congruent. A child or adolescent might be gender role non-conforming, that is, a predominantly feminine boy or a predominantly masculine girl.

**Sexual Orientation and Behavior**

*Sexual orientation* refers to attractions, behaviors, fantasies, and emotional attachments toward men, women, or both. *Sexual behavior* refers to any sexual activity to pleasure oneself or another person sexually.

**Gender Variant and Transgender**

*Gender variant* refers to any gender identity or role that varies from what is typically associated with one's sex assigned at birth. Sometimes the term *gender variant identity* is used to refer to variation in gender identity and in that case is synonymous with transgender. *Transgender* people are a diverse group of individuals who cross or transcend culturally defined categories of gender. They include *transsexuals* (who typically live in the cross-gender role and seek hormonal and/or surgical interventions to modify primary or secondary sex characteristics); *cross-dressers* or *transvestites* (who wear clothing and adopt behaviors associated with the other sex for emotional or sexual gratification and may spend part of the time in the cross-gender role); *drag queens* and kings (female and male impersonators); and individuals identifying as *bigender* (both man and woman) or *genderqueer* (gender variant). Transgender individuals may be attracted to men, women, or other transgender persons.

**FACTORS THAT INFLUENCE SEXUAL IDENTITY DEVELOPMENT**

During prenatal sexual development, a gene located on the Y chromosome (XRY) induces the development of testes. The hormones produced by the testes direct sexual differentiation in the male direction resulting in the development of male internal and external genitalia. In the absence of this gene in XX chromosomal females, ovaries develop and sexual differentiation proceeds in the female direction resulting in female internal and external genitalia. These hormones may also play a role in sexual differentiation of the brain. In disorders of sex development, chromosomal and prenatal hormonal sex varies from this typical developmental pattern and may result in ambiguous genitalia at birth.

Gender identity develops early in life and is typically fixed by 2-3 yr of age. Children first learn to identify their own and others’ sex (gender labeling), then learn that gender is stable over time (gender constancy), and finally learn that gender is permanent (gender consistency). What determines gender identity remains largely unknown, but it is thought to be an interaction of biologic, environmental, and sociocultural factors.

Some evidence has been found for the impact of biologic and environmental factors on social sex role and gender role behavior, while their impact on gender identity remains less clear. Animal research shows the influence of prenatal hormones on sexual differentiation of the brain. In humans, prenatal exposure to unusually high levels of androgens in girls with congenital adrenal hyperplasia is associated with more masculine gender role behavior, gender variant identity, and same-sex sexual orientation, but cannot account for all of the variance found (see Chapter 576). Research on environmental factors has focused on the influence of sex-typed socialization. Social sex role stereotypes develop early in life. Until later in adolescence, boys and girls are typically socially segregated by gender, reinforcing sex-typed characteristics such as boys’ focus on rough-and-tumble play and asserting dominance, and girls focus on verbal communication and creating relationships. Parents, other adults, teachers, peers, and the media serve as gender socializing role models and agents by treating boys and girls differently.

For information on the development of sexual orientation, see Chapter 110.3.

**GENDER VARIANCE/GENDER ROLE NONCONFORMITY AMONG CHILDREN AND ADOLESCENTS**

**Prevalence**

Gender variance and gender role nonconformity need to be distinguished from a transgender or a gender variant identity. The former operate on the level of social sex role, whereas the latter is about variation in core gender identity. Gender role nonconformity is more common among girls (7%) than boys (5%), but boys are referred more often than girls for concerns regarding gender identity and role. This is likely a result of parents, teachers, and peers being less tolerant of gender-variant behaviors in boys than in girls.

Gender variance as part of exploring one’s gender identity and role is part of normal sexual development. Gender variance in childhood may or may not persist into adolescence. Marked gender variance in adolescence often persists into adulthood. Only a minority of gender-variant children develop an adult transgender identity; most develop a gay or lesbian identity, and some, a heterosexual identity.

**Etiology of Gender- Variant Behavior**

Prenatal hormones play a role in the development of gender role nonconformity, but cannot completely account for all of the variance. A heritable component of gender-variant behavior exists, but twin studies indicate that genetic factors do not account for all of the variance. Family of origin factors hypothesized to play a role in the development of gender variance lack empirical support. Maternal psychopathology and emotional absence of the father are the only factors shown to be associated with gender variance, yet it is unclear whether these factors are cause or effect.

**Stigma, Stigma Management, and Advocacy**

Children with gender variance are subject to ostracism and bullying (see Chapter 39.1) from peers, which may negatively impact their psychosocial adjustment and lead to social isolation, loneliness, low self-esteem, depression, suicide, and behavioral problems. To assist children and families, individual stigma management strategies, as well as interventions to change the environment, can be offered. Stigma management might involve consultation with a health professional to provide support and education, normalizing the gender-variant behavior and encouraging the child and family to build on the child’s strengths and interests to foster self-esteem. It might also involve making choices about certain preferences (e.g., a boy who likes to wear head bands) to limit these to times and environments that are more accepting. Most health professionals agree that too much focus on curtailing gender-variant behavior leads to increased shame and undermines the child’s self-esteem.

The health professional and family can also assist the child or adolescent to find others with similar interests (within and beyond the gender-related interests) to strengthen positive peer support. Equally important are interventions in school and society to raise awareness and promote accepting and positive attitudes. To take a stand against bullying and abuse, and implement antibullying policies and initiatives. Gay, lesbian, bisexual, transgender, and straight alliance groups are helpful in providing a haven for gender-variant youth, as well as recognizing them as part of diversity to be respected and embraced within the school system.

**GENDER-VARIANT AND TRANSGENDER IDENTITY AMONG CHILDREN AND ADOLESCENTS**

**Prevalence**

Approximately 1% of parents of 4-11 yr old boys report that their son wished to be of the opposite sex; for girls this percentage is 3.5% for 4-11 yr old boys. Boys are referred by caregivers more often than girls for concerns regarding gender identity. Only a minority of children’s gender identity concerns persist into adolescence (20% in 1 study of boys). Persistence of gender identity concerns from adolescence into adulthood is higher; the majority identify as transgender in adulthood and may pursue sex
reassignment. On the basis of adults enrolled in a national sex reassign-
mant program in the Netherlands, the prevalence of transsexual adults is estimated at 1:11,900 for male-to-females and 1:30,400 for female-to-males. The prevalence of transgender adults in the United States is estimated at 1:200.

**Etiology of a Gender Variant Identity**
The etiology of transgender identity remains unknown. Factors hypothesized to play a role in the development of a transgender identity include environmental and biologic factors. Gender variant children seem to have more trouble than other children with basic cognitive concepts concerning their gender. They may experience emotional distance from their father. Whether these factors are cause or effect remains unclear.

There may be an influence of prenatal and perinatal hormones on sexual differentiation of the brain. Some girls with congenital adrenal hyperplasia develop a male gender identity, yet most do not. The size of the sex-dimorphic central part of the bed nucleus of the stria termi-
nalis in the hypothalamus of male-to-female transgender individuals is smaller than in males and within the range of nontransgender women; the opposite is true for female-to-male transgender individu-
als. This structure is regulated by hormones in animals, but in humans no evidence yet exists of a direct relationship between prenatal and perinatal hormones and the sexually dimorphic nature of this nucleus.

**Clinical Presentation**
Children with a gender variant identity may experience 2 sources of stress: internal distress inherent to the incongruence between sex assigned at birth and gender identity (gender dysphoria) or distress associated with social stigma. The first source of distress is reflected in discomfort with the developing primary and secondary sex characteristics and the gender role assigned at birth. The second source of distress relates to feeling different, not fitting in, peer ostracism, and social isolation, and may result in shame, low self-esteem, anxiety, or depression.

Boys with a gender variant identity may at an early age identify as a girl, expect to grow up female, or express the wish to do so. They may experience distress about being a boy and/or having a male body, prefer to urinate in a sitting position, and express a specific dislike of their male genitals and even want to cut off their genitals. They may dress up in girls’ clothes as part of playing dress up or in private. Girls may identify as a boy, expect or wish to grow up male. They may experience distress about being a girl and/or having a female body, pretend to have a penis, or expect to grow one. Girls may express a dislike of feminine clothing and hairstyles. In early childhood, children may spontaneously express these concerns, yet depending on the response of the social environment, these feelings may go underground and be kept more private. The distress may intensify by the onset of puberty; the physical changes of puberty are described by many trans-
gender adolescents and adults as traumatic.

Gender variant children and transgender adolescents may struggle with a number of general behavior problems. Both boys and girls have a predominance of internalizing (anxious and depressed) as opposed to externalizing behavioral difficulties. Boys are more prone to anxiety, have more negative emotions and a higher stress response, and are rated lower in self-worth, social competence, and psychological well-
being. Gender variant children have more peer relationship difficulties than controls. Both femininity in boys and masculinity in girls are socially stigmatized, although the former seems to carry a higher level of stigma. Boys have been shown to be teased more than girls; teasing for boys increases with age. Poor peer relations is the strongest predic-
tor of behavior problems in both boys and girls.

Transgender adolescents may struggle with a number of adjustment problems as a result of social stigma and lack of access to transgender-specific healthcare. Transgender youth, especially those of ethnic/racial minority groups, are vulnerable to verbal and physical abuse, academic difficulties, school dropout, illicit hormone and silicone use, substance use, difficulty finding employment, homelessness, sex work, forced sex, incarceration, HIV/sexually transmitted infections (STIs), and suicide. Parental support can buffer against psychologic distress, yet many parents react negatively to their child’s gender variance, although mothers tend to be more supportive than fathers.

**The Diagnosis of Gender Dysphoria: Criteria and Critique**
Gender dysphoria (or incongruence) is classified as a mental disorder in the Diagnostic and Statistical Manual of Mental Disorders (DSM) and International Classification of Diseases, which, particularly for children, is controversial (Table 110-4). Critics have argued that the distress children experience is mainly the result of social stigma rather than being inherent to gender variance per se and hence should not be considered a mental disorder. Critics have also expressed concern about children with normal variation in gender role being labeled with a mental disorder perpetuating social stigma, yet there is a tendency of clinicians to underdiagnose rather than overdiagnose children whose gender variance goes beyond behavior and who report gender dysphoria. These children will benefit from the diagnosis to receive early treatment in the form of support, education, advocacy, and, in case of persistent puberty-delaying hormone therapy as a precursor to feminizing or masculinizing hormone therapy.

**Transgender Identity Development**
A stage model of coming out might be helpful to understand the expe-
rience and potential challenges transgender youth might face. In the pre–coming out stage, the individual is aware that their gender identity is different from that of most boys and girls. In addition to a gender identity that varies from sex assigned at birth, some of these children are also gender-role nonconforming while others are not. Those who are also gender-role nonconforming cannot hide their transgender identity, are noticed for who they are, and may face teasing, ridicule, abuse, and rejection. They must learn to cope with these challenges at an early age and usually proceed quickly to the next stage of coming out. Children who are not visibly gender role nonconforming are able to avoid stigma and rejection by hiding their transgender feelings. They often experience a split between their gender identity cherished in private and expressed in fantasy and a false self-presented outwardly to fit in and meet gendered expectations. These individuals often proceed to coming out later in life.

Coming out involves acknowledging one’s transgender identity to self and others (parents, other caregivers, trusted health providers, peers). An open and accepting attitude is essential; rejection can per-
petuate stigma and its negative emotional consequences. By accessing transgender community resources, including peer support (either online or offline), the transgender youth can then proceed to the explo-
ration stage. This is a time of learning as much as possible about being transgender, getting to know similar others, and experimenting with various options for gender expression. Changes in gender role are care-
fully considered, as are medical interventions to feminize or masculinize the body to alleviate dysphoria. Successful resolution of this stage is a sense of pride in being transgender and comfort with gender role.

Once gender dysphoria has been alleviated, the individual can proceed with other human development tasks, including dating and relationships in the intimacy stage. As a result of social stigma and rejection, transgender individuals may struggle with feeling unlovable. Sexual development has often been compromised by gender and genital dysphoria. Now that greater comfort has been achieved with gender identity and role, dating and sexual intimacy have a greater chance of succeeding. Finally, in the integration stage, transgender is no longer the most important signifier of identity but one of several important parts of overall identity.

**Interventions and Treatment**
Health providers can assist gender variant children, adolescents, and their families by directing them to resources and by helping them to make informed decisions about changes in gender role and the avail-
able medical interventions to reduce intense and persistent gender dysphoria. To alleviate socially induced distress, interventions focus on stigma management and stigma reduction. It might be in the child’s best interest to set reasonable limits on transgender expression
Table 110-4  Summary of DSM 5 Diagnostic Criteria for Gender Dysphoria

GENDER DYSPHORIA IN CHILDREN (302.6) (F64.2)
A. A marked incongruence between one’s experienced/expressed gender and assigned gender, of at least 6 mo duration, as manifested by at least 6 of the following (1 of which must be criterion A1):
   1. A strong desire to be of the other gender or an insistence that one is the other gender (or some alternative gender different from one’s assigned gender).
   2. In boys (assigned gender), a strong preference for cross-dressing or simulating female attire; or in girls (assigned gender), a strong preference for wearing only typical masculine clothing and a strong resistance to the wearing of typical feminine clothing.
   3. A strong preference for cross-gender roles in make-believe play or fantasy play.
   4. A strong preference for the toys, games, or activities stereotypically used or engaged in by the other gender.
   5. A strong preference for playmates of the other gender.
   6. In boys (assigned gender), a strong rejection of typically masculine toys, games, and activities and a strong avoidance of rough-and-tumble play; or in girls (assigned gender), a strong rejection of typically feminine toys, games, and activities.
   7. A strong desire for the primary and/or secondary sex characteristics that match one’s experienced gender.
B. The condition is associated with clinically significant distress or impairment in social, occupational, or other important areas of functioning.

SPECIFY IF WITH A DISORDER OF SEX DEVELOPMENT (E.G., CONGENITAL ADRENAL HYPERPLASIA OR ANDROGEN INSENSITIVITY SYNDROME)

GENDER DYSPHORIA IN ADOLESCENTS OR ADULTS
A. A marked incongruence between one’s experienced/expressed gender and assigned gender, of at least 6 mo duration, as manifested by at least 2 of the following:
   1. A marked incongruence between one’s experienced/expressed gender and primary and/or secondary sex characteristics (or in young adolescents, the anticipated secondary sex characteristics).
   2. A strong desire to be rid of one’s primary and/or secondary sex characteristics because of a marked incongruence with one’s experienced/expressed gender (or in young adolescents, a desire to prevent the development of the anticipated secondary sex characteristics).
   3. A strong desire for the primary and/or secondary sex characteristics of the other gender.
   4. A strong desire to be of the other gender (or some alternative gender different from one’s assigned gender).
   5. A strong desire to be treated as the other gender (or some alternative gender different from one’s assigned gender).
   6. A strong conviction that one has the typical feelings and reactions of the other gender (or some alternative gender different from one’s assigned gender).
B. The condition is associated with clinically significant distress or impairment in social, occupational, or other important areas of functioning.

SPECIFY IF WITH A DISORDER OF SEX DEVELOPMENT (E.G., CONGENITAL ADRENAL HYPERPLASIA OR ANDROGEN INSENSITIVITY SYNDROME)

SPECIFY IF POSTTRANSITION: The individual has transitioned to full-time living in the desired gender (with or without legalization of gender change) and has undergone (or is preparing to have) at least one cross-sex medical procedure or treatment regimen, namely, regular cross-sex hormone treatment or gender reassignment surgery confirming the desired gender (e.g., penectomy, vaginoplasty in a natal male; mastectomy or phalloplasty in a natal female).


contributing to teasing and ridicule. The main goal of these interventions is not to change the child’s gender variant behavior but to assist families, schools, and the wider community to create a supportive environment in which the child can thrive and safely explore his or her gender identity and expression. Decisions to change gender roles, particularly in school, are not to be taken lightly and are best carefully anticipated and planned in consultation with parents, child, teachers, school counselor, and other providers involved in the adolescent’s care.

Medical interventions are available as early as Tanner Stage 2. Such treatment is guided by the Standards of Care set forth by the World Professional Association for Transgender Health. Although some controversy still exists about the appropriateness of early medical intervention, follow up studies of adolescents treated in accordance with these guidelines show it to be effective in alleviating intense and persistent gender dysphoria. Care needs to be taken not to foreclose the child’s exploration of identity.

Pediatricians who encounter transgender youth in their practice should be careful not to make assumptions about gender and sexual identity, but rather ask youth how they would describe themselves. This includes asking if they like being a boy or girl, have ever questioned their own gender, or how they feel about their anatomy. When considering contraceptive options for female-to-males, alternatives to femi-

nizing agents should be explored. For transgender-specific medical interventions, transgender youth should be referred to specialists in the treatment of gender dysphoria (see World Professional Association for Transgender Health, www.wpath.org). For other health concerns, ensure referral to transgender or lesbian, gay, bisexual, transgender (LGBT)-friendly providers, especially in the case of gender segregated treatment facilities. Gender Spectrum (www.genderspectrum.org), Advocates for Youth (www.advocatesforyouth.org), and Parents, Families and Friends of Lesbians and Gays (www.pflag.org) offer excellent support resources for transgender youth and their families.

Bibliography is available at Expert Consult.

110.3 Gay, Lesbian, and Bisexual Adolescents
Stewart L. Adelson and Mark A. Schuster

Understanding a child or adolescent’s sexual and emotional development is an essential part of any comprehensive pediatric evaluation. For youth who are or might be gay, lesbian, or bisexual (GLB), such understanding is particularly important. GLB youth as a group have the same health and developmental needs as all youth, and their sexual orientation is a normal variation of human sexuality; however, they encounter distinct developmental challenges and can have additional health and mental health needs related to their orientation and others’
Bibliography
reaction to it. Their sexual orientation is often different from that expected by family, peers, and society and they must cope with peer rejection, bullying, or family nonacceptance more frequently than most youth. Although the majority of GLB adolescents grow up physically and mentally healthy, they are at increased risk for certain medical and psychological problems as a result of these stresses and the epidemiology of health threats like HIV and other STIs. Pediatric healthcare providers are key in monitoring for such issues, supporting healthy development, and intervening when necessary to prevent or treat the problems for which GLB youth are at risk.

DEFINITIONS
Sexual orientation is the degree of attraction to the people of a particular sex. It encompasses emotional and erotic desires, physiologic arousal, sexual behavior, sexual identity, and social role. As sexuality develops, youth can be oriented entirely toward males, females, or both to various degrees on a continuum. Romantic attraction to the opposite sex is heterosexuality, to the same sex is homosexuality, and to both is bisexuality. Gay is a common term for homosexual, in both males and females; lesbian refers to homosexual females. Those unsure of their orientation are curious or questioning. The term young men who have sex with men (MSM) is sometimes used in the research literature to denote male youth who are engaging in sexual activity with other males, regardless of how they identify themselves.

PREVALENCE OF HOMOSEXUALITY AND BISEXUALITY IN YOUTH
Some junior high and high school students are unsure of their sexual orientation, while others say they are gay, lesbian, or bisexual. Some who do not identify as GLB report same-sex attraction, fantasies, or behavior. Certainty about sexual orientation and identity increases through adolescence with sexual experience. Those who fear nonacceptance may try to suppress or deny their orientation. Consequently, various aspects of orientation—feelings, behavior, and identity—may not be consistent in an individual, and may change during development. Only some youth with homosexual experience identify as "gay," consistent with reluctance about having or revealing a gay identity and underscoring the difference between identity and behavior. Population surveys of youth from 2001–2009 found a median of 2.5% reported that they were “unsafe” of their sexual orientation, 1.3% said they were “gay/lesbian,” and 3.7% said they were “bisexual.” In New York City in 2005–2007, 38.9% of adolescents with only same- or both-sex partners identified as straight.

DEVELOPMENT OF SEXUAL ORIENTATION IN CHILDHOOD AND ADOLESCENCE
See also Chapter 110.2.

Sexual orientation development begins prenatally and continues through childhood and adolescence and into adulthood. Both gender role behavior in childhood and sexual orientation in puberty and adolescence are partly influenced by prenatal genetic and neuroendocrine factors. Sociocultural and psychological factors also influence sexual development. A gay or lesbian sexual orientation is sometimes preceded developmentally by childhood gender nonconformity, or variation from population averages in gender role behavior. These are activities, interests, styles, and other attributes recognized as masculine or feminine, like toy preferences and preference for opposite-sex playmates. Although childhood gender nonconformity is not experienced by all gay people—and not all gender nonconforming children grow up to be gay—nonconformity is not uncommon (particularly among males) and leads many gay or lesbian people to feel different from peers in childhood, even before sexual desire or identity emerges. When not protected from stigma, gender-nonconforming children may experience ostracism, bullying, or family nonacceptance. These reactions to gender nonconformity can lead to later difficulty integrating a healthy, positive self-image and to long-term mental health problems.

Less frequently, gay or lesbian sexual orientation in adolescence is preceded by childhood gender incongruity/dysphoria, a distinct phenomenon in which an individual's gender identity differs from phenotypic sex and assigned gender at birth.

STIGMA, RISK, AND RESILIENCE
Homosexuality has been documented across cultures and historical periods; its meaning and acceptance vary greatly with social context. Gay people are now generally more visible and accepted than previously in the United States; still, youth are often exposed to antigay sexual attitudes. For many GLB youth, revealing their sexual orientation (“coming out”) to family, peers, healthcare providers, and others is a significant step. Specific racial/ethnic groups may experience unique developmental stressors: African-American youth report feeling less comfortable than white peers with a gay identity and less comfortable disclosing it.

Some GLB youth experience difficulty coping with stigma. Family nonacceptance, feeling unsafe because of school harassment, and peer bullying related to sexual orientation elevate risk in GLB adolescents for depression, substance abuse, suicidal thoughts and attempts, and social problems like truancy, dropping out, running away, and homelessness. Even when not overly threatened, GLB youth frequently encounter negative attitudes that force them to hide at a developmental period when acceptance holds great significance. Mental health problems, risk taking, or substance use may increase exposure to HIV/STIs. Stigma may also impede access to healthcare in some communities. Thus, along with factors influencing exposure and susceptibility to health threats, stigma partly mediates elevated risk for health and mental health problems in GLB youth.

It is important to reduce stigma against, support acceptance of, and promote resilient coping among GLB youth. Family connectedness and school support and safety are important protective factors against depression, suicidal thoughts and attempts, and substance abuse. GLB antiharassment policies and gay-straight alliances as well as anti-bullying programs increase school safety.

HEALTH AND MENTAL HEALTH
Depression and Suicidality
Rates of suicidality are about 2 or 3 times higher among gay and lesbian youth, and up to 5 times higher among bisexual youth, than among the general population. Family rejection, bullying, and other victimization motivated by homophobia accounts statistically for increased depression and suicidal thoughts and attempts in GLB adolescents. Suicidal thoughts or attempts are highest during the interval following a same-sex sexual experience and prior to self-acceptance as gay.

Sexually Transmitted Infections
The epidemiology of STIs (see Chapter 120), related to specific sexual practices, as well as prevalence of certain STIs in GLB communities, informs recommended counseling, screening, and treatment strategies. Anal intercourse has been shown to be the most efficient route of infection by hepatitis B (see Chapter 358), cytomegalovirus (see Chapter 255), and HIV (see Chapter 276). Oral–anal and digital–anal contact can transmit enteric pathogens, such as hepatitis A. Unprotected oral sex also can lead to oropharyngeal disease in the receptive partner and gonococcal and nongonococcal urethritis in the insertive partner. Certain STIs, particularly ulcerative diseases, such as syphilis (see Chapter 218) and herpes simplex virus infection (see Chapter 252.5), facilitate spread of HIV.

Among U.S. adolescents and young adults, young MSM continue to face the greatest toll of HIV/AIDS for various reasons, including misinformation, noncommunication with partners about risk reduction, potentially false assumptions about partners’ serostatus, substance use, and impaired reasoning and judgment. Rates are especially high among black young MSM. Although possible, female-to-female sexual transmission of HIV is inefficient, and females who only engage in same-sex behavior are less likely than other youth to acquire an STI. However, boys and girls who identify as gay or lesbian may engage in sexual activity with partners of the other gender, so counseling and screening for all types of STIs are still relevant.
Substance Abuse
See also Chapter 114.

A subset of GLB youth display increased rates of alcohol and substance use, including more binge drinking and earlier onset and more rapid trajectory of substance use. Problem drinking may be greatest in youth who do not identify as GLB but have same-sex attractions or engage in same-sex sexual behavior. Marijuana and other illicit drug use is more common among bisexual females, but studies have found no increased rates among young gay and bisexual males, and males with bisexual behavior and identity are less likely to drink than young heterosexual males. Smoking is increased among bisexual adolescent females and possibly in adolescent lesbians; studies are conflicting regarding smoking in other GLB adolescent groups.

Obesity and Disordered Eating
See also Chapter 26.

Existing studies suggest certain GLB youth are at risk for disordered eating. Compared with heterosexual girls, lesbian and bisexual girls generally have a more positive body image, although they are more likely to be overweight. In contrast, young gay and bisexual males are more likely to have body image concerns and are more likely to restrict eating or engage in compensatory weight loss strategies. Binge eating may also be more common in GLB youth. Behaviorally bisexual youth may be at greatest risk for disordered eating.

Psychosocial Problems
Academic underachievement, truancy, and dropping out among GLB adolescents are frequently associated with homophobic victimization, harassment, violence, and feeling unsafe at school. Youth who eventually identify as GLB appear to experience higher rates than other youth of child abuse, running away, or being thrown out of their homes. Homosexual young people are overrepresented in homeless and runaway populations across the United States. Life on the streets or in shelters exposes them to drugs and sexual abuse and promotes illegal conduct for survival.

RECOMMENDATIONS FOR CARE Evaluation
The goal of GLB pediatric care is physical health, social and emotional well-being, and promotion of healthy development. Physicians should provide nonjudgmental care to all adolescents, including those who are GLB or questioning. They should receive the age-appropriate history, examination, and anticipatory guidance recommended for adolescents in general. With some exceptions noted below, the physical examination and laboratory evaluation of GLB and questioning adolescents are the same as for any teenager. However, providers should screen for special potential medical and psychosocial threats to GLB teenagers' health appropriately.

A nonjudgmental healthcare environment, with open communication and a positive relationship with youth and families, is important. In the waiting room, written material about sexual orientation, support groups, and community resources will signal openness to discussing sexuality. Registration forms recognizing the possibility of same-gender parents signal a safe setting (e.g., forms can list parent/guardian #1, parent/guardian #2). Sexual history questions should avoid heterosexual assumptions (e.g., “are you dating someone” instead of “do you have a boyfriend/girlfriend?”). This is important at all ages. Discussing confidentiality and incorporating into each adolescent visit private time with no parent in the room (see Chapter 112) may facilitate discussing sexual orientation, as may use of appropriate health history forms, like the American Medical Association’s Guidelines for Adolescent Prevention Services Questionnaire.

Clinicians should remember that any youth might be GLB whether or not they are identified or perceived as such, so clinicians should not presuppose a particular orientation. Competency in conveying sensitivity, acceptance, and respectfulness; effective communication skills; and appropriate attention to privacy and confidentiality (including practices related to billing and record requests; see Chapter 112) are fundamental to providing high-quality care. While attuned to youth's preferences—explicit or implied—for discussing sexual orientation, providers should take the lead tactfully, if necessary, regarding any pressing areas of clinical concern.

Medical and Sexual Health
Sexually transmitted infections (see Chapter 120) pose additional issues specific to GLB youth. Use of latex condoms for anal and oral intercourse should be discussed with boys, and the use of dental dams, cut open latex condoms, or plastic wrap during oral sex should be discussed with girls; the use of latex condoms for sexual appliances are recommended as well. It is important to emphasize that people who have been using alcohol or other drugs are at increased likelihood for engaging in riskier sexual activity. It is important not to assume that a gay boy or lesbian girl who does not identify as bisexual has not had sex with the opposite gender. Lesbians can have an unplanned pregnancy. Similarly, youth who identify as heterosexual and are attracted only to the opposite sex may still have sexual activity with a partner of the same sex.

Although vaccination against hepatitis A and B is recommended for all children, it is particularly recommended that nonvaccinated adolescent males who are having sex or are likely to have sex with males get catchup vaccines. The same recommendation applies to the quadrivalent human papillomavirus vaccine for males. The Centers for Disease Control and Prevention recommends that males who are engaging in sexual activity with males have annual testing for HIV, hepatitis A, hepatitis B, syphilis, urethral gonorrhea and chlamydia (if engaging in insertive oral or anal intercourse), oral gonorrhea (if engaging in receptive oral intercourse), and rectal gonorrhea and chlamydia (if engaging in receptive anal intercourse). For treatment of STIs, see Chapter 120.

Mental Health
Awareness of mental health and social problems is important when caring for GLB youth, as for all youth (see Chapter 111). Clinicians should monitor for depression, suicidality, anxiety, and substance abuse, and know their community’s mental health resources. Minor psychosocial problems might be handled by referral to a support group for patients (e.g., Gay, Lesbian & Straight Education Network [GLSEN]) or for parents and others (e.g., Parents, Families, & Friends of Lesbians and Gays [PFLAG]). In some communities, agencies and organizations serving the GLB community can help with social, educational, vocational, housing, and other needs.

Individuals or families who harbor negative attitudes may inquire about mental health treatment to avert or change a homosexual or bisexual orientation. GLB orientation is not an illness, and leading health organizations, including the American Academy of Pediatrics, the American Academy of Family Physicians, the Society for Adolescent Health and Medicine, the American Academy of Child and Adolescent Psychiatry, and the American Medical Association, have concluded that such change is neither possible nor warranted. It is important to distinguish between a GLB orientation, which is not a mental illness, and mental health problems like depression for which GLB youth are at elevated risk. While understanding different families’ values, clinicians must recognize the morbidity and mortality associated with stigma and aim to foster physical and emotional health. Individual or family therapy might be indicated for some. Clinicians should also monitor for specific stressors such as bullying and other homophobic victimization, family nonacceptance, and abuse. Failure to confront harassment constitutes tacit assent.

Anticipatory guidance, referral, and substance abuse treatment should be considered for the subset of GLB youth who use alcohol, drug, or tobacco; some of whom may be using these to manage painful feelings related to conflicts over their sexuality.

Adolescents with serious psychiatric symptoms, such as suicidality, depression, and substance abuse should be referred to mental health specialists with competency in treating GLB adolescents. It is essential to know how to recognize and manage psychiatric emergencies such as suicidal thoughts and attempts (see Chapter 27).

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Adolescence is the first period of life where the major determinants of morbidity and mortality are behavioral rather than congenital or infectious. As adolescents make the transition from childhood to adulthood, they establish behaviors that affect both their current and future health. Adolescence is a time of immense biologic, psychologic, and social change (see Chapter 110). Many of the psychological changes have a biologic substrate in the development and eventual maturation of the central nervous system, particularly the frontal lobe areas responsible for executive functioning (Fig. 111-1). In addition to cognitive development, there are both risk and protective factors for adverse adolescent health behaviors that are dependent on the social environment as well as the mental health of an adolescent (Table 111-1).

Many adolescents continually confront the task of making healthy choices while struggling with impulsivity that can lead to unintentional consequences, such as injuries, sexually transmitted infections, or drug overdoses. Adolescents are also challenged with adopting behaviors that will affect their future adult health, such as eating nutritionally, engaging in physical activity, and choosing not to use tobacco. Environmental factors, such as family, peers, school, community, and religiosity, also contribute to adolescents’ health and risk behaviors. The Centers for Disease Control and Prevention (CDC) Youth Risk Behavior Surveillance Survey, a school-based survey of a nationally representative sample of U.S. high school students, demonstrates that youth begin engaging in behaviors that place their health at risk during adolescence (Fig. 111-2).

Although according to the 2012 CDC National Health Interview Survey, a probability sample survey conducted annually, an estimated 81% of 12-17 yr olds report excellent or very good health, 23% missed 3-5 school days in the past year, 9% are uninsured, 6% have no usual place of healthcare, 11% have asthma, 11% have respiratory allergies, 10% have a learning disability, 12% have attention deficit hyperactivity disorder, and 17% take prescription medications routinely. In 2010, the mortality rate among adolescents 15-19 yr of age was 49 deaths per 100,000 population. While varying by gender, the leading causes of death overall among adolescents 15-19 yr of age are (1) unintentional injuries; (2) homicide; and (3) suicide (Table 111-2).

Within the adolescent population, disparities in health occur. Adolescent health outcomes and behaviors vary among populations that can be defined by race or ethnicity, gender, education or income, disability, geographic location (e.g., rural or urban), or sexual orientation. Health disparities result from multiple factors, including poverty, environmental threats, inadequate access to healthcare, individual and behavioral factors, and educational inequalities (Table 111-3).

### Table 111-1 Identified Risk and Protective Factors for Adolescent Health Behaviors

<table>
<thead>
<tr>
<th>BEHAVIOR</th>
<th>RISK FACTORS</th>
<th>PROTECTIVE FACTORS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking</td>
<td>Depression and other mental health problems, alcohol use, disconnectedness from school or family, difficulty talking with parents, minority ethnicity, low school achievement, peer smoking</td>
<td>Family connectedness, perceived healthiness, higher parental expectations, low prevalence of smoking in school</td>
</tr>
<tr>
<td>Alcohol and drug misuse</td>
<td>Depression and other mental health problems, low self-esteem, easy family access to alcohol, working outside school, difficulty talking with parents, risk factors for transition from occasional to regular substance misuse (smoking, availability of substances, peer use, other risk behaviors)</td>
<td>Connectedness with school and family, religious affiliation</td>
</tr>
<tr>
<td>Teenage pregnancy</td>
<td>Deprivation, city residence, low educational expectations, lack of access to sexual health services, drug and alcohol use</td>
<td>Connectedness with school and family, religious affiliation</td>
</tr>
<tr>
<td>Sexually transmitted infections</td>
<td>Mental health problems, substance misuse</td>
<td>Connectedness with school and family, religious affiliation</td>
</tr>
</tbody>
</table>


**Figure 111-1** It has been speculated that the impact of puberty on arousal and motivation occurs before the maturation of the frontal lobes is complete. This gap may create a period of heightened vulnerability to problems in the regulation of affect and behavior, which might help to explain the increased potential in adolescence for risk taking, recklessness, and the onset of emotional and behavioral problems. (From Steinberg L: Cognitive and affective development in adolescence, Trends Cogn Sci 9:69–74, 2005.)
### ACCESS TO HEALTHCARE

Access to healthcare may be limited for adolescents compared to other age groups. Adolescents in the United States make fewer visits to physicians for ambulatory office visits than does any other age group; school-age children and adolescents are more likely than younger children to have unmet health needs and delayed medical care. Adolescents and young adults are less likely to be insured than all other age groups. Young adults 18–24 yr are more likely to be uninsured because they no longer eligible to receive benefits from their parents’ health plans. In addition, health insurance status differs based on income and race/ethnicity. Adolescents and young adults who transition to self-sufficiency from foster care experience insurance coverage than those with higher family incomes; and Hispanic and black adolescents and young adults are less likely to have health insurance coverage than their non-Hispanic white and Asian peers. Uninsured children and adolescents are less likely to receive preventive visits and have a regular source of care than the insured, and are more likely to go without treatment of symptoms.

Adolescents who actually receive preventive care may still not have access to time alone with their provider or discuss important confidential health issues, such as sexually transmitted infections, HIV, or pregnancy prevention. Less than half (40%) of adolescents have time alone with their healthcare provider during a preventive healthcare visit; sexually experienced teens report sexual health discussions more often than nonsexually experienced teens, but the frequency is still low at 64% and 33.5% for sexually experienced females and males, respectively.

Under the Patient Protection and Affordable Care Act, healthcare providers will strive to improve the health of their patient population. Healthy People provides science-based, 10-year national objectives for measuring and improving the health of all Americans by establishing benchmarks and monitoring progress over time. The Healthy People 2020 agenda includes 11 adolescent-specific objectives with a goal of improving the healthy development, health, safety, and well-being of adolescents and young adults over the next 10 yr (Table 111-4). This agenda focuses on 11 objectives:

1. Increase the proportion of adolescents who have had a wellness checkup in the past 12 months.
2. Increase the proportion of adolescents who participate in extracurricular and out-of-school activities.
3. Increase the proportion of adolescents who are connected to a parent or other positive adult caregiver.
4. Increase the proportion of adolescents who have an adult in their lives with whom they can talk about serious problems.
5. Increase the proportion of parents who attend events and activities in which their adolescents participate.
6. Increase the proportion of adolescents and young adults who transition to self-sufficiency from foster care.
7. Increase educational achievement of adolescents and young adults.
8. Increase the proportion of students who graduate with a regular diploma 4 years after starting 9th grade.
9. Increase the proportion of students whose reading skills are at or above the proficient achievement level for their grade.
10. Increase the proportion of students whose mathematics skills are at or above the proficient achievement level for their grade.
11. Increase the proportion of students who participate in the school breakfast program.

### Table 111-3: Adolescent Health Outcomes by Race/Ethnicity, United States, 2010-2012

<table>
<thead>
<tr>
<th>OUTCOME</th>
<th>WHITE</th>
<th>BLACK</th>
<th>AI/AN</th>
<th>API</th>
<th>HISPANIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deaths*</td>
<td>47.5</td>
<td>70.6</td>
<td>61.5</td>
<td>22.8</td>
<td>41.5</td>
</tr>
<tr>
<td>Births†</td>
<td>20.5</td>
<td>43.9</td>
<td>34.9</td>
<td>9.7</td>
<td>46.3</td>
</tr>
<tr>
<td>Obese†</td>
<td>11.5</td>
<td>18.2</td>
<td>N/A</td>
<td>N/A</td>
<td>14.1</td>
</tr>
<tr>
<td>Asthma†</td>
<td>22.8</td>
<td>26.8</td>
<td>N/A</td>
<td>N/A</td>
<td>20.3</td>
</tr>
<tr>
<td>Depressed†</td>
<td>27.2</td>
<td>24.7</td>
<td>N/A</td>
<td>N/A</td>
<td>32.6</td>
</tr>
<tr>
<td>Chlamydia*</td>
<td>830.1</td>
<td>4,977.7</td>
<td>2,509.8</td>
<td>313.0***</td>
<td>1,191.0</td>
</tr>
<tr>
<td>Gonorrhea*</td>
<td>85.3</td>
<td>1,513.5</td>
<td>324.6</td>
<td>36.5***</td>
<td>139.7</td>
</tr>
<tr>
<td>HIV*</td>
<td>2.5</td>
<td>46.3</td>
<td>5.8</td>
<td>2.9***</td>
<td>8.1</td>
</tr>
</tbody>
</table>

**Rates of infection in 2011 per 100,000 15-19 year old population by race/ethnicity.
***Rates of death in 2010, per 100,000 15-19 year old population by race/ethnicity.
### Table 111-4: Healthy People 2020 Adolescent Health (AH) Objectives

- AH-1: Increase the proportion of adolescents who have had a wellness checkup in the past 12 months.
- AH-2: Increase the proportion of adolescents who participate in extracurricular and out-of-school activities.
- AH-3: Increase the proportion of adolescents who are connected to a parent or other positive adult caregiver.
- AH-3.1: Increase the proportion of adolescents who have an adult in their lives with whom they can talk about serious problems.
- AH-3.2: Increase the proportion of parents who attend events and activities in which their adolescents participate.
- AH-4: Increase the proportion of adolescents and young adults who transition to self-sufficiency from foster care.
- AH-5: Increase educational achievement of adolescents and young adults.
- AH-5.1 (Leading Health Indicator): Increase the proportion of students who graduate with a regular diploma 4 years after starting 9th grade.
- AH-5.2: Increase the proportion of students whose reading skills are at or above the proficient achievement level for their grade.
- AH-5.4: Increase the proportion of students whose mathematics skills are at or above the proficient achievement level for their grade.
- AH-5.5: Increase the proportion of adolescents who consider their school work to be meaningful and important.
- AH-5.6: Decrease school absenteeism among adolescents due to illness or injury.
- AH-6: Increase the proportion of schools with a school breakfast program.
- AH-7: Reduce the proportion of adolescents who have been offered, sold, or given an illegal drug on school property.
- AH-8: Increase the proportion of adolescents whose parents consider them to be safe at school.
- AH-9: Increase the proportion of middle and high schools that prohibit harassment based on a student’s sexual orientation or gender identity.
- AH-10: Decrease the proportion of public schools with a serious violent incident.
- AH-11: Reduce adolescent and young adult perpetration of, as well as victimization by, crimes.
- AH-11.1: Decrease the rate of minor and young adult perpetration of violent crimes.
- AH-11.2: Decrease the rate of minor and young adult perpetration of serious property crimes.
- AH-11.3: Decrease the percentage of counties and cities reporting youth gang activity.
- AH-11.4: Decrease the rate of adolescent and young adult victimization from crimes of violence.

A science-based initiative is centered around a framework for public health prevention priorities and actions to improve the health status of U.S. youth.

*Figure 111-2 Selected health behaviors among 9th and 12th grade high school students. (Data from Centers for Disease Control and Prevention: 2011 Youth risk behavior surveillance system. [http://www.cdc.gov/healthyyouth/yrbs/index.htm](http://www.cdc.gov/healthyyouth/yrbs/index.htm).)*

Bibliography is available at Expert Consult.
Bibliography
Healthcare providers play an important role in nurturing healthy behaviors among adolescents because the leading causes of death and disability among adolescents are preventable. Adolescence provides a unique opportunity to prevent or modify health conditions arising from behaviors that develop in the second decade of life and that can lead to substantial morbidity and mortality, such as trauma, cardiovascular and pulmonary disease, type 2 diabetes, reproductive health disease, and cancer.

Health systems in each community should be in place to ensure comprehensive and high-quality care to adolescents. Health insurance coverage that is affordable, continuous, and not subject to exclusion for preexisting conditions, should be available for all adolescents and young adults who have no access to private insurance. Comprehensive, coordinated benefits should meet the developmental needs of adolescents, particularly for reproductive, mental health, dental, and substance abuse services. Safety net providers and programs that provide confidential services, such as school-based health centers, federally qualified health centers, family planning services, and clinics that treat sexually transmitted infections (STIs) in adolescents and young adults, need to have assured funding for viability and sustainability. Quality-of-care data should be collected and analyzed by age so that the performance measures for age-appropriate healthcare needs of adolescents are monitored. Affordability is important for access to preventive services. Family involvement should be encouraged, but confidentiality and adolescent consent are critically important.

Healthcare providers, trained and experienced to care for adolescents, should be available in all communities. Healthcare providers should be adequately compensated to support the range and intensity of services required to address the developmental and health service needs of adolescents. The creation and dissemination of provider education about adolescent preventive health guidelines have been demonstrated to improve the content of recommended care (Table 112-1). The ease of recognition or expectation that an adolescent’s needs can be addressed in a setting relates to the visibility and flexibility of sites and services. Staff at sites should be approachable, linguistically capable, and culturally competent. Health services should be coordinated to respond to goals for adolescent health at the local, state, and national levels. The coordination should address service financing and delivery in a manner that reduces disparities in care.

### Table 112-1

**Bright Futures/American Academy of Pediatrics Recommendations for Preventive Healthcare for 11-21 Yr Olds**

<table>
<thead>
<tr>
<th>PERIODICITY AND INDICATIONS</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>HISTORY</td>
<td>Annual</td>
</tr>
<tr>
<td>MEASUREMENTS</td>
<td></td>
</tr>
<tr>
<td>Body mass index</td>
<td>Annual</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>Annual</td>
</tr>
<tr>
<td>SENSORY SCREENING</td>
<td></td>
</tr>
<tr>
<td>Vision</td>
<td>At 11, 15, and 18 yr visits or if risk assessment positive</td>
</tr>
<tr>
<td>Hearing</td>
<td>If risk assessment positive</td>
</tr>
<tr>
<td>DEVELOPMENTAL/BEHAVIORAL ASSESSMENT</td>
<td></td>
</tr>
<tr>
<td>Developmental surveillance</td>
<td>Annual</td>
</tr>
<tr>
<td>Alcohol and drug use assessment</td>
<td>Annual</td>
</tr>
<tr>
<td>Psychosocial/behavioral assessment</td>
<td>If risk assessment positive</td>
</tr>
<tr>
<td>PHYSICAL EXAMINATION</td>
<td></td>
</tr>
<tr>
<td>Immunization</td>
<td>Annual</td>
</tr>
<tr>
<td>Hematocrit or hemoglobin</td>
<td>If risk assessment positive</td>
</tr>
<tr>
<td>Tuberculin test</td>
<td>If risk assessment positive</td>
</tr>
<tr>
<td>Dyslipidemia screening</td>
<td>If risk assessment positive</td>
</tr>
<tr>
<td>STI screening</td>
<td>If sexually active</td>
</tr>
<tr>
<td>HIV screening</td>
<td>Discussed and offer</td>
</tr>
<tr>
<td>Cervical dysplasia screening</td>
<td>Beginning at age 21 yr</td>
</tr>
<tr>
<td>ORAL HEALTH</td>
<td></td>
</tr>
<tr>
<td>Annual refer to dental home or administer oral health risk assessment</td>
<td></td>
</tr>
<tr>
<td>ANTICIPATORY GUIDANCE</td>
<td>Annual</td>
</tr>
</tbody>
</table>

*Schedules as per the Advisory Committee on Immunization Practices, published annually at [http://www.cdc.gov/vaccines/schedules/hcp/index.html](http://www.cdc.gov/vaccines/schedules/hcp/index.html) and in the January issue of Pediatrics.


‡Refer to specific guidance by age as listed in Bright Futures Guidelines.

§CDC recommends universal, voluntary HIV screening of all sexually active people, beginning at age 13 yr. The American Academy of Pediatrics recommends offering routine HIV screening to all adolescents at least once by 16-18 yr of age and to those younger if at risk. U.S. Preventive Services Task Force recommends offering routine HIV screening to all adolescents age 15 yr and older at least once and to those younger if at risk. Patients who test positive for HIV should receive prevention counseling and referral to care before leaving the testing site.

Although most adolescents in the United States have seen a healthcare provider in the past year and report a usual source of healthcare, adolescents are less likely to receive preventive care services. According to the 2011 National Health Interview Survey, an estimated 90% of 12-17 yr old U.S. adolescents had 1 or more contacts with a healthcare professional in the past year, 98% identify a usual source of care at a doctor’s office or clinic, and 17% made at least 1 emergency department visit in the past year. Uninsured adolescents are the least likely to receive care. In 2011, an estimated 9% of 12-17 yr olds were without health insurance, 2% had unmet healthcare needs and 4% delayed healthcare because of cost. However, even among adolescents who are fully insured with a usual source of care, most do not receive preventive healthcare. An analysis of claims data from a large Minnesota health plan with approximately 700,000 members found that among patients ages 11-18 yr who were enrolled for at least 4 yr between 1998 and 2007, few received preventive care visits. One-third of adolescents had no preventive care visits from age 13 through 17 yr, and another 40% had only a single such visit. Nonpreventive care visits were more frequent in all age-groups, averaging about 1 per yr at age 11 yr, climbing to about 1.5 per yr at age 17 yr. Among older adolescence, females had both more preventive care and more nonpreventive care visits than did males (Table 112-2).

The Patient Protection and Affordable Care Act (ACA), enacted in March, 2010, has significantly expanded access to both commercial health plans and Medicaid for young adults age 19-26 yr (Fig. 112-1). From June 2010 through June 2012, the proportion of young adults with insurance increased from 65.7% to 73.8%. ACA provisions require that commercial health plans (a) continuing dependent coverage to 26 yr, regardless of the young adults’ financial or dependent status, marriage, or educational enrollment; (b) mandate university, and college student health plans to enhance consumer protections for students; (c) provide financial assistance for young adults to enroll into health insurance exchanges with incomes ranging from 133% to 399% of the federal poverty level; and offer preventive healthcare services free of any cost sharing, deductibles or copayments. For Medicaid, states must offer enrollment to all adults with incomes less than 133% of the federal poverty level.

The complexity and interaction of physical, cognitive, and psychosocial developmental processes during adolescence require sensitivity and skill on the part of the health professional (see Chapter 110). Health education and promotion, as well as disease prevention, should be the focus of every visit. In 2008, the American Academy of Pediatrics in collaboration with the U.S. Department of Health and Human Services, Health Resources and Services Administration, Maternal and Child Health Bureau, published the 3rd edition of *Bright Futures: Guidelines for Health Supervision of Infants, Children, and Adolescents*, which offers providers a strategy for delivery of adolescent preventive health services with screening and counseling recommendations for early, middle, and late adolescence (Table 112-3). Bright Futures is rooted in the philosophy of preventive care and reflects the concept of caring for children in a “medical home.” These guidelines emphasize effective partnerships with parents and the community to support the adolescent’s health and development.

The Centers for Disease Control and Prevention’s Advisory Committee on Immunization Practices currently recommends routine adolescent vaccines for universal administration beginning at the 11-12 yr old visit or as soon as possible, (a) tetanus–diphtheria–acellular pertussis vaccine (Tdap), (b) the meningococcal conjugate vaccine (MCV4), and (c) the human papillomavirus vaccine (see Chapter 172). The Advisory Committee on Immunization Practices recommends annual influenza vaccination and hepatitis A vaccination (HAV) to adolescents and young adults who have not previously received the HAV vaccine series if immunity against HAV is desired or for those at increased risk for infection, such as men who have sex with men, injection drug users, and those with chronic liver disease or clotting factor disorders, or who live in areas that target older children for HAV vaccine.

The time spent on various elements of the screening will vary with the issues that surface during the assessment. For gay and lesbian youth (see Chapter 110.3), emotional and psychologic issues related to their experiences, from fear of disclosure to the trauma of homophobia, may direct the clinician to spend more time assessing emotional and psychologic supports in the young person’s environment. For youth with

![Figure 112-1](image_url)

**Figure 112-1** Percentage of adults age 19-25 yr with health insurance by coverage type and percentage uninsured at the time of the interview: United States, 1997–September, 2012. Note: Estimates for 2012 are based on data collected in January through September. Data are based on household interviews of a sample of the civilian noninstitutionalized population. (Data from CDC/NCHS, National Health Interview Survey, 1997-2012, Family Core Component.)

<table>
<thead>
<tr>
<th>Table 112-2</th>
<th>Adjusted Mean Number of Preventive and Nonpreventive Care Visits Among Continuously Enrolled Adolescents Between the Ages of 13 and 18 Yr, Health Partners 1998-2007</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CHARACTERISTIC</strong></td>
<td><strong>PREVENTIVE CARE VISITS MEAN NUMBER (SD)</strong></td>
</tr>
<tr>
<td><strong>INSURANCE TYPE</strong></td>
<td></td>
</tr>
<tr>
<td>Commercial</td>
<td>1.070 (0.947)</td>
</tr>
<tr>
<td>Governmental</td>
<td>1.1781 (1.094)</td>
</tr>
<tr>
<td><strong>SEX</strong></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1.162 (0.985)</td>
</tr>
<tr>
<td>Female</td>
<td>0.991 (0.916)</td>
</tr>
</tbody>
</table>

Note. Among adolescents with continuous enrollment (≥333 days between birthdays) for 4 or more yr. Regression model adjusted mutually for insurance type and sex.

SD: standard deviation.

Adolescent Screening Recommendations

### Universal Screening

<table>
<thead>
<tr>
<th>Age Group</th>
<th>11-14 YR OLD VISIT</th>
<th>15-17 YR OLD VISIT</th>
<th>18-21 YR OLD VISIT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vision (once during each of 3 adolescent age groups)</td>
<td>Snellen test</td>
<td>Snellen test</td>
<td>Snellen test</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>Lipid screen (once between 9-11 yr)</td>
<td>NA</td>
<td>Lipid screen (once between 18-21 yr)</td>
</tr>
</tbody>
</table>

### Selective Screening

<table>
<thead>
<tr>
<th>Condition</th>
<th>Risk Assessment</th>
<th>Action If RA+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vision at other ages</td>
<td>+ on risk screening questions</td>
<td>Snellen test</td>
</tr>
<tr>
<td>Hearing</td>
<td>+ on risk screening questions</td>
<td>Audiometry</td>
</tr>
<tr>
<td>Anemia</td>
<td>+ on risk screening questions</td>
<td>Hemoglobin or hematocrit</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>+ on risk screening questions</td>
<td>Tuberculin skin test</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>+ on risk screening questions and not previously screened with normal results</td>
<td>Lipid screen</td>
</tr>
<tr>
<td>STIs</td>
<td>Sexually active</td>
<td>Chlamydia and gonorrhea screen (use tests appropriate for population and clinical setting)</td>
</tr>
<tr>
<td>HIV</td>
<td>Discuss and offer</td>
<td>HIV test*</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>Sexually active, without contraception, late menses or amenorrhea</td>
<td>Urine hCG</td>
</tr>
<tr>
<td>Cervical dysplasia</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Alcohol or drug use</td>
<td>+ on risk screening questions</td>
<td>Administer alcohol and drug screening tool</td>
</tr>
</tbody>
</table>

*CDC recommends universal, voluntary HIV screening of all sexually active people, beginning at age 13 yr. American Academy of Pediatrics recommends routine HIV screening offered to all adolescents at least once by 16-18 yr of age and to those younger if at risk. U.S. Preventive Services Task Force recommends routine HIV screening offered to all adolescents age 15 yr and older at least once and to those younger if at risk. Patients who test positive for HIV should receive prevention counseling and referral to care before leaving the testing site.

HCG, human chorionic gonadotropin; NA, not applicable; RA, risk assessment.


The rights of an individual, including those of adolescents, vary widely between nations. In the United States, the right of a minor to consent to treatment without parental knowledge varies between states and is governed by state-specific minor consent laws. Some consent laws are based on a minor’s status, such as minors who are emancipated, parents, married, pregnant, in the armed services, or mature. In some states, minors can be considered emancipated if they are or have served in the armed services or are living apart from parents and are economically independent through gainful employment. A mature minor is a minor who is emotionally and intellectually mature enough to give informed consent and who lives under the supervision of a parent or guardian. Courts have held that if a minor is mature, a physician is not liable for providing beneficial treatment. There is no formal process for recognition of a mature minor. The determination is made by the healthcare provider.

Some minor consent laws are based on services a minor is seeking, such as emergency care, sexual healthcare, substance abuse, or mental healthcare (Table 112-4). All 50 states and the District of Columbia explicitly allow minors to consent for their own health services for STIs. Approximately 25% of states require that minors be a certain age (generally 12-14 yr) before they are allowed to consent for their own care for STIs. No state requires parental consent for STI care or requires that providers notify parents that an adolescent minor child has received STI services, except in limited or unusual circumstances.

Minors’ right to consent for contraceptive services varies from state to state. Nearly 50% of states and the District of Columbia explicitly authorize all minors to consent for their own contraceptive services; and 50% of states permit minors to consent for their own contraceptive services under specific circumstances, such as being married, a parent, currently or previously pregnant, over a certain age, or a high school graduate, or per physician’s discretion. A minor’s right to consent for mental healthcare and substance abuse treatment services vary by state and age of minor, whether care is medical versus nonmedical (e.g., counseling), and whether care is delivered as an inpatient versus outpatient basis. Minor consent laws often contain provisions regarding confidentiality and disclosure, even when general state consent laws do not have such provisions.

### Bibliography

Bibliography is available at Expert Consult.

#### 112.1 Legal Issues

**Gale R. Burstein**

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Bibliography
English A, Park MJ: Access to health care for young adults: the Affordable Care Act is making a difference, Chapel Hill, NC, 2012, Center for Adolescent Health and the Law; and San Francisco, CA: National Adolescent Health and Young Adult Information Center.
The confidentiality of medical information and records of a minor who has consented for his or her own reproductive healthcare is governed by numerous federal and state laws. Laws in some states explicitly protect the confidentiality of STI or contraceptive services for which minors have given their own consent and do not allow disclosure of the information without the minor’s consent. In other states, laws grant physicians discretion to disclose information to parents.

The confidentiality of medical information and records of a minor who has consented for his or her own healthcare is also governed by numerous federal and state laws. Laws in some states explicitly protect the confidentiality of STI, contraceptive, or mental health services for which minors have given their own consent and do not allow disclosure of the information without the minor’s consent. In other states, laws grant physicians discretion to disclose information to parents. Federal regulations issued under the Federal Health Insurance Portability and Accountability Act of 1996, known as the HIPAA Privacy Rule, defer to state and “other applicable laws” with respect to the question of whether parents’ have access to information about care for which a minor has given consent. Thus both the state laws that either prohibit or permit disclosure of confidential information and the federal Title X and Medicaid both provide confidentiality protection for family planning services provided to minors with funding from these programs.

The confidentiality of medical information and records of a minor who has consented for his or her own care is also governed by numerous federal and state laws. Laws in some states explicitly protect the confidentiality of STI, contraceptive, or mental health services for which minors have given their own consent and do not allow disclosure of the information without the minor’s consent. In other states, laws grant physicians discretion to disclose information to parents. Federal regulations issued under the Federal Health Insurance Portability and Accountability Act of 1996, known as the HIPAA Privacy Rule, defer to state and “other applicable laws” with respect to the question of whether parents’ have access to information about care for which a minor has given consent. Thus both the state laws that either prohibit or permit disclosure of confidential information and the federal Title X and Medicaid both provide confidentiality protection for family planning services provided to minors with funding from these programs.

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Billing for confidential services is complex. Commercial health plans send home an explanation of benefit to the primary insured or the primary beneficiary listing services rendered by the provider and reimbursed by the health plan. An explanation of benefit documenting that confidential health services were rendered to their adolescent dependent that is received by a parent may disclose those services. In addition, copayments automatically generated with certain billing codes for office visits and medications can be a barrier for adolescents receiving care, including treatment.

Providers may elect to establish a policy of discussing with their adolescent patients when medical records and other information will be disclosed and developing a mechanism to alert office staff as to what information in the chart is confidential. For legal and other reasons, a chaperone should be present whenever an adolescent female patient is examined by a male physician.

Bibliography is available at Expert Consult.

### 112.2 Screening Procedures

Gale R. Burstein

The preparation for a successful interview with an adolescent patient varies based on the history of the relationship with the patient. Patients (and their parents) who are going from preadolescence to adolescence while seeing the same provider, should be guided through the transition. Although the rules for confidentiality are the same for new and continuing patients, the change in the physician-patient relationship, allowing more privacy during the visit and more autonomy in the health process, may be threatening for the parent as well as the adolescent. For new patients, the initial phases of the interview are more challenging given the need to establish rapport rapidly with the patient in order to meet the goals of the encounter. Issues of confidentiality and privacy should be explicitly stated along with the conditions under which that confidentiality may need to be altered, that is, in life- or safety-threatening situations. For new patients, the parents should be interviewed with the adolescent or before the adolescent to ensure that the adolescent does not perceive a breach of confidentiality. The clinician who takes time to listen avoids judgmental statements and the use of street jargon and shows respect for the adolescent’s emerging maturity while seeing the same provider.

The use of open-ended questions, rather than closed-ended questions, will further facilitate history taking. (The closed-ended question “Do you get along with your father?” leads to the answer “yes” or “no,” in contrast to the question, “What might you like to be different in your relationship with your mother?” which may lead to an answer such as “I would like her to stop always worrying about me.”)

The goals of the interview or clinical encounter are to establish an information base, identify problems and issues from the patient’s perspective, and identify problems and issues from the perspective of the
Bibliography
clinician based on knowledge of the health and other issues relevant to the adolescent age group. The adolescent should be given an opportunity to express concerns and the reasons for seeking medical attention. The adolescent as well as the parent should be given an opportunity to express the strengths and successes of the adolescent, in addition to communicating problems.

The effectiveness of an interview can be compromised when the interviewer is distracted by other events or individuals in the office, when there are extreme time limitations obvious to either party, or when there is expressive discomfort with either the patient or the interviewer. The need for an interpreter when a patient is hearing impaired or if the patient and interviewer are not language compatible provides a challenge but not necessarily a barrier under most circumstances (see Chapter 4). Observations during the interview can be useful to the overall assessment of the patient’s maturity, presence or absence of depression, and the parent-adolescent relationship. Given the key role of a successful interview in the screening process, adequate training and experience should be sought by clinicians wishing to give comprehensive care to adolescent patients.

**PSYCHOSOCIAL ASSESSMENT**
A few questions should be asked in order to identify the adolescent who is having difficulty with peer relationships (“Do you have a best friend with whom you can share even the most personal secret?”), self-image (“Is there anything you would like to change about yourself?”), depression (“What do you see yourself doing 5 yr from now?”), school (“How are your grades this year compared with last year?”), personal decisions (“Are you feeling pressured to engage in any behavior for which you do not feel you are ready?”), and an eating disorder (“Do you ever feel that food controls you rather than vice versa?”). Bright Futures materials provide questions and patient encounter forms to structure the assessments that are available at their website (http://brightfutures.aap.org/index.html). The HEADS/SF/FIRST mnemonic, basic or expanded, can be useful in guiding the interview if encounter forms are not available (Table 112-5). Based on the assessments, appropriate counseling or referrals are recommended for more thorough probing or for in-depth interviewing.

**PHYSICAL EXAMINATION**

**Vision Testing**
The pubertal growth spurt may involve the optic globe, resulting in its elongation and myopia in genetically predisposed individuals (see Chapter 621). Vision testing should, therefore, be performed in order to detect this problem before it affects school performance.

**Audiometry**
Highly amplified music of the kind enjoyed by many adolescents may result in hearing loss (see Chapter 637). A hearing screening is recommended by the Bright Futures guidelines for adolescents who are exposed to loud noises regularly, have had recurring ear infections, or have a family history of hearing loss.

**Blood Pressure Determination**
Criteria for a diagnosis of hypertension are based on age-specific norms that increase with pubertal maturation (see Chapter 445). An individual whose blood pressure exceeds the 95th percentile for his or her age is suspect for having hypertension, regardless of the absolute reading. Those adolescents with blood pressure between the 90th and 95th percentiles should receive appropriate counseling relative to weight and have a follow-up examination in 6 mo. Those with blood pressure above the 90th percentile should have their blood pressure measured on three separate occasions to determine the stability of the elevation before moving forward with an intervention strategy. The technique is important; false-positive results may be obtained if the cuff covers less than two thirds of the upper arm. The patient should be seated, and an average should be taken of the 2nd and 3rd consecutive readings, using the change rather than the disappearance as the diastolic pressure. Most adolescents with elevations of blood pressure have labile hypertension. If the blood pressure is below 2 SD for age, anorexia nervosa and Addison disease should be considered.

**Scoliosis**
See Chapter 679.

Approximately 5% of male and 10-14% of female adolescents have a mild curvature of the spine. This is 2-4 times the rate in younger children. Scoliosis is typically manifested during the peak of the height velocity curve, at approximately 12 yr in females and 14 yr in males. Curves measuring greater than 10 degrees should be monitored by an orthopedist until growth is complete.

**Breast Examination**
See Chapters 115 and 551.

Examination of the female adolescent’s breasts is performed to detect masses, evaluate progression of sexual maturation, provide reassurance about development, and teach the technique of self-examination with the hope that this practice will continue into the higher risk later years. However, there is disagreement on the justification for promoting this routinely, given the rare instances of malignant breast masses in this age group.
112.3 Transitioning to Adult Care

Cynthia Holland-Hall and Gale R. Burstein

The importance of successfully transitioning the care of adolescents with special healthcare needs (SHCN) from pediatric to adult services has been recognized for over a decade. Successful transition is associated with improved health outcomes and quality of life; poorly managed transition may lead to worsening of chronic disease control. Nonetheless, few pediatric practices incorporate explicit, comprehensive transition services into the care of their patients with SHCN. Barriers to providing transition services include lack of access to appropriate providers of adult primary and subspecialty care, time, and reimbursement by insurance companies. Internists accepting young adult patients with SHCN also perceive a need for better training in congenital and child-onset medical conditions. Families may experience anxiety about leaving trusted pediatric providers, or fear that their child is incapable of assuming care for his or her medical condition. Among the patients themselves, a higher degree of self-efficacy for disease management and independently negotiating the healthcare system, as well as a positive attitude toward transition, lead to a greater perceived readiness to transition their care to an adult model. Medical providers, family members, and adolescent patients therefore each play a critical role in implementing and executing a plan for successful transition.

The American Academy of Pediatrics, in conjunction with other key professional societies, has published detailed, comprehensive guidelines for incorporating transition services into the medical home for all adolescents, regardless of the presence or absence of SHCN. These guidelines are based on expert opinion, since the evidence on transition outcomes is limited. Transition encompasses much more than simply the transfer of care to another provider. In fact, many of the elements of transition apply even to family physicians who do not intend to transfer the patient’s care, but who still should assist the patient in adapting to an adult model of healthcare delivery. Table 112-6 includes the key elements of healthcare transition. Tools to assist providers with all of these steps are available online from the National healthcare Transition Center (www.gottransition.org).

The process begins with the development of a transition policy and its dissemination to all families of young adolescents, ensuring that families understand that transition planning will be an element of health maintenance and chronic care management visits throughout the adolescent years. By middle adolescence, a transition plan should be developed with the youth and family caregivers, and this plan should be updated at subsequent visits until the patient is ready for implementation of the adult care model in early adulthood. Critical to the transition process is skills training for the adolescent in communication, self-advocacy, and self-care. The ultimate goal is to help all young people maximize their potential as they become young adults.

Bibliography is available at Expert Consult.
Bibliography
**Bibliography**


Chapter 113
Violent Behavior
Margaret M. Stager

Violence is recognized by the World Health Organization (WHO) as a leading worldwide public health problem. WHO defines violence as "The intentional use of physical force or power, threatened or actual, against oneself, another person, or against a group or community that either results in or has a high likelihood of resulting in injury, death, psychologic harm, maldevelopment or deprivation" (see Chapter 39). Youths may be perpetrators, victims, or observers of violence (or any combination of the 3 roles) with varying severity of impact on the individual, family, and larger community. Multiple factors have been identified that may increase the risk of a youth engaging in violence, including poverty, war, substance abuse, mental health disorders, and poor family functioning.

EPIDEMIOLOGY
In 2010, homicide in the United States was the second leading cause of death for 10–24 yr olds totaling 4,828 deaths, which were largely males (86%) killed by a handgun (82.8%). The 2010 homicide rate for teens ages 12–17 yr was 3.0/100,000 youth down 65% from 8.4/100,000 youth in 1993. The WHO reports that other than the United States, where the youth and young adult homicide rate was 11 per 100,000, most countries with homicide rates above 10 per 100,000 are developing nations or countries with rapid socioeconomic changes. The prevalence of behaviors that contribute to violence has not decreased from 1999 to 2011; fighting and weapon carrying remain prevalent among U.S. youth. The rate of homicide by handgun is considerably higher than homicide by other weapon type, suggesting that access to firearms may play a major role in youth injuries and deaths (Fig. 113-1). Gang-related homicides among youths in 5 major U.S. cities are more likely to involve young (15–19 yr) males (80%), racial/ethnic minority (73%), and a firearm (90%) in comparison to nongang homicides. In addition, gang homicides are more likely to occur in public places, in the afternoon/evening hours, and rarely are related to drug trade/use. One quarter of the gang homicides are classified as drive-by shootings.

Violence at schools in the United States remains a significant problem with 32.8% of students reported being in a fight on school property 1 or more times in the preceding 12 mo. The 2011 Youth Risk Behavior Surveillance System reported 16.6% youths overall carried a weapon such as a gun, knife, or club in the last 30 days; 5.4% carried the weapon to school; and 7.4% reported being threatened or injured with a type of weapon on school property. Males are more likely than females to carry a gun or weapon and therefore may need increased monitoring at home and at school. Weapon carrying is highest among white males overall, which may begin as early as 9th grade. Student reports of physical fighting at schools have nearly tripled in the last 4 yr. These violence-related behaviors at school affect the students’ perception of safety. More than 5% of students did not go to school on 1 or more days in the preceding 30 days because they felt it was unsafe at school.

Dating violence (or intimate partner violence) occurs between people in a close relationship and can be physical (punching, kicking, hitting or shoving), emotional (shaming, bullying, controlling or stalking), or sexual (forcing one's partner to engage in a sexual act when he/she does not consent to it). Incidents of dating violence often occur during the adolescent years with 22.4% of women and 15% of men experiencing some type of partner violence between the ages of 11 and 17 yr. The highest prevalence rates are seen in African-American students and older students. It may start with teasing, name calling, or shaming. It may progress electronically, such as frequent calls, texting, or posting sexual pictures of a partner on social media. Risk factors for being a victim of dating violence includes those who use alcohol, believe dating violence is acceptable, have lack of parental supervision, or have a friend who is in a violent relationship. Most teens do not report the behaviors because they fear retaliation from the partner. Teens who are victims of dating violence are more likely to experience decreased school performance, use drugs and alcohol, have an eating disorder, or experience depression. School-based prevention programs that address attitudes and behaviors linked with dating violence, such as Safe Dates, offer training experiences to change social norms amongst teens. School-based prevention programs initiated at the elementary school level have been found to decrease violent behaviors in students. Increased surveillance of students is warranted both on and around school property to improve student safety.

ETIOLOGY
The WHO places youth violence in a model within the context of 3 larger types of violence: self-inflicted, interpersonal, and collective. **Interpersonal violence** is subdivided into violence largely between family members or partners and includes child abuse. **Community violence** occurs between individuals who are unrelated. **Collective violence** incorporates violence by people who are members of an identified group against another group of individuals with social, political, or economic motivation. The types of violence in this model have behavioral links, in that child abuse victims are more likely to experience violent and aggressive interpersonal behavior as adolescents and adults. Overlapping risk factors exist for the types of violence, such as firearm availability, alcohol use, and socioeconomic inequalities. The benefit to identifying common risk factors for the types of violence lies in the potential for intervening with prevention efforts and gaining positive outcomes for more than one type of violent behavior. The model further acknowledges 4 categories that explore the potential nature of violence as involving physical, sexual, or psychological force, or deprivation.

There may be 2 types of antisocial youth: 1 that is life-course persistent and 1 that is life-course limited. **Adolescent-limited offenders** have no childhood aberrant behaviors and are more likely to commit status offenses such as vandalism, running away, and other behaviors symbolic of their struggle for autonomy from parents. **Life course–persistent offenders** exhibit aberrant behavior in childhood, such as problems with temperament, behavioral development, and cognition; as adolescents they participate in more victim-oriented crimes. The public health model emphasizes the environment and other external influences. A third theoretical model examines violent behaviors across the spectrum occurring within and outside the family and is referred to as the **cycle of violence**. This hypothesis proposes that precursors such as child abuse and neglect, a child witnessing violence, adolescent sexual and physical abuse, and adolescent exposure to violence and
violent assaults predispose youths to outcomes of violent behavior, violent crime, delinquency, violent assaults, suicide, or premature death. An additional common paradigm for high-risk violence behavior poses a balance of risk and protective factors at the individual, family, and community levels.

**CLINICAL MANIFESTATIONS**

There are several identified risk factors for youth violence, including poverty, association with delinquent peers, poor school performance/low education status, disconnection from adult role models or mentors, prior history of violence or victimization, poor family functioning, childhood abuse, substance abuse, and certain mental health disorders. The most common disorders associated with aggressive behavior in adolescents are mental retardation, learning disabilities, moderately severe language disorders, and mental disorders such as attention-deficit/hyperactivity and mood disturbances. The link between severe mental illness and violent behaviors is strongest for those with cooccurring alcohol or substance abuse or dependence.

Inability to master prosocial skills such as the establishment and maintenance of positive family and peer relations and poor resolution of conflict may put adolescents with these disorders at higher risk of physical violence and other risky behaviors. **Conduct disorder** and **oppositional defiant disorder** are specific psychiatric diagnoses whose definitions are associated with violent behavior (Table 113-1). They occur comorbidly with other disorders, such as attention-deficit/hyperactivity disorder (see Chapter 30), and increase an adolescent's vulnerability for juvenile delinquency, substance use or abuse, sexual promiscuity, adult criminal behavior, incarceration, and antisocial personality disorder. Other cooccurring risk factors for youth violence include use of anabolic steroids, gang tattoos, belief in one's premature death, preteen alcohol use, and placement in a juvenile detention center.

**DIAGNOSIS**

The assessment of an adolescent at risk or with a history of violent behavior or victimization should be a part of the health maintenance visit of all adolescents. The answers to questions about recent history of involvement in a physical fight, carrying a weapon, or firearms in the household, as well as concerns that the adolescent may have about his or her personal safety may suggest a problem requiring a more in-depth evaluation. The FISTS mnemonic provides guidance for structuring the assessment (Table 113-2). The additional factors of physical or sexual abuse, serious problems at school, poor school performance and attendance, multiple incidents of trauma, substance use, and symptoms associated with mental disorders are indications for evaluation by a mental health professional. In a situation of acute trauma, assault victims are not always forthcoming about the circumstances of their injuries for fear of retaliation or police involvement. Stabilization of the injury or the gathering of forensic evidence in sexual assault is the treatment priority; however, once this is achieved, addressing a more comprehensive set of issues surrounding the assault is appropriate.

**TREATMENT**

In the instance of acute injury secondary to violent assault, the treatment plan should follow standards established by the American Academy of Pediatrics model protocol, which includes, but is not limited to, the stabilization of the injury, evaluation and treatment of the injury, evaluation of the assault circumstance, psychologic evaluation and support, social service evaluation of the circumstance surrounding the assault, and a treatment plan on discharge that is designed to protect the adolescent from subsequent injury episodes and minimize the development of psychologic disability. Victims as well as witnesses of violence are at risk for posttraumatic stress disorder, and future aggressive and/or violent behavior.

Multiple treatment modalities are used simultaneously in managing adolescents with persistent violent and aggressive behavior and range from cognitive-behavioral therapy involving the individual and family to specific family interventions (parent management training, multisystemic treatment) and pharmacotherapy. Treatment of existing comorbid conditions, such as attention-deficit/hyperactivity disorder, depression, and substance abuse, appears to reduce aggressive behavior.

**PREVENTION**

The WHO recognizes a multifactorial approach to prevention: individual approaches, relationship approaches, community approaches, and societal approaches (Table 113-3). **Individual approaches** concentrate on changing attitudes and behaviors to avoid aggressive and

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**Table 113-2 FISTS Mnemonic to Assess an Adolescent’s Risk of Violence**

| F: Fighting | (How many fights were you in last year? What was the last?) |
| I: Injuries | (Have you ever been injured? Have you ever injured someone else?) |
| S: Sex | (Has your partner hit you? Have you hit your partner? Have you ever been forced to have sex?) |
| T: Threats | (Has someone with a weapon threatened you? What happened? Has anything changed to make you feel safer?) |
| S: Self-defense | (What do you do if someone tries to pick a fight? Have you carried a weapon in self-defense?) |


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**Table 113-1 Oppositional Defiant Disorder, Conduct Disorder, and Juvenile Delinquency**

<table>
<thead>
<tr>
<th>Oppositional Defiant Disorder</th>
<th>Conduct Disorder</th>
<th>Juvenile Delinquency</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PSYCHIATRIC DISORDER LABELS</strong></td>
<td><strong>Legal Label Juvenile Delinquency</strong></td>
<td></td>
</tr>
<tr>
<td>Recurrent pattern of negativistic, defiant, disobedient, and hostile behavior toward authority figures that has a significant adverse effect on functioning (e.g., social, academic, occupational)</td>
<td>Repetitive and persistent pattern of behavior that violates the basic rights of others or major age-appropriate societal norms or rules</td>
<td>Offenses that are illegal because of age; illegal acts</td>
</tr>
<tr>
<td>Examples: losing temper; arguing with adults; defying or refusing to comply with request or rules of adults; annoying behavior; blaming others; and being irritable, spiteful, resentful</td>
<td>Examples: physical fighting, deceitfulness, stealing, destruction of property, threatening or causing physical harm to people or animals, driving without a license, prostitution, rape (even if not adjudicated in the legal system)</td>
<td>Examples: single or multiple instances of being arrested or adjudicated for any of the following: stealing, destruction of property, threatening or causing physical harm to people or animals, driving without a license, prostitution, rape</td>
</tr>
</tbody>
</table>

Diagnosed by a mental health clinician | Diagnosed by a mental health practitioner | Adjudicated in the legal system |

violent behavior as well as teaching coping strategies and nonviolent conflict resolution for all children as well as youths who have already displayed some violent tendencies. **Relationship approaches** focus more on victims, families, and peer relationships, especially those with the potential to trigger aggressive or violent responses. Solutions include improving skills in coping or problem solving in recent perceived crises, interpersonal conflicts, and close relationships. Family-based programs provide training for parents in areas of effective communication, child development, and solving problems in nonviolent methods. **Community-based approaches** raise public awareness in an effort to stimulate action by community members to reduce violence and protect vulnerable community members. Universal school-based violence prevention programs have been found to be effective in reducing violent and aggressive behaviors. Interventions beginning as early as preschool have been found to have positive outcomes years later. **Societal approaches** include broader advocacy and legislative actions, as well as changing the cultural norm toward violent behaviors. A specific prevention strategy can incorporate several approaches, such as the handgun/firearm prevention recommendations that include gun-lock safety, public education, and legislative advocacy. Other efforts are directed toward establishing a national database to track and define the problem of youth violence. The National Violent Death Reporting System collects and analyzes violent death data from 18 states and aims to improve surveillance of current trends, to share information state to state, to build partnerships among state and community organizations, and to develop and implement prevention and intervention programs. Ultimately, the National Violent Death Reporting System will be expanded to include all 50 states. The CDC characterizes specific successful programs and summarizes program content on its website (www.cdc.gov).

**Bibliography is available at Expert Consult.**
Bibliography


Elbogen EB, Johnson SC: The intricate link between violence and mental disorder: results from the national epidemiologic survey on alcohol and related conditions, Arch Gen Psychiatry 66:152–161, 2009.


Although varying in percentages by nation and culture, a substantial proportion of adolescents will engage in use of a wide range of substances such as alcohol, tobacco, or marijuana. Their reactions to and the consequences of these exposures are influenced by a complex interaction between biologic and psychosocial development, environmental messages, and societal attitudes. Occasional or situational use of certain substances, such as alcohol in the United States, may be viewed as normative given the proportion of youths who report some experience with these substances. Others view the potential for adverse outcomes even with occasional use in immature adolescents, such as motor vehicle crashes and other injuries, sufficient justification to consider any drug use in younger adolescents a considerable risk.

Individuals who initiate drug use at an early age are at a greater risk for becoming addicted than those who try drugs in early adulthood. Drug use in younger, less-experienced adolescents can act as a substitute for developing age-appropriate coping strategies and enhance vulnerability to poor decision making. The first use of the most commonly used drugs occurs before age 18 yr, with 88% of people reporting age of first alcohol use at <21 yr old, the legal drinking age in the United States. Inhalants have been identified as a popular first drug for youth in grade 8. When drug use begins to negatively alter functioning in adolescents at school and at home, and risk-taking behavior is seen, intervention is warranted. Serious drug use is not an isolated phenomenon. It occurs across every segment of the population and is 1 of the most challenging public health problems facing society. The challenge to the clinician is to identify youths at risk for substance abuse and offer early intervention. The challenge to the community and society is to create norms that decrease the likelihood of adverse health outcomes for adolescents and promote and facilitate opportunities for adolescents to choose healthier and safer options. Recognizing those drugs with the greatest harm, and at times focusing on harm reduction with or without abstinence, is an important modern approach to adolescent substance abuse (Figs. 114-1 and 114-2).

ETIOLOGY
Substance abuse is biopsychosocially determined (Fig. 114-3). Biologic factors, including genetic predisposition, are established contributors. Behaviors such as rebelliousness, poor school performance, delinquency, and criminal activity and personality traits such as low self-esteem, anxiety, and lack of self-control are frequently associated with or predate the onset of drug use. Psychiatric disorders are often comorbidly associated with adolescent substance use. Conduct disorders and antisocial personality disorders are the most common diagnoses coexisting with substance abuse, particularly in males. Teens with depression (see Chapter 26), attention deficit disorder (see Chapter 33), and eating disorders (see Chapter 28) have high rates of substance use. The determinants of adolescent substance use and abuse are explained using a number of theoretical models, with factors at the individual level, the level of significant relationships with others, and the level of the setting or environment. Models include a balance of risk and protective or coping factors contributing to individual differences among adolescents with similar risk factors who escape adverse outcomes.
Risk factors for adolescent drug use may differ from those associated with adolescent drug abuse. Adolescent use is more commonly related to social and peer factors, whereas abuse is more often a function of psychological and biologic factors. The likelihood that an otherwise normal adolescent would experiment with drugs may be dependent on the availability of the drug to the adolescent, the perceived positive or otherwise functional value to the adolescent, the perceived risk associated with use, and the presence or absence of restraints as determined by the adolescent’s cultural or other important value systems. An abusing adolescent may have genetic or biologic factors coexisting with dependence on a particular drug for coping with day-to-day activities.

Specific historical questions can assist in determining the severity of the drug problem through a rating system (Table 114-1). The type of drug used (marijuana vs. heroin), the circumstances of use (alone or with others), and the setting of drug use (in group vs. alone) can provide important clues to the severity of the problem. The presence of accidents or the use of drugs before driving can also indicate the seriousness of the problem.

Table 114-1  Assessing the Seriousness of Adolescent Drug Abuse

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>0</th>
<th>+1</th>
<th>+2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>&gt;15</td>
<td>&lt;15</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td>Male</td>
<td>Female</td>
<td></td>
</tr>
<tr>
<td>Family history of drug abuse</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Setting of drug use</td>
<td>In group</td>
<td>Alone</td>
<td></td>
</tr>
<tr>
<td>Affect before drug use</td>
<td>Happy</td>
<td>Always poor</td>
<td>Sad</td>
</tr>
<tr>
<td>School performance</td>
<td>Good, improving</td>
<td>Recently poor</td>
<td></td>
</tr>
<tr>
<td>Use before driving</td>
<td>None</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>History of accidents</td>
<td>None</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Time of week</td>
<td>Weekend</td>
<td>Weekdays</td>
<td></td>
</tr>
<tr>
<td>Time of day</td>
<td>After school</td>
<td>Before or during school</td>
<td></td>
</tr>
<tr>
<td>Type of drug</td>
<td>Marijuana, beer, wine</td>
<td>Hallucinogens, amphetamines</td>
<td>Whiskey, opiates, cocaine, barbiturates</td>
</tr>
</tbody>
</table>

Total score: 0-3, less worrisome; 3-8, serious; 8-18, very serious.
in a group setting), the frequency and timing of use (daily before school vs. rarely on a weekend), the premorbid mental health status (depressed vs. happy), as well as the teenager’s general functional status should all be considered in evaluating any youngster found to be abusing a drug. The stage of drug use/abuse should also be considered (Table 114-2). A teen may spend months or years in the experimentation phase trying a variety of illicit substances, including the most common drugs, cigarettes, alcohol, and marijuana. Often it is not until regular use of drugs resulting in negative consequences (problem use) that the teen is identified as having a problem, either by parents, teachers, or a physician. Certain protective factors play a part in buffering the risk factors as well as anticipating the long-term outcome of experimentation. Having emotionally supportive parents with open communication styles, involvement in organized school activities, having mentors or role models outside of the home, and recognition of the importance of academic achievement are examples of the important protective factors.

**EPIDEMIOLOGY**

Alcohol, cigarettes, and marijuana are the most commonly reported substances used among U.S. teens (Table 114-3). The prevalence of substance use and associated risky behaviors vary by age, gender, race/ethnicity, and other sociodemographic factors. Younger teenagers tend to report less use of drugs than do older teenagers, with the exception of inhalants (in 2012, 6.0% in 8th grade, 5.1% in 10th grade, 4.7% in 12th grade). Males have higher rates of both licit and illicit drug use than females, with greatest differences seen in their higher rates of frequent use of smokeless tobacco, cigars, and anabolic steroids. In school surveys, drug use rates of Hispanics are between whites and African-Americans, with the exception of 12th grade Hispanics reporting highest rates of cocaine use. African-Americans report less use of inhalants (in 2012, 6.0% in 8th grade, 5.1% in 10th grade, 4.7% in 12th grade) than in the previous 3 yr (Table 114-4). In 2012, 14.8% of high school seniors had used a prescription drug or an OTC medicine for nonmedical reasons in the past year. The most commonly used substances were Adderall (7.6%), Vicodin (7.5%), OTC cough medicine (5.6%),

![Figure 114-3 Protection and risk model for distal and proximal determinants of risky substance use and related harms. (From Toubourou JW, Stockwell T, Neighbors C, et al: Interventions to reduce harm associated with adolescent substance use, Lancet 369:1391–1401, 2007.)](image)

### Table 114-2

<table>
<thead>
<tr>
<th>STAGE</th>
<th>DESCRIPTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Potential for abuse • Decreased impulse control • Need for immediate gratification • Available drugs, alcohol, inhalants • Need for peer acceptance</td>
</tr>
<tr>
<td>2</td>
<td>Experimentation: learning the euphoria • Use of inhalants, tobacco, marijuana, and alcohol with friends • Few, if any, consequences • Use may increase to weekends regularly • Little change in behavior</td>
</tr>
<tr>
<td>3</td>
<td>Regular use: seeking the euphoria • Use of other drugs, e.g., stimulants, LSD, sedatives • Behavioral changes and some consequences • Increased frequency of use; use alone • Buying or stealing drugs</td>
</tr>
<tr>
<td>4</td>
<td>Regular use: preoccupation with the “high” • Daily use of drugs • Loss of control • Multiple consequences and risk taking • Estrangement from family and “straight” friends</td>
</tr>
<tr>
<td>5</td>
<td>Burnout: use of drugs to feel normal • Polysubstance use/cross-addiction • Guilt, withdrawal, shame, remorse, depression • Physical and mental deterioration • Increased risk taking, self-destructive, suicidal</td>
</tr>
</tbody>
</table>

### Table 114-3

<table>
<thead>
<tr>
<th>8TH GRADERS (%)</th>
<th>10TH GRADERS (%)</th>
<th>12TH GRADERS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALCOHOL (ANY USE)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2010 13.8</td>
<td>2012 11.0</td>
<td>2010 4.1</td>
</tr>
<tr>
<td>CIGARETTES (ANY USE)</td>
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<td></td>
</tr>
<tr>
<td>2005 7.1</td>
<td>2008 4.9</td>
<td>2010 4.1</td>
</tr>
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<td>SMOKELESS TOBACCO</td>
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<td>2012 2.8</td>
<td>2010 4.1</td>
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<td></td>
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<td>2012 6.5</td>
<td>2010 8.0</td>
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<td>INHALANTS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2010 3.6</td>
<td>2012 2.7</td>
<td>2010 3.6</td>
</tr>
<tr>
<td>AMPHETAMINES</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2010 0.5</td>
<td>2012 0.5</td>
<td>2010 0.5</td>
</tr>
</tbody>
</table>


Prescription drug abuse, or nonmedical use of a prescription drug or an over-the-counter (OTC) medicine has gained popularity among teens in the last 3 yr (Table 114-4). In 2012, 14.8% of high school seniors had used a prescription drug or an OTC medicine for nonmedical reasons in the past year. The most commonly used substances were Adderall (7.6%), Vicodin (7.5%), OTC cough medicine (5.6%),
# Commonly Abused Prescription Drugs

Visit NIDA at www.drugabuse.gov

<table>
<thead>
<tr>
<th>Substances: Category and Name</th>
<th>Examples of Commercial and Street Names</th>
<th>DEA Schedule*/How Administered</th>
<th>Intoxication Effects/Health Risks</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Depressants</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Barbiturates</td>
<td>Amytal, Nembutal, Seconal, Phenobarbital bars, reds, red birds, phennies, toodies, yellows, yellow jackets</td>
<td>II, III, IV, injected, swallowed</td>
<td>SEDATION/STUPOR/DROWSINESS, REDUCED ANXIETY, FEELINGS OF WELL-BEING, LOWERED INHIBITIONS, SLURRED SPEECH, POOR CONCENTRATION, CONFUSION, DIZZINESS, IMPAIRED COORDINATION AND MENTAL FUNCTION, SLOWED OR ARRESTED BREATHING, LOWERED BLOOD PRESSURE, TOLERANCE, WITHDRAWAL, ADDICTION; INCREASED RISK OF RESPIRATORY DISTRESS AND DEATH WHEN COMBINED WITH ALCOHOL</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>Ativan, Halcion, Librium, Valium, Xanax, Klonopin candy downers, sleeping pills, tranquil</td>
<td>IV, swallowed</td>
<td>FOR BARIUS</td>
</tr>
<tr>
<td><strong>Sleep Medications</strong></td>
<td>Ambien (zolpidem), Sonata (zaleplon), Lunesta (eszopiclone)</td>
<td>IV, swallowed</td>
<td></td>
</tr>
<tr>
<td><strong>Opioids and Morphine Derivatives</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Codeine</td>
<td>Empirin with Codeine, Finton with Codeine, Robitussin A-C, Tylenol with Codeine: Captain Cody, Cody, schoolboy (with glutethimide: doors &amp; founs, loads, pancailes and oryup)</td>
<td>II, III, IV, injected, swallowed</td>
<td>PAIN RELIEF, EUPHORIA, DROWSINESS, SEDATION, WEAKNESS, DIZZINESS, NAUSEA, IMPAIRED COORDINATION, CONFUSION, DRY MOUTH, FISHING SWELLING, DUMMY SKIN, CONSTIPATION/STIMULATED BOWEL MOVEMENT, SLOWED OR ARRESTED BREATHING, LOWERED OR ARRESTED BLOOD PRESSURE, TOLERANCE, ADDICTION, UNCONSCIOUSNESS, COMA, DEATH; RISK OF DEATH INCREASED WHEN COMBINED WITH ALCOHOL OR OTHER CNS DEPRESSANTS</td>
</tr>
<tr>
<td>Morphine</td>
<td>Roxanol, Duramorph: M, Miss Emma, monkey, white stuff</td>
<td>II, IV, injected, swallowed, smoked</td>
<td></td>
</tr>
<tr>
<td>Methadone</td>
<td>Methadose, Dilaphine fuziers, amidone, (with MDMA: chocolate chip cookies)</td>
<td>IV, swallowed, injected</td>
<td>FOR FENTANYL—90–100 TIMES MORE POTENT ANALGESIC THAN MORPHINE</td>
</tr>
<tr>
<td>Fentanyl and analogs</td>
<td>Actiq, Duragesic, Sublimaze: Apache, China girl, dance fever, friend, goodfella, jackpot, murder 8, TNT, Tango and Cash</td>
<td>IV, injected, smoked, snorted</td>
<td>FOR HEROIN—MUSCLE RELAXATION/TWICE AS POTENT ANALGESIC AS MORPHINE; HIGH ABUSE POTENTIAL</td>
</tr>
<tr>
<td><strong>Other Opioid Pain Relievers</strong>:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxycodeine HCL</td>
<td>Tylox, Oxycontin, Percodan, Percocet: Dry O.C., oxycotin, oxeyt, hillbilly heroin, perco</td>
<td>II, IV, swallowed, snorted, injected, suppositories</td>
<td>FOR CODEINE—LESS ANALGESIA, SEDATION, AND RESPIRATORY DEPRESSION THAN MORPHINE</td>
</tr>
<tr>
<td>Hydrocodone bitartrate Hydromorphine</td>
<td>Vicodin, Lorat, Loric: vike, Watson-3387</td>
<td>II, IV, chewed, swallowed, snorted, injected, suppositories</td>
<td></td>
</tr>
<tr>
<td>Oxymorphone</td>
<td>Dilaudid: jiquer, smack, G, footballs, dillies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meperidine</td>
<td>Opana, Numorphan, Numorphan bicuits, blue heaven, blues, Mrs. O, octagons, stop sigags, O Bomb</td>
<td>II, IV, chewed, swallowed, snorted, injected, suppositories</td>
<td></td>
</tr>
<tr>
<td>Propoxyphene</td>
<td>Demeral, meperidine hydrochloride: demmies, pain killer</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Stimulants</strong></td>
<td>Biphetamine, Dexedrine, Adderal: brannies, black beauties, crosses, hearts, LA hurrnound, speed, truck drivers, uppers</td>
<td>IV, injected, swallowed, smoked, snorted</td>
<td>FEELINGS OF EXALTATION, INCREASED ENERGY, MENTAL ALERTNESS/INCREASED HEART RATE, BLOOD PRESSURE, AND METABOLISM, REDUCED APPETITE, WEIGHT LOSS, NERVOSITY, INSOMNIA, SEIZURES, HEART ATTACK, STROKE</td>
</tr>
<tr>
<td>Amphetamines</td>
<td>Concerta, Ritalin: JF, MPH, R-ball, Skippy, the smart drug, vitamin R</td>
<td>IV, injected, swallowed, snorted</td>
<td>FOR AMPHETAMINES—RAPID BREATHING, TREMOR, LOSS OF COORDINATION, IRRITABILITY, ANXIETY, RESTLESSNESS, SEDATION, PANIC, PARAVERA, HALLUCINATIONS, IMPULSIVE BEHAVIOR, AGGRESSIVENESS, TOLERANCE, ADDICTION</td>
</tr>
<tr>
<td>Methylphenidate</td>
<td></td>
<td>IV, injected, swallowed, snorted</td>
<td>FOR METHYLPHENIDATE—INCREASE OR DECREASE IN BLOOD PRESSURE, DIZZINESS, LOSS OF APPETITE, WEIGHT LOSS</td>
</tr>
<tr>
<td><strong>Other Compounds</strong></td>
<td>Dextromethorphan (DXM)</td>
<td>not scheduled/swallowed</td>
<td>EUPHORIA, STUNNED SPEECH/INCREASED HEART RATE AND BLOOD PRESSURE, DIZZINESS, NAUSEA, VOMITING, CONFUSION, PARAVERA, DISTORTED VISUAL PERCEPTIONS, IMPAIRED MOTOR FUNCTION</td>
</tr>
</tbody>
</table>

* Schedule I and II drugs have a high potential for abuse. They require greater storage security and have a quota on manufacturing, among other restrictions. Schedule I drugs are available for research only and have no approved medical use. Schedule II drugs are available only by prescription and require a new prescription for each refill. Schedule III and IV drugs are available by prescription, may have five refills in 6 months, and may be ordered orally. Most Schedule V drugs are available over the counter.

** Taking drugs by injection can increase the risk of infection through needle contamination with staphylococci, HIV, hepatitis, and other organisms. Injection is a more common practice for opioids, but risks apply to any medication taken by injection.

transmitters. Treatment for depression may involve the use of antidepressants, psychotherapy, or a combination of the two.

Abstinence from substance use is the cornerstone of treatment for addiction. It involves the abstinence from all substances, including legal substances such as alcohol and nicotine. Detoxification may be necessary to remove the drug from the body. Medications are often used to help manage withdrawal symptoms and cravings.

Behavioral therapies, such as counseling and support groups, are also an important part of treatment. These therapies help individuals learn skills to manage their thoughts and behaviors related to substance use. They also help individuals develop coping strategies to deal with triggers and cravings.

Recovery is a lifelong process. It involves maintaining sobriety and learning to cope with life’s challenges. It is important for individuals to have a support system, including family, friends, and other individuals who are also in recovery.

In conclusion, addiction is a complex disorder that requires a multidisciplinary approach to treatment. Treatment should be individualized and tailored to the specific needs of the individual. It is important for individuals to seek help and support as they work towards recovery.

References:

CLINICAL MANIFESTATIONS

Although manifestations vary by the specific substance of use, adolescents who use drugs often present in an office setting with no obvious physical findings. Drug use is more frequently detected in adolescents who experience trauma such as motor vehicle crashes, bicycle injuries, or violence. Eliciting appropriate historical information regarding substance use, followed by blood alcohol and urine drug screens, is recommended in emergency settings; while waning in popularity, the illicit substances known as “club drugs” still need to be considered in the differential diagnosis of a teen with an altered sensorium (Table 114-5).

An adolescent presenting to an emergency setting with an impaired sensorium should be evaluated for substance use as a part of the differential diagnosis (Table 114-6). Screening for substance use is recommended for patients with psychiatric and behavioral diagnoses. Other clinical manifestations of substance use are associated with the route of use; intravenous drug use is associated with venous “tracks” and needle marks, while nasal mucosal injuries are associated with nasal insufflation of drugs. Seizures can be a direct effect of drugs such as cocaine and amphetamines or an effect of drug withdrawal in the case of barbiturates or tranquilizers.

SCREENING FOR SUBSTANCE ABUSE DISORDERS

In a primary care setting the annual health maintenance examination provides an opportunity for identifying adolescents with substance use or abuse issues. The direct questions as well as the assessment of school performance, family relationships, and peer activities may necessitate a more in-depth interview if there are suggestions of difficulties in those areas. Additionally, there are several self-report screening questionnaires available with varying degrees of standardization, length, and reliability. The CRAFFT mnemonic is specifically designed to screen for adolescents’ use in the primary setting (Table 114-7). Privacy and confidentiality need to be considered when asking the teen about specifics of their substance experimentation or use. Interviewing the parents can provide additional perspective on early warning signs that go unnoticed or disregarded by the teen. Examples of early warning signs of teen substance use are change in mood, appetite, or sleep pattern; decreased interest in school or school performance; loss of weight; secretive behavior about social plans; or valuables such as money or jewelry missing from the home. The use of urine drug screening is recommended when select circumstances are present: (1) psychiatric symptoms to rule out comorbidity or dual diagnoses, (2) significant changes in school performance or other daily behaviors, (3) frequently occurring accidents, (4) frequently occurring episodes of respiratory problems, (5) evaluation of serious motor vehicular or other injuries, and (6) as a monitoring procedure for a recovery program. Table 114-8 demonstrates the types of tests commonly used for detection by substance, along with the approximate retention time between the use and the identification of the substance in the urine. Most initial screening uses an immunoassay method such as the enzyme-multiplied immunoassay technique followed by a confirmatory test using highly sensitive, highly specific gas chromatography–mass spectrometry. The substances that can cause false-positive results should be considered, especially when there is a discrepancy between the physical findings and the urine drug screen result. In 2007 the American Academy of Pediatrics released guidelines that strongly discourage home-based or school-based testing.

DIAGNOSIS

The Diagnostic and Statistical Manual of Mental Disorders (DSM-5) no longer identifies substance use disorders as those of abuse or of dependence as was done in previous editions. A substance use disorder is defined by a cluster of cognitive, behavioral, and physiologic symptoms that indicate that an adolescent is using a substance even though there is evidence that the substance is harming the adolescent. Even after detoxification, a substance abuse disorder may leave persisting changes in brain circuits with resulting behavioral changes. There are 11 criteria that describe a pathologic pattern of behaviors related to use of the substance, falling into 4 categories. The first category includes the criterion of impaired control, social impairment, risky use, and pharmacologic criteria. These criteria describe an individual taking increasing amounts of the substance and one who expresses a persistent desire to cut down substance use with unsuccessful efforts and the increased time, effort, and other resources the teen may be using to obtain the substance. The individual may spend a great deal of time obtaining the substance, using the substance, or recovering from its effects and expresses an intense desire for the drug that is most likely to occur in settings in which the drug had been available, such as a specific type of social situation. The second criterion of criterion (5-7) reflects social impairment, including the inability to perform as expected in school, home or at a job, increasing social problems and withdrawing from the individual’s family. The third criterion addresses increased risk-involvement associated with use of the substance, and the final criterion includes 2 criteria addressing pharmacologic responses (tolerance and/or withdrawal). The total number of criterion present is associated with a determination of a mild, moderate, or severe disorder.

These criteria may have limitations in use with adolescents because of differing patterns of use, developmental implications, and other age-related consequences. Adolescents who meet diagnostic criteria should be referred to a program for substance use disorder treatment unless the primary care physician has additional training in addiction medicine.

COMPLICATIONS

Substance use in adolescence is associated with comorbidities and acts of juvenile delinquency. Youth may engage in other high-risk behaviors such as robbery, burglary, drug dealing, or prostitution for the purpose of acquiring the money necessary to buy drugs or alcohol. Regular use of any drug eventually diminishes judgment and is associated with unprotected sexual activity with its consequences of pregnancy and sexually transmitted infections, including HIV, as well as physical violence and trauma. Drug and alcohol use is closely associated with trauma in the adolescent population. Several studies of adolescent trauma victims have identified cannabinoids and cocaine in blood and urine samples in significant proportions (40%), in addition to the more common identification of alcohol. Any use of injected substances involves the risk of hepatitides B and C viruses as well as HIV (see Chapter 276).

TREATMENT

Adolescent drug abuse is a complex condition requiring a multidisciplinary approach that attends to the needs of the individual, not just drug use. Fundamental principles for treatment include accessibility to treatment; utilizing a multidisciplinary approach; employing individual or group counseling; offering mental health services; monitoring of drug use while in treatment; and understanding that recovery from drug abuse/addiction may involve multiple relapses. For most patients,
### Table 114-5: Common Names and Salient Features of Club Drugs Used Recreationally

<table>
<thead>
<tr>
<th>MDMA</th>
<th>EPHEDRINE</th>
<th>γ-HYDROXYBUTYRATE</th>
<th>γ-BUTOYROLACTONE</th>
<th>1,4-BUTANEDIOL</th>
<th>KETAMINE</th>
<th>FLUNITRAZEPAM</th>
<th>NITRITES</th>
<th>BATH SALTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common name</td>
<td>Ecstasy, XTC, E, X, Adam, hug drug, Molly</td>
<td>Herbal Ecstasy, herbal fuel, zest</td>
<td>Liquid Ecstasy, goop soap, Georgia homeboy, grievous bodily harm</td>
<td>Blue nitro, longevity, revivariant, GH revitalizer, gamma G, nitro, insom-X, remforce, firewater, invigorate</td>
<td>Thunder nectar, serenity, pine needle extract, zen, enleven, revitalize plus, lemon drops</td>
<td>K, special K, vitamin K, ket, kat</td>
<td>Roofies, circles, rophies, rib, roche, roaches, forget pill, R2, Mexican valium, roopies ruffies</td>
<td>Poppers, ram, rock hard, thrust, TNT</td>
</tr>
<tr>
<td>Duration of action</td>
<td>4-6 hr</td>
<td>4-6 hr</td>
<td>1.5-3.5 hr</td>
<td>1.5-3.5 hr</td>
<td>1-3 hr</td>
<td>6-12 hr</td>
<td>Minutes</td>
<td>2-8 hr</td>
</tr>
<tr>
<td>Elimination half-life</td>
<td>8-9 hr</td>
<td>5-7 hr</td>
<td>27 min</td>
<td>ND</td>
<td>ND</td>
<td>2 hr</td>
<td>9-25 hr</td>
<td>ND</td>
</tr>
<tr>
<td>Peak plasma concentration</td>
<td>1-3 hr</td>
<td>2-3 hr</td>
<td>20-60 min*</td>
<td>15-45 min</td>
<td>15-45 min</td>
<td>20 min</td>
<td>1 hr</td>
<td>Seconds</td>
</tr>
<tr>
<td>Physical dependence</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Antidote</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>DEA schedule</td>
<td>I</td>
<td>None</td>
<td>III</td>
<td>None</td>
<td>None</td>
<td>III</td>
<td>IV</td>
<td>None</td>
</tr>
<tr>
<td>Detection with routine drug screen</td>
<td>Yes†</td>
<td>Yes†</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No‡</td>
<td>No‡</td>
<td>No</td>
</tr>
<tr>
<td>Best detection method (time frame)</td>
<td>GC/MS (4 hr-2 days)</td>
<td>GC/MS (4 hr-2 days)</td>
<td>GC/MS (1-12 hr)</td>
<td>GC/MS (1-12 hr)</td>
<td>GC/MS (1-12 hr)</td>
<td>GC/MS (1-12 hr)</td>
<td>GC/MS (1-12 hr)</td>
<td>GC/MS (1-12 hr)</td>
</tr>
</tbody>
</table>

*Depends on dose.
†Concentrations that are sufficiently high can give positive results for amphetamine because of cross-reactions.
‡Flunitrazepam can give positive results for benzodiazepines; ketamine can give positive results for phencyclidine.

DEA, U.S. Drug Enforcement Agency; currently reviewing possibility of flunitrazepam being placed into schedule of the U.S. Controlled Substance Act; GC/MS, gas chromatography–mass spectroscopy. Duration, half-life, and peak plasma are probably different after high or sequential doses because of nonlinear kinetics; ND, not determined in human beings.

### Table 114-6: The Most Common Toxic Syndromes

<table>
<thead>
<tr>
<th>SYNDROME</th>
<th>Common signs</th>
<th>Common causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANTICHOLINERGIC</td>
<td>Delirium with mumbling speech, tachycardia, dry, flushed skin, dilated pupils, myoclonus, slightly elevated temperature, urinary retention, and decreased bowel sounds. Seizures and dysrhythmias may occur in severe cases.</td>
<td>Antihistamines, antiparkinsonian medication, atropine, scopolamine, amantadine, antipsychotic agents, antidepressant agents, antispasmodic agents, mydriatic agents, skeletal muscle relaxants, and many plants (notably jimson weed and Amanita muscaria).</td>
</tr>
<tr>
<td>SYMPATHOMIMETIC</td>
<td>Delusions, paranoia, tachycardia (or bradycardia if the drug is a pure α-adrenergic agonist), hypertension, hyperpyrexia, diaphoresis, piloerection, mydriasis, and hyperreflexia. Seizures, hypotension, and dysrhythmias may occur in severe cases.</td>
<td>Cocaine, amphetamine, methamphetamine (and its derivatives 3,4-methylenedioxyamphetamine, 3,4-methylenedioxyamphetamine, and 2,5-dimethoxy-4-bromoamphetamine), and OTC decongestants (phenylpropanolamine, ephedrine, and pseudoephedrine). In caffeine and theophylline overdoses, similar findings, except for the organic psychiatric signs, result from catecholamine release.</td>
</tr>
<tr>
<td>OPIATE, SEDATIVE, OR ETHANOL INTOXICATION</td>
<td>Coma, respiratory depression, miosis, hypotension, bradycardia, hyperthermia, pulmonary edema, decreased bowel sounds, hyporeflexia, and needle marks. Seizures may occur after overdoses of some narcotics, notably propoxyphene.</td>
<td>Narcotics, barbiturates, benzodiazepines, ethchlorvynol, glutethimide, methyprylon, methaqualone, meprobamate, ethanol, clonidine, and guanabenz.</td>
</tr>
<tr>
<td>CHOLINERGIC</td>
<td>Confusion, central nervous system depression, weakness, salivation, lacrimation, urinary and fecal incontinence, gastrointestinal cramping, emesis, diaphoresis, muscle fasciculations, pulmonary edema, miosis, bradycardia or tachycardia, and seizures.</td>
<td>Organophosphate and carbamate insecticides, physostigmine, edrophonium, and some mushrooms.</td>
</tr>
</tbody>
</table>


### Table 114-7: CRAFFT Mnemonic Tool

- Have you ever ridden in a car driven by someone (including yourself) who was high or had been using alcohol or drugs?
- Do you ever use alcohol or drugs to relax, feel better about yourself or fit in?
- Do you ever use alcohol or drugs while you are by yourself (Alone)?
- Do you ever Forget things you did while using alcohol or drugs?
- Do your Family or Friends ever tell you that you should cut down on your drinking or drug use?
- Have you ever gotten into trouble while you were using alcohol or drugs?

*From the Center for Adolescent Substance Abuse Research (CeASAR). The CRAFFT Screening Interview. © John R. Knight, MD, Boston Children’s Hospital, 2015.*

### Table 114-8: Urine Screening for Drugs Commonly Abused by Adolescents

<table>
<thead>
<tr>
<th>DRUG</th>
<th>MAJOR METABOLITE</th>
<th>INITI AL CONFIRMATION</th>
<th>FIRST CONFIRMATION</th>
<th>SECOND CONFIRMATION</th>
<th>APPROXIMATE RETENTION TIME</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol (blood)</td>
<td>Acetaldehyde</td>
<td>GC</td>
<td>IA</td>
<td></td>
<td>7-10 hr</td>
</tr>
<tr>
<td>Alcohol (urine)</td>
<td>Acetaldehyde</td>
<td>GC</td>
<td>IA</td>
<td></td>
<td>10-13 hr</td>
</tr>
<tr>
<td>Amphetamines</td>
<td>TLC</td>
<td>IA</td>
<td>GC, GC/MS</td>
<td></td>
<td>48 hr</td>
</tr>
<tr>
<td>Barbiturates</td>
<td>IA</td>
<td>TLC</td>
<td>GC, GC/MS</td>
<td>Short-acting (24 hr); long-acting (2-3 wk)</td>
<td></td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>IA</td>
<td>TLC</td>
<td>GC, GC/MS</td>
<td></td>
<td>3 days</td>
</tr>
<tr>
<td>Cannabinoids</td>
<td>Carboxy- and hydroxymetabolites</td>
<td>IA</td>
<td>TLC</td>
<td>GC/MS</td>
<td>3-10 days (occasional user); 1-2 mo (chronic user)</td>
</tr>
<tr>
<td>Cocaine</td>
<td>Benzoylecgonine</td>
<td>IA</td>
<td>TLC</td>
<td>GC/MS</td>
<td>2-4 days</td>
</tr>
<tr>
<td>Methaqualone</td>
<td>Hydroxylated metabolites</td>
<td>TLC</td>
<td>IA</td>
<td>GC/MS</td>
<td>2 wk</td>
</tr>
<tr>
<td>Opiates</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heroin</td>
<td>Morphine glucuronide</td>
<td>IA</td>
<td>TLC</td>
<td>GC, GC/MS</td>
<td>2 days</td>
</tr>
<tr>
<td>Morphine</td>
<td>Morphine glucuronide</td>
<td>IA</td>
<td>TLC</td>
<td>GC, GC/MS</td>
<td>2 days</td>
</tr>
<tr>
<td>Codeine</td>
<td>Morphine glucuronide</td>
<td>IA</td>
<td>TLC</td>
<td>GC, GC/MS</td>
<td>2 days</td>
</tr>
<tr>
<td>Phencyclidine</td>
<td>TLC</td>
<td>IA</td>
<td>GC, GC/MS</td>
<td></td>
<td>8 days</td>
</tr>
</tbody>
</table>

GC, gas chromatography; IA, immunoassay; MS, mass spectrometry; TLC, thin-layer chromatography.

remaining in treatment for a minimum period of 3 mo will result in a significant improvement.

**PROGNOSIS**
For adolescent substance abusers who have been referred to a drug treatment program, positive outcomes are directly related to regular attendance in posttreatment groups. For males with learning problems or conduct disorder, outcomes are poorer than for those without such disorders. Peer use patterns and parental use have a major influence on all classes of drugs. For females, factors such as self-esteem and anxiety are more important influences on outcomes. The chronicity of a substance use disorder makes relapse an issue that must always be kept in mind when managing patients after treatment, and appropriate assistance from a health professional qualified in substance abuse management should be obtained.

**PREVENTION**
Preventing drug use among children and teens requires prevention efforts aimed at the individual, family, school, and community levels. The National Institute on Drug Abuse (NIDA) has identified essential principles of successful prevention programs. Programs should enhance protective factors (parent support) and reduce risk factors (poor self-control); should address all forms of drug abuse (legal and illegal); should address the specific type(s) of drug abuse within an identified community; and should be culturally competent to improve effectiveness (Table 114-9). The highest risk periods for substance use in children and adolescents are during life transitions such as the move from elementary school to middle school, or from middle school to high school. Prevention programs need to target these emotionally and socially intense times for teens in order to adequately anticipate potential substance use or abuse. Examples of effective research-based drug abuse prevention programs featuring a variety of strategies are listed on the NIDA website (www.drugabuse.gov), and on the Center for Substance Abuse Prevention website (www.prevention.samhsa.gov).

**Bibliography** is available at Expert Consult.

### 114.1 Alcohol

**Margaret M. Stager**

Alcohol is the most popular drug among teens in the United States. By 12th grade, approximately 75% of adolescents in high schools report ever having an alcoholic drink, with 20.5% having their first drink before age 13 yr. Multiple factors can affect a young teen's risk of developing a drinking problem at an early age (Table 114-10). One-third of high school seniors admit to combining drinking behaviors with other risky behaviors, such as driving or taking additional substances. Binge drinking remains especially problematic among the older teens and young adults. Thirty-one percent of high school seniors report having 5 or more drinks in a row in the last 30 days. Higher use is seen in males (23.8%) than in females (19.8%), and whites (24.0%) and Hispanics (24.2%) than in blacks (12.4%). Overall, the prevalence of binge drinking decreased from 2009 (24.2%) to 2011 (21.9%). Teens with binge drinking patterns are more likely to be assaulted, engage in high risk sexual behaviors, have academic problems, and acquire injuries than those teens without binge drinking patterns.

Alcohol contributes to more deaths in young individuals in the United States than all the illicit drugs combined. Among studies of adolescent trauma victims, alcohol is reported to be present in 32-45% of hospital admissions. Motor vehicle crashes are the most frequent type of event associated with alcohol use, but the injuries spanned several types, including self-inflicted wounds.

Alcohol is often mixed with energy drinks (caffeine, taurine, sugars), which can result in a spectrum of alcohol related negative behaviors. Caffeine may counter the sedative effects of alcohol resulting in more alcohol consumption and a perception of not being intoxicated thus leading to risk taking behavior like driving while intoxicated. In addition, aggressive behavior, including sexual assaults and motor vehicle or other injuries has been reported. Both alcohol and caffeine overdoses have also been reported.

### PHARMACOLOGY AND PATHOPHYSIOLOGY
Alcohol (ethyl alcohol or ethanol) is rapidly absorbed in the stomach and is transported to the liver and metabolized by 2 pathways. The primary metabolic pathway contributes to the excess synthesis of triacylglycerides, a phenomenon that is responsible for producing a fatty liver, even in those who are well nourished. Engorgement of hepatocytes with fat causes necrosis, triggering an inflammatory process (alcoholic hepatitis), which is later followed by fibrosis, the hallmark of cirrhosis. Early hepatic involvement may result in elevation in γ-glutamyl transpeptidase and serum glutamic-pyruvic transaminase.

The second metabolic pathway, which is utilized at high serum alcohol levels, involves the microsomal enzyme system of the liver, in which the cofactor is reduced nicotinamide-adenine dinucleotide phosphate. The net effect of activation of this pathway is to decrease metabolism of drugs that share this system and to allow for their accumulation, enhanced effect, and possible toxicity.

### CLINICAL MANIFESTATIONS
Alcohol acts primarily as a central nervous system depressant. It produces euphoria, grogginess,talkativeness, impaired short-term memory, and an increased pain threshold. Alcohol's ability to produce vasodilation and hypothermia is also centrally mediated. At very high serum levels, respiratory depression occurs. Its inhibitory effect on pituitary antidiuretic hormone release is responsible for its diuretic effect. The gastrointestinal complications of alcohol use can occur from a single large ingestion. The most common is acute erosive gastritis, which is manifested by epigastric pain, anorexia, vomiting, and

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*From National Institute on Drug Abuse: Preventing drug use among children and adolescents. A research based guide for parents, educators, and community leaders. NIH publication No. 04-4212(B), ed 2, Bethesda, MD, 2003, National Institute on Drug Abuse.*
Bibliography


The usual mechanism of death from the alcohol overdose syndrome is respiratory depression, and artificial ventilatory support must be provided until the liver can eliminate sufficient amounts of alcohol from the body. In a patient without alcoholism, it generally takes 20 hr to reduce the blood level of alcohol from 400 mg/dL to zero. Dialysis should be considered when the blood level is >400 mg/dL. As a follow-up to acute treatment, referral for treatment of the alcohol use disorder is indicated. Group counseling, individualized counseling, and multifamily educational intervention have been found to be quite effective interventions for teens.

Bibliography is available at Expert Consult.

114.2 Tobacco

Margaret M. Stager

CIGARETTES
The average smoker in the United States starts at age 12 yr, and most are regular smokers by age 14 yr. More than 90% of adolescent smokers become adult smokers. Factors associated with youth tobacco use include exposure to smokers (friends, parents), availability of tobacco, low socioeconomic status, poor school performance, low self-esteem, lack of perceived risk of use, and lack of skills to resist influences to tobacco use.

Current smoking rates among U.S. high school students (as is the case for students in many industrialized nations) have trended downward over the last decade for lifetime cigarette use (from 20.0% to 12.4%) and current frequent cigarette use (from 16.8% to 6.4%). Overall, more whites report current tobacco use (20.3%) than Hispanics (17.5%) or blacks (10.5%). Clove cigarettes (kretets) and flavored cigarettes (bidis) are popular with younger students. Both types of flavored cigarettes contain tobacco with other additives and deliver more nicotine and other harmful substances because they are unfiltered. Use of cigars and mini-cigars (cigarillos) has not changed in the past 3 yr, with 13.1% of students reporting smoking at least 1 during the 30 days prior to the survey. Cigar/cigarillo use is highest among males (17.8% vs. females 8.0%), and high school seniors (23.9%) versus lower grades (9th grade 12.3%, 10th grade 15.4% and 11th grade 20.4%). Tobacco use is linked to other high-risk behaviors. Teens who smoke are more likely than nonsmokers to use alcohol and engage in unprotected sex, are 8 times more likely to use marijuana, and are 22 times more likely to use cocaine.

Tobacco is used by teens in all regions of the world, although the form of tobacco used differs. In the Americas and Europe, cigarette smoking prevalence is higher than other tobacco use, although cigars and smokeless tobacco are also used; in the Eastern Mediterranean, shisha (flavored tobacco smoked in hookah pipes) is prevalent; in Southeast Asia, smokeless tobacco products are used; in the Western Pacific, betel nut is chewed with tobacco; and pipe, snuff, and rolled tobacco leaves are used in Africa. Cigarette use rates by teens in low- and middle-income nations are increasing.

PHARMACOLOGY
Nicotine, the primary active ingredient in cigarettes, is addictive. Nicotine is absorbed by multiple sites in the body, including the lungs, skin, gastrointestinal tract, and buccal and nasal mucosa. The action of nicotine is mediated through nicotinic acetylcholine receptors located on noncholinergic presynaptic and postsynaptic sites in the brain and causes increased levels of dopamine. Nicotine also stimulates the adrenal glands to release epinephrine, causing an immediate elevation in blood pressure, respiration and heart rate. The average nicotine content of 1 cigarette is 10 mg and the average nicotine intake per cigarette ranges from 1-3 mg. Nicotine, as delivered in cigarette smoke, has a half-life of about 2 hr. Cotinine is the major metabolite of nicotine via C-oxidation. It has a biologic half-life of 19-24 hr and can be detected in urine, serum, and saliva.

CLINICAL MANIFESTATIONS
Adverse health effects from regular smoking include an increased prevalence of chronic cough, sputum production, and wheezing.

### Table 114-11: Alcohol Use Disorders Identification Test (AUDIT)

<table>
<thead>
<tr>
<th>SCORE (0-4)*</th>
<th>1. How often do you have a drink containing alcohol?</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Never (0) to more than 4 per wk (4)</td>
</tr>
<tr>
<td>2. How many drinks containing alcohol do you have on a typical day?</td>
<td></td>
</tr>
<tr>
<td></td>
<td>One or 2 (0) to more than 10 (4)</td>
</tr>
<tr>
<td>3. How often do you have 6 or more drinks on 1 occasion?</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Never (0) to daily or almost daily (4)</td>
</tr>
<tr>
<td>4. How often during the last year have you found that you were not able to stop drinking once you had started?</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Never (0) to daily or almost daily (4)</td>
</tr>
<tr>
<td>5. How often during the last year have you failed to do what was normally expected from you because of drinking?</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Never (0) to daily or almost daily (4)</td>
</tr>
<tr>
<td>6. How often during the last year have you needed a first drink in the morning to get yourself going after a heavy drinking session?</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Never (0) to daily or almost daily (4)</td>
</tr>
<tr>
<td>7. How often during the last year have you had a feeling of guilt or remorse after drinking?</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Never (0) to daily or almost daily (4)</td>
</tr>
<tr>
<td>8. How often during the last year have you been unable to remember what happened the night before because you had been drinking?</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Never (0) to daily or almost daily (4)</td>
</tr>
<tr>
<td>9. Have you or someone else been injured as a result of your drinking?</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No (0) to yes, during the last year (4)</td>
</tr>
<tr>
<td>10. Has a relative, friend, doctor or other health worker been concerned about your drinking or suggested that you should cut down?</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No (0) to yes, during the last year (4)</td>
</tr>
</tbody>
</table>

*Score ≥8 = problem drinking.

From Schuckit MA: Alcohol-use disorders, Lancet 373:492–500, 2009, Table 1.
Bibliography


Smoking during pregnancy is associated with an average decrease in fetal weight of 200 g; this decrease, added to the already smaller size of infants born to teenagers, increases perinatal morbidity and mortality. Tobacco smoke induces hepatic smooth endoplasmic reticulum enzymes and, as a result, may also influence metabolism of drugs such as phenacetin, theophylline, and imipramine. Withdrawal symptoms can occur when adolescents try to quit. Irritability, decreased concentration, increased appetite, and strong cravings for tobacco are common withdrawal symptoms.

**ELECTRONIC CIGARETTES (E-CIGARETTES)**

E-cigarettes are electronic nicotine delivery systems that are battery operated, which heat and then vaporize nicotine dissolved in propylene glycol, glycerin, or other solvents. They come in tobacco, mint, cherry, or chocolate flavors, and are highly marketed to adolescents. They have the potential to create nicotine dependency and have not been effective in smoking-cessation programs.

Adverse effects include dry cough, throat irritation, and lipid pneumonia. Potentially toxic substances have been detected in the vapor (diethylene glycol) as well as carcinogens (nitrosamines). Second-hand exposure is a possibility. These products have been banned in some countries; they are not regulated by the FDA.

**SMOKELESS TOBACCO**

The 2 forms of smokeless tobacco (SLT) are “chew,” a leafy tobacco product sold in pouches, and “snuff,” a finely ground tobacco product sold in tins or packets. Users place the SLT along the gum line of the lower jaw whereby the nicotine is absorbed by the mucous membranes. Smokeless tobacco use is largely reported by males in 10th (11.2%) and 12th grades (13.5%) for the 30-day prevalence rates. Snus, is a Swedish tobacco product that is available as a loose powder, or in a small teabag-like sachet. It is placed under the lower lip and unlike American chewing tobacco there is no need to spit. Annual prevalence of Snus use in 2012 was 2.4%, 6.9%, and 7.9% among 8th, 10th, and 12th graders, respectively.

Introduced in 2009, there are several dissolvable SLT products on the market. The Orbs are pellets of ground tobacco that resemble candy and come in various flavors. The Sticks are twin, matchstick-like ground tobacco, and the Strips are flat sheets that quickly dissolve in the mouth. All of these products are small and easily concealed, and therefore can be used throughout the day without detection, especially as there is no need to spit.

**Table 114-12 Smoking Cessation Pharmacotherapy Available in the United States**

<table>
<thead>
<tr>
<th>THERAPY BRAND</th>
<th>NAME</th>
<th>STRENGTHS</th>
<th>FDA-APPROVED ADULT DOSING</th>
<th>AVAILABILITY*</th>
<th>STUDIED IN ADOLESCENTS</th>
<th>QUIT DATE</th>
</tr>
</thead>
<tbody>
<tr>
<td>NICOTINE REPLACEMENT THERAPY</td>
<td>Nicorette</td>
<td>2 mg, 4mg</td>
<td>The 0.4-mg strength should be used by patients who smoke 25 or more cigarettes a day; otherwise the 2-mg strength should be used Wk 1-6: 1 piece every 1-2 hr Wk 7-9: 1 piece every 2-4 hr Wk 10-12: 1 piece every 4-8 hr 6-16 cartridges a day for up to 12 wks</td>
<td>OTC*</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Inhaler</td>
<td>Nicotrol Inhaler</td>
<td>4 mg</td>
<td></td>
<td>Rx</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Lozenge</td>
<td>CommitTM, Nicorette mini</td>
<td>2 mg, 4 mg</td>
<td>The 4-mg strength should be used by patients who smoke their first cigarette within 30 minutes of waking; otherwise, the 2-mg strength should be used Wk 1-6: 1 lozenge every 1-2 hr Wk 7-9: 1 lozenge every 2-4 hr Wk 10-12: 1 lozenge every 4-8 hr</td>
<td>OTC</td>
<td>No</td>
<td>Prior to beginning nicotine replacement therapy</td>
</tr>
</tbody>
</table>

Exposure to SLT increases the users risk for oral cancers of the mouth, pharynx, larynx, and esophagus, as well as gum disease and nicotine addiction. Use of SLT among high school boys exceeds 20% in Arkansas, Kentucky, Montana, North Dakota, Oklahoma, South Dakota, Tennessee, Wyoming, and West Virginia (the latter with the highest rate at 25.5%).

**TREATMENT**

The approach to smoking cessation in adolescents includes the 5 As (Ask, Advise, Assess, Assist, and Arrange) and use of nicotine replacement therapy in addicted teens who are motivated to quit and are not using SLT. Consensus panels recommend the 5 As, although evidence of efficacy in adolescents is limited. Nicotine patch studies to date in adolescents suggest a positive effect on reducing withdrawal symptoms and that pharmacotherapy should be combined with behavioral therapy to reach higher cessation and lower relapse rates. In a limited number of students, cessation rates of 15% were reported at 3 and 6 mo. Nicotine replacement therapy is also available as a gum, inhaler, nasal spray, lozenge, or microtab (Table 114-12). However, the nicotine patch and nasal spray were found to have numerous side effects in adolescent subjects. Medications such as bupropion are not FDA approved for use in adolescents <18 yr old; some pilot studies in adolescents report cessation efficacy with 150 mg or 300 mg of bupropion daily. Varenicline has successfully been used in adults; however, it now includes a black box warning of neuropsychiatric side effects such as agitation, hostility, depressed mood, and suicidal ideation.

The American Lung Association’s Not-On-Tobacco Program (NOT) is a nationally recognized best-practice model for teen smoking cessation. More than 100,000 teens in 48 states have participated in the NOT, which resulted in either quitting (15% on average) or decreased tobacco use. The NOT is a 10 wk, developmentally appropriate, teen-focused, small group program that addresses topics such as stress management, effects of smoking, preparing to quit, dealing with peer pressure, and establishing support networks. The program is available as a train-the-trainer model, including training manuals and student materials (see [www.lung.org](http://www.lung.org)).

In keeping with teens’ high use of cell phones, support for teen smoking cessation is now available as a text-messaging service. Smokefree TXT, a free text messaging service, is offered by the National Cancer Institute and aims to engage teens to quit smoking using daily text messaging on their cell phone. Teens can sign up online (teen. smokefree.gov) or text QUIT to iQUIT (47848). Another cell phone
application, QuitSTART, is available for teens as an interactive cell phone-based guide that helps them track cravings, monitor moods, offer cessation tips, and follow quit attempts. Both Smokefree TXT and QuitSTART link teens to social media webpages which offer additional information on cessation tools and programs.

Bibliography is available at Expert Consult.

### 114.3 Marijuana

**Margaret M. Stager**

Marijuana (THC, “pot,” “weed,” “hash,” “grass”), derived from the Cannabis sativa hemp plant, is the most commonly abused illicit drug. The main active chemical, tetrahydrocannabinol (THC), is responsible for its hallucinogenic properties. THC is absorbed rapidly by the nasal or oral routes, producing a peak of subjective effect at 10 min and 1 hr, respectively. Marijuana is generally smoked as a cigarette (“reefer” or “joint”) or in a pipe. Although there is much variation in content, each cigarette contains 8-10% THC. Another popular form that is smoked, a “blunt,” is a hollowed-out small cigar refilled with marijuana. Hashish is the concentrated THC resin in a sticky black liquid or oil. Although marijuana use by U.S. teens has declined in the last decade, 23.1% of high school students have used marijuana at least once during the previous 30 days, and current marijuana use is highest in black males and seniors. Eight percent of students report having tried marijuana before the age of 13 yr, with a range from 4.3-18.3% across various states, indicating the need for early prevention efforts.

#### CLINICAL MANIFESTATIONS

In addition to the “desired” effects of elation and euphoria, marijuana may cause impairment of short-term memory, poor performance of tasks requiring divided attention (e.g., those involved in driving), loss of critical judgment, decreased coordination, and distortion of time perception (Table 114-13). Visual hallucinations and perceived body distortions occur rarely, but there may be “flashbacks” or recall of frightening hallucinations experienced under marijuana’s influence that usually occur during stress or with fever.

Smoking marijuana for a minimum of 4 days/wk for 6 mo appears to result in dose-related suppression of plasma testosterone levels and spermatogenesis, prompting concern about the potential deleterious effect of smoking marijuana before completion of pubertal growth and development. There is an antiemetic effect of oral THC or smoked marijuana, often followed by appetite stimulation, which is the basis of the drug’s use in patients receiving cancer chemotherapy. Although the possibility of teratogenicity has been raised because of findings in animals, there is no evidence of such effects in humans. An amotivational syndrome has been described in long-term marijuana users who lose interest in age-appropriate behavior, yet proof of the causative relationship remains equivocal. Chronic use is associated with increased anxiety and depression, learning problems, poor job performance, hyperemesis, and respiratory problems such as pharyngitis, sinusitis, bronchitis, and asthma (see Table 114-13).

The increased THC content of marijuana of 5-15–fold compared to that of the 1970s, is related to the observation of a withdrawal syndrome, occurring 24-48 hr after discontinuing the drug. Heavy users experience malaise, irritability, agitation, insomnia, drug craving, shakiness, diaphoresis, night sweats, and gastrointestinal disturbance. The symptoms peak by the 4th day, and they resolve in 10-14 days. Certain drugs may interact with marijuana to potentiate sedation (alcohol, diazepam), potentiate stimulation (cocaine, amphetamines), or be antagonistic (propranolol, phenytoin).

Behavioral interventions, including cognitive-behavioral therapy and motivational incentives, have shown to be effective in treating marijuana dependency.
Bibliography


SYNTHETIC MARIJUANA
Spice, K2, crazy clown, aroma, black mamba, blaze, dream, and funky monkey are common street names for synthetic marijuana, which is a mixture of herbs or plant materials that have been sprayed with artificial chemicals similar to THC, the psychoactive ingredient in marijuana. One active group of chemicals is the carboxamides, which are not detected by assays to detect THC. In the United States, the chemicals in Spice are designated a schedule I controlled substance by the DEA, thereby making it illegal to sell, buy, or possess them. Nonetheless, synthetic marijuana is the second most common illicit drug used by high school seniors. More than 1 in 10 high school seniors used synthetic marijuana in the last year.

Synthetic marijuana is mainly used by smoking, or mixed with marijuana, or brewed as a tea for drinking. The chemicals in synthetic marijuana affect the same receptors as THC and produce similar effects as seen in marijuana such as relaxation, elevated mood, and altered perception. In addition, sympathomimetic symptoms are quite common and are the cause of significant toxicity. Symptoms of intoxication include vomiting, tachycardia, hypertension, hyperthermia, confusion, extreme anxiety, profuse sweating, agitation, aggression, dysphoria, hallucinations, seizures, rhabdomyolysis, dystonia, unresponsiveness, confusion, and myocardial ischemia. In response to legislation to ban the chemicals in OTC synthetic marijuana products, manufacturers alter and substitute the chemicals in the product, keeping it on the legal market and leaving teens particularly vulnerable to potential health effects.

Bibliography is available at Expert Consult.

114.4 Inhalants
Margaret M. Stager

Inhalants, found in many common household products, comprise a diverse group of volatile substances whose vapors can be inhaled to produce psychoactive effects. The practice of inhalation is popular among younger adolescents and decreases with age. Young adolescents are attracted to these substances because of their rapid action, ease of availability, and low cost. Products that are abused as inhalants include volatile solvents (paint thinners, glue), aerosols (spray paint, hair spray), gases (propane tanks, lighter fluid), nitrites (“poppers” or “video head cleaner”) and propellants used in whipped cream dispensers. The most popular inhalants among young adolescents are glue, shoe polish, and spray paint. The various products contain a wide range of chemicals with serious adverse health effects (Table 114-14). Huffing, the practice of inhaling fumes can be accomplished using a paper bag containing a chemical-soaked cloth, spraying aerosols directly into the nose/mouth, or using a balloon, plastic bag, or soda can filled with fumes. The percentage of adolescents using inhalants has remained stable, with 11.4% of high school students reporting having ever used inhalants in. Eighth and 9th graders report highest use, suggesting targeted prevention strategies are warranted for this age group.

CLINICAL MANIFESTATIONS
The major effects of inhalants are psychoactive (Table 114-15). The intoxication lasts only a few minutes, so a typical user will huff repeatedly over an extended period of time (hours) in order to maintain the high. The immediate effects of inhalants are similar to alcohol: euphoria, slurred speech, decreased coordination, and dizziness. Toluene, the main ingredient in model airplane glue and some rubber cements, causes relaxation and pleasant hallucinations for up to 2 hr. Euphoria is followed by violent excitement; coma may result from prolonged or rapid inhalation. Volatile nitrites, such as amyl nitrite, butyl nitrite, and related compounds marketed as room deodorizers, are used as euphorants, enhancers of musical appreciation, and sexual enhancements among older adolescents and young adults. They may result in headaches, syncope, and lightheadedness; profound hypotension and cutaneous flushing followed by vasoconstriction and tachycardia; transiently inverted T waves and depressed ST segments on electrocardiography; methemoglobinemia; increased bronchial irritation; and increased intraocular pressure.

COMPLICATIONS
Model airplane glue is responsible for a wide range of complications, related to chemical toxicity, to the method of administration (in plastic bags, with resultant suffocation), and to the often dangerous setting in which the inhalation occurs (inner-city roof tops). Common neuromuscular changes reported in chronic inhalant abusers include difficulty coordinating movement, gait disorders, muscle tremors, and spasticity, particularly in the legs (Table 114-16). Chronic use may cause pulmonary hypertension, restrictive lung defects or reduced
Bibliography


diffusion capacity, peripheral neuropathy, hematuria, tubular acidosis, and possibly cerebral and cerebellar atrophy. Chronic inhalant abuse has long been linked to widespread brain damage and cognitive abnormalities that can range from mild impairment (poor memory, decreased learning ability) to severe dementia. High-frequency inhalant users were significantly more likely than moderate- and low-frequency users to experience adverse consequences of inhalant intoxication such as behavioral, language, and memory problems. Certain risky behaviors and consequences, such as engaging in unprotected sex or fighting while high on inhalants, were dramatically more common among high-frequency inhalant users than among low-frequency inhalant users. Death in the acute phase may result from cerebral or pulmonary edema or myocardial involvement (Table 114-16).

### Table 114-15  Stages in Symptom Development After Use of Inhalants

<table>
<thead>
<tr>
<th>STAGE</th>
<th>SYMPTOMS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1: Excitatory</td>
<td>Euphoria, excitement, exhilaration, dizziness, hallucinations, sneezing, coughing, excess salivation, intolerance to light, nausea and vomiting, flushed skin and bizarre behavior</td>
</tr>
<tr>
<td>2: Early CNS depression</td>
<td>Confusion, disorientation, dullness, loss of self-control, ringing or buzzing in the head, blurred or double vision, cramps, headache, insensitivity to pain, and pallor or paleness</td>
</tr>
<tr>
<td>3: Medium CNS depression</td>
<td>Drowsiness, muscular uncoordination, slurred speech, depressed reflexes, and nystagmus or rapid involuntary oscillation of the eyeballs</td>
</tr>
<tr>
<td>4: Late CNS depression</td>
<td>Unconsciousness that may be accompanied by bizarre dreams, epileptiform seizures, and EEG changes</td>
</tr>
</tbody>
</table>

CNS, central nervous system; EEG, electroencephalogram

From Harris D: Volatile substance abuse, Arch Dis Child Educ Pract Ed 91:ep93-ep100, 2006, Table 1.

### Table 114-16  Documented Clinical Presentations of Volatile Substance Abuse

<table>
<thead>
<tr>
<th>CLINICAL PRESENTATIONS OF ACUTE AND CHRONIC VOLATILE SUBSTANCE ABUSE</th>
<th>SYMPTOMS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ventricular fibrillation</td>
<td>Muscle weakness</td>
</tr>
<tr>
<td>Asystolic cardiac arrest</td>
<td>Abdominal pain</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>Cough</td>
</tr>
<tr>
<td>Ataxia</td>
<td>Aspiration pneumonia</td>
</tr>
<tr>
<td>Agitation</td>
<td>Chemical pneumonitis</td>
</tr>
<tr>
<td>Limb and trunk uncoordination</td>
<td>Coma</td>
</tr>
<tr>
<td>Tremor</td>
<td>Visual and auditory hallucinations</td>
</tr>
<tr>
<td>Visual loss</td>
<td>Acute delusions</td>
</tr>
<tr>
<td>Tinnitus</td>
<td>Nausea and vomiting</td>
</tr>
<tr>
<td>Dysarthria</td>
<td>Pulmonary edema</td>
</tr>
<tr>
<td>Vertigo</td>
<td>Photophobia</td>
</tr>
<tr>
<td>Hyperreflexia</td>
<td>Rash</td>
</tr>
<tr>
<td>Acute confusional state</td>
<td>Jaundice</td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td>Anorexia</td>
</tr>
<tr>
<td>Acute paranoia</td>
<td>Slurred speech</td>
</tr>
<tr>
<td>Depression</td>
<td>Diarrhea</td>
</tr>
<tr>
<td>Oral and nasal mucosal ulceration</td>
<td>Weight loss</td>
</tr>
<tr>
<td>Haltitus</td>
<td>Epistaxis</td>
</tr>
<tr>
<td>Convulsions/fits</td>
<td>Rhinitis</td>
</tr>
<tr>
<td>Headache</td>
<td>Cerebral edema</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>Visual loss</td>
</tr>
<tr>
<td>Methemoglobinemia</td>
<td>Burns</td>
</tr>
<tr>
<td>Acute trauma</td>
<td>Renal tubular acidosis</td>
</tr>
</tbody>
</table>

From Harris D: Volatile substance abuse, Arch Dis Child Educ Pract Ed 91:ep93-ep100, 2006, Table 2.

### DIAGNOSIS

Diagnosis of inhalants is difficult because of the ubiquitous nature of the products and decreased parental awareness of their dangers. In the primary care setting, providers need to enquire of parents if they have witnessed any unusual behaviors in their teen; noticed high-risk products in their bedrooms; seen paint on the teen’s hands, nose, or mouth; or found paint-coated or chemical coated rags. Complete blood counts, coagulation studies, and hepatic and renal function studies may identify the complications. In extreme intoxication, a user may manifest symptoms of restlessness, general muscle weakness, dysartria, nystagmus, disruptive behavior, and occasionally hallucinations. Toluene is excreted rapidly in the urine as hippuric acid, with the residual detectable in the serum by gas chromatography.

### TREATMENT

Treatment is generally supportive and directed toward control of arrhythmia and stabilization of respirations and circulation. Withdrawal symptoms do not usually occur.

Bibliography is available at Expert Consult.

### 114.5 Hallucinogens

Margaret M. Stager

Several naturally occurring and synthetic substances are used by adolescents for their hallucinogenic properties. They have chemical structures similar to neurotransmitters such as serotonin, yet their exact mechanism of action remains unclear. Lysergic acid diethylamide (LSD) and methylenedioxymethamphetamine (MDMA) (Ecstasy or Molly) are the most commonly reported hallucinogens used.

### LYSERGIC ACID DIETHYLAMIDE

LSD (acid, big “d,” blotters) is a very potent hallucinogen that is made from lysergic acid found in ergot, a fungus that grows on rye and other grains. Its high potency allows effective doses to be applied to absorbent paper, or it can be taken as a liquid or a tablet. The onset of action can be between 30 and 60 min, and it peaks between 2 and 4 hr. By 10-12 hr, an individual returns to the predrug state. Four percent of U.S. 12th graders report trying LSD at least once.

### Clinical Manifestations

The effects of LSD can be divided into 3 categories: somatic (physical effects), perceptual (altered changes in vision and hearing), and psychic effects (changes in sensorium). The common somatic symptoms are dizziness, dilated pupils, nausea, flushing, elevated temperature, and tachycardia. The sensation of synesthesia, or “seeing” smells and “hearing” colors, as well as major distortions of time and self, have been reported with high doses of LSD. Delusional ideation, body distortion, and suspiciousness to the point of toxic psychosis are the more serious of the psychotic symptoms. LSD is not considered to be an addictive drug as it does not typically produce drug-seeking behavior.

### Treatment

An individual is considered to have a “bad trip” when the sensory experiences causes the user to become terrified or panicked. These episodes should be treated by removing the individual from the aggravating situation and placing him in a quiet room with a calming friend. In situations of extreme agitation or seizures, use of benzodiazepines may be warranted. “Flashbacks” or LSD-induced states after the drug has worn off and tolerance to the effects of the drug are additional complications of its use.

### METHYLENEDIOXYMETHAMPHETAMINE

MDMA (“X,” Ecstasy, Molly), a phenylisopropylamine hallucinogen, is a synthetic compound similar to hallucinogenic mescaline and the stimulant methamphetamine. Like other hallucinogens, this drug is
Bibliography
proposed to interact with serotonergic neurons in the central nervous system (CNS). It is the preferred drug at “raves,” all-night dance parties, and is also known as one of the “club drugs” along with γ-hydroxybutyrate (GHB) and ketamine (see Table 114-5). Between 2009 and 2010, past-year use of MDMA increased among both 8th and 10th graders in the US but then declined in both grades. Nationwide, the prevalence of having ever used MDMA was 8.2% of students with highest use reported among males and Hispanics (10.6%). MDMA use increased among high school students from 2009-2011 (8.2%). LSD use remained stable during this time period (2009: 8%; 2011: 8.7%).

Clinical Manifestations
Euphoria, a heightened sensual awareness, and increased psychic and emotional energy are acute effects. Compared to other hallucinogens, MDMA is less likely to produce emotional lability, depersonalization, and disturbances of thought. Nausea, jaw clenching, teeth grinding, and blurred vision are somatic symptoms, whereas anxiety, panic attacks, and psychosis are the adverse psychiatric outcomes. A few deaths have been reported after ingestion of the drug. In high doses, MDMA can interfere with the body’s ability to regulate temperature. The resultant hyperthermia in association with vigorous dancing at a “rave” has resulted in severe liver, kidney, and cardiovascular system failure and death. There are no specific treatment regimens recommended for acute toxicity. Chronic MDMA use can lead to changes in brain function, affecting cognitive tasks and memory. These symptoms may occur because of MDMA’s effects on neurons that use serotonin as a neurotransmitter. The serotonin system plays an important role in regulating mood, aggression, sexual activity, sleep, and sensitivity to pain. A high rate of dependence has been found among MDMA users. MDMA exposure may be associated with long-term neurotoxicity and damage to serotonin-containing neurons. In nonhuman primates, exposure to MDMA for only 4 days caused damage to serotonin nerve terminals that was evident 6-7 yr later. There are no specific pharmacologic treatments for MDMA addiction. Drug abuse recovery groups are recommended.

PHENCYCLIDINE
Phencyclidine (PCP) (sternyl, angel dust, “hог,” “peace pill,” “sheets”) is an arylcyclohexalaminelike substance whose activity is related, in part, to its ease of synthesis in home laboratories. One of the by-products of home synthesis causes cramps, diarrhea, and hematemesis. It is a “dissociative drug” that produces feelings of detachment from the surrounding environment and self. The drug is thought to potentiate adreneric effects by inhibiting neuronal reuptake of catecholamines. PCP is available as a tablet, liquid, or powder, which may be used alone or sprinkled on cigarettes (“sheets”). The powders and tablets generally contain 2-6 mg of PCP, whereas joints average 1 mg for every 150 mg of tobacco leaves, or approximately 30-50 mg per joint. The prevalence of PCP use (hallucinogenic drug) among U.S. high school students remained stable from 2009 (8.0%) to 2011 (8.7%).

Clinical Manifestations
The clinical manifestations are dose related and produce alterations of perception, behavior, and autonomic functions. Euphoria, nystagmus, ataxia, and emotional lability occur within 2-3 min after smoking 1-5 mg and last for 4-6 hr. At these low doses the user is likely to experience shallow breathing, flushing, generalized numbness of extremities, and loss of motor coordination. Hallucinations may involve bizarre distortions of body image that often precipitate panic reactions. With doses of 5-15 mg, a toxic psychosis may occur, with disorientation, hypersalivation, and abusive language lasting for >1 hr. Hypotension, generalized seizures, and cardiac arrhythmias commonly occur with plasma concentrations from 40-200 mg/dL. Death has been reported during psychotic delirium, from hypertension, hypotension, hypothermia, seizures, and trauma. The coma of PCP may be distinguished from that of the opiates by the absence of respiratory depression; the presence of muscle rigidity, hyperreflexia, and nystagmus; and lack of response to naloxone. PCP psychosis may be difficult to distinguish from schizophrenia. In the absence of a history of use, analysis of urine must be depended on for diagnosis.

Treatment
Management of the PCP-intoxicated patient includes placement in a darkened, quiet room on a floor pad, safe from injury. Acute alcohol intoxication may be present also. For recent oral ingestion, gastric aspiration is poor and induction of emesis or gastric lavage is useful. Diazepam, in a dose of 5-10 mg orally or 2-5 mg intravenously, may be helpful if the patient is agitated and not comatose. Rapid excretion of the drug is promoted by acidification of the urine. Supportive therapy of the comatose patient is indicated with particular attention to hydration, which may be compromised by PCP-induced diuresis. Inpatient and/or behavioral treatments can be helpful for chronic PCP users.

Bibliography is available at Expert Consult.

114.6 Cocaine
Margaret M. Stager

Cocaine, an alkaloid extracted from the leaves of the South American Erythroxylum coca, is supplied as the hydrochloride salt in crystalline form. With “snorting” it is rapidly absorbed into the bloodstream from the nasal mucosa, detoxified by the liver, and excreted in the urine as benzoylecgonine. Smoking the cocaine alkaloid (“freebase”) involves inhaling the cocaine vapors in pipes, or cigarettes mixed with tobacco or marijuana. Accidental burns are potential complications of this practice. With crack cocaine, the crystallized rock form, the smoker feels “high” in <10 sec. The risk of addiction with this method is higher and more rapidly progressive than from snorting cocaine. Tolerance develops and the user may increase the dose or change the route of administration, or both, to achieve the same effect. To sustain the high, cocaine users repeatedly use cocaine in short periods of time known as “binges.” Drug dealers often place cocaine in plastic bags or condoms and swallow these containers during transport. Rupture of a container produces a sympathomimetic crisis (see Table 114-6). Cocaine use among high school students has decreased in the last decade, with 8.5% of 12th graders having tried the drug (any route) at least once. Current cocaine use in last 30 days remains stable at 3% of students.

CLINICAL MANIFESTATIONS
Cocaine is a strong CNS stimulant that increases dopamine levels by preventing reuptake. Cocaine produces euphoria, increased motor activity, decreased fatigueability, and mental alertness. Its sympathomimetic properties are responsible for pupillary dilation, tachycardia, hypertension, and hypothermia. Snorting cocaine chronically results in loss of sense of smell, nosebleeds, and chronic rhinorrhea. Injecting cocaine increases risk for HIV infection. Chronic abusers experience anxiety, irritability, and sometimes paranoid psychosis. Lethal effects are possible, especially when cocaine is used in combination with other drugs, such as heroin, in an injectable form known as a “speedball.” Cocaine, when taken with alcohol, is metabolized by the liver to produce cocaethylene, a substance that enhances the euphoria and is associated with a greater risk of sudden death than cocaine alone. Pregnant adolescents who use cocaine place their fetus at risk of premature delivery, complications of low birthweight, and possibly developmental disorders.

TREATMENT
There are no FDA-approved medications for treatment of cocaine addiction. Cognitive-behavioral therapy has been shown to be effective when provided in combination with additional services and social support.

Bibliography is available at Expert Consult.
Bibliography
Bibliography


**114.7 Amphetamines**

Methamphetamine, commonly known as “ice,” is a nervous system stimulant and schedule II drug with a high potential for abuse. Most of the methamphetamine currently abused is produced in illegal laboratories. It is a white, odorless, bitter tasting powder that is particularly popular among adolescents and young adults because of its potency and ease of absorption. It can be ingested orally, by smoking, needle injection, or absorption across mucous membranes. Amphetamines have multiple CNS effects, among them the release of neurotransmitters and an indirect catecholamine agonist effect. In recent years, there has been a general decline of methamphetamine use among high school students. In the 2012 Monitoring the Future Study, 1.1% of 12th graders report using methamphetamine at least once reflecting a steady decline in use over the last 10 yr.

**CLINICAL MANIFESTATIONS**

Methamphetamine rapidly increases the release and blocks the reuptake of dopamine, a powerful “feel good” neurotransmitter (Table 114-17). The effects of amphetamines can be dose related. In small amounts amphetamine effects resemble other stimulants: increased physical activity, rapid and/or irregular heart rate, increased blood pressure and decreased appetite. High doses produce slowing of cardiac conduction in the face of ventricular irritability. Hypertensive and hyperpyrexic episodes can occur as seizures (see Table 114-6). Binge effects result in the development of psychotic ideation with the potential for sudden violence. Cerebrovascular damage, psychosis, severe convulsions, and seizures may occur. Seizures are especially grave in the immediate effect, whereas effects from the subcutaneous route occur in minutes, and from snorting, in 30 minutes. After injection, heroin crosses the blood–brain barrier, is converted to morphine, and binds to opiate receptors. Tolerance develops to the euphoric effect, and the chronic user must use more heroin to achieve the same intense effect. Heroin use among teens peaked in the mid-1990s but is resurgent in some suburban communities, as is the use of prescription opioids found in the home. Nationwide 2.9% of high school students report having tried heroin at least once. Highest use is seen in black males, with a growing prevalence in suburban high school students; ranges vary from 0.8% to 5.3% across large urban, suburban, and rural school districts.

**TREATMENT**

Acute agitation and delusional behaviors can be treated with haloperidol or droperidol. Phenothiazines are contraindicated and may cause a rapid drop in blood pressure or seizure activity. Other supportive treatment consists of a cooling blanket for hyperthermia and treatment of the hypertension and arrhythmias, which may respond to sedation with lorazepam or diazepam. For the chronic user, comprehensive cognitive-behavioral interventions have been shown to effective treatment options.

**Bibliography is available at Expert Consult.**

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**Table 114-17 Signs and Symptoms of Intoxication and Withdrawal**

<table>
<thead>
<tr>
<th>Table 114-17</th>
<th>Signs and Symptoms of Intoxication and Withdrawal</th>
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</thead>
<tbody>
<tr>
<td><strong>INTOXICATION</strong></td>
<td><strong>AMPHETAMINES/COCAINE</strong></td>
</tr>
<tr>
<td><strong>Behavior</strong></td>
<td>Apathy and sedation; disinhibition; psychomotor retardation; impaired attention and judgment</td>
</tr>
<tr>
<td><strong>Signs</strong></td>
<td>Drowsiness; slurred speech; pupillary constriction (except anoxia from severe overdosage—dilation); decreased level of consciousness</td>
</tr>
<tr>
<td><strong>Overdose</strong></td>
<td>Respiratory depression; hypothermia</td>
</tr>
<tr>
<td><strong>Withdrawal</strong></td>
<td>Craving to use; lacrimation; yawning; rhinorrhea/sneezing; muscle aches or cramps; abdominal cramps; nausea/vomiting/diarrhea; sweating; dilated pupils; anorexia; irritability; tremor; mood swings; psychomotor retardation or agitation; craving; increased appetite; insomnia or hypersomnia; bizarre or unpleasant dreams</td>
</tr>
</tbody>
</table>

Bibliography


Skin abscesses secondary to unsterile techniques of drug administration are commonly found. There is a loss of libido; the mechanism is unknown. The chronic heroin user may resort to prostitution to support the habit, thus increasing the risk of sexually transmitted diseases (including HIV), pregnancy, and other infectious diseases. Constipation results from decreased smooth muscle propulsive contractions and increased anal sphincter tone. The absence of sterile technique in injection may lead to cerebral microabscesses or endocarditis, usually caused by *Staphylococcus aureus* or *Pseudomonas aeruginosa*. Abnormal serologic reactions are also common, including false-positive Venereal Disease Research Laboratory and latex fixation tests.

**WITHDRAWAL**

After a period of ≥28 hr without heroin, the addicted individual undergoes, during a 24-36 hr period, a series of physiologic disturbances referred to collectively as “withdrawal” or the **abstinence syndrome** (see Table 114-17). The earliest sign is yawning, followed by lacrimation, mydriasis, restlessness, insomnia, “goose flesh,” cramping of the voluntary musculature, bone pain, hyperactive bowel sounds and diarrhea, tachycardia, and systolic hypertension. Although the administration of methadone is the most common method of detoxification, the addition of buprenorphine, an opiate agonist–antagonist, is available for detoxification and maintenance treatment of heroin and other opiates. Buprenorphine has the advantage of offering less risk of addiction and overdose, and withdrawal effects and can be dispensed in the privacy of a physician’s office. Combined with behavioral interventions, it has a greater success rate of detoxification. A combination drug, buprenorphine + naloxone, has been formulated to minimize abuse during detoxification.

**OVERDOSE SYNDROME**

The overdose syndrome is an acute reaction after the administration of an opiate. It is the leading cause of death among drug users. The clinical signs include stupor or coma, seizures, miotic pupils (unless severe anoxia has occurred), respiratory depression, cyanosis, and pulmonary edema. The differential diagnosis includes CNS trauma, diabetic coma, hepatic (and other) encephalopathy, Reye syndrome, as well as overdose of alcohol, barbiturates, PCP, or methadone. Diagnosis of opiate toxicity is facilitated by intravenous administration of the opiate antagonist naloxone, 0.01 mg/kg (2 mg is a common initial dose for an adolescent), which causes dilatation of pupils constricted by the opiate. Diagnosis is confirmed by the finding of morphine in the serum.

**TREATMENT**

Treatment of acute heroin overdose consists of maintaining adequate oxygenation and continued administration of naloxone, a pure opioid antagonist. It may be given intravenously, intramuscularly, subcutaneously, or through the endotracheal tube. Naloxone has an ultrarapid onset of action (1 min) and a duration of action of 20-60 min. If there is no response, other etiologies for the respiratory depression must be explored. Naloxone may have to be continued for 24 hr if methadone, rather than shorter-acting heroin, has been taken. Admission to the intensive care unit is indicated for patients who require continuous naloxone infusions (rebound coma, respiratory depression), and for those with life-threatening arrhythmias, shock, and seizures.

*Bibliography is available at Expert Consult.*

### 114.9 Bath Salts

*Margaret M. Stager*

Bath salts refers to a group of previously OTC, but now illicit, substances containing 1 or more synthetic chemicals similar to cathinone, an amphetamine-like stimulant found in the Khat plant. The bath salts, marketed under brand names such as Ivory Wave, Cloud Nine, or Vanilla Sky, are sold online or in drug paraphernalia stores as a white or brown crystalline powder and can be ingested, inhaled, or injected. The most current information about teen use of bath salts is derived from the 2012 Monitoring the Future survey of 8th, 10th, and 12th grade students, who use at 0.8%, 0.6%, and 1.3%, respectively. The synthetic cathinones found in bath salts include methylene, mephedrone, and 3,4-methylenedioxypyrovalerone (MDPV) all of which are chemically similar to amphetamines and ecstasy (MDMA). The chemicals in bath salts raise brain dopamine levels causing the user to feel a surge of euphoria, increased sociability and sex drive. In addition, the user may experience a surge in norepinephrine, causing reactions such as an elevated heart rate, chest pain, vasoconstriction, diaphoresis, hyperthermia, dilated pupils, seizures, arrhythmias, and high blood pressure. Users also experience psychiatric symptoms such as aggressive behavior, panic attacks, paranoia, psychosis, delirium, self-mutilation, and hallucinations as a consequence of elevations of serotonin. Intoxication from bath salts may cause excited delirium syndrome, which includes dehydration, rhabdomyolysis, and kidney failure. Treatment of overdose should be directed at specific complications but often includes benzodiazepines or propofol for agitation and other neuropsychiatric manifestations. The synthetic cathinones in bath salts are highly addictive, triggering intense cravings in those who consume them frequently. This may result in dependence, tolerance, and strong withdrawal symptoms as seen in other highly addictive substances. The sale of 2 of the synthetic cathinones, mephedrone and MDPV, is illegal in the United States.

*Bibliography is available at Expert Consult.*
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Bibliography


Breast development is often the first visible sign of puberty in the adolescent female. Pediatric practitioners must be able to distinguish normal breast development, including normal variants, from pathologic breast disorders. Visual inspection of the breast tissue should routinely be a component of the young adolescent’s general physical examination. Breast development during puberty is described using the Sexual Maturity Rating (SMR) scale, progressing from SMR 1 to SMR 5 as the breast becomes more mature (see Fig. 110-2 in Chapter 110).

**FEMALE DISORDERS**
See Chapter 551.

**MALE DISORDERS**
Pubertal gynecomastia (see Chapter 585), occurring in up to 60% of normal adolescent males, has long been attributed to a transient imbalance of estrogen and androgen concentrations. Onset typically is between 10 and 13 yr, peaking at SMR 3-4. This physiologic condition usually regresses within 18-24 mo. Careful physical examination is essential to distinguish between true gynecomastia, characterized by a discreet disc of palpable glandular tissue under the nipple–areolar complex, and pseudogynecomastia, characterized by more diffuse adiposity of the anterior chest wall. Reassurance and continued observation are recommended in most cases; surgery may be indicated in severe or persistent cases. No medical therapies for gynecomastia have been approved for use in adolescents by the U.S. Food and Drug Administration. Small, noncontrolled trials of antiestrogens, such as tamoxifen, appear promising, but more evidence is needed. Conditions associated with nonphysiologic gynecomastia include endocrine disorders, liver disease, neoplasms, chronic disease, and trauma. Although
dozens of medications are implicated as possible causes of gyneco-
mastia, convincing evidence exists only for a few, including several
antiandrogens and other exogenous hormones, antiretrovirals, and
histamine-\(_2\)-receptor blockers. Calcium channel blockers, certain anti-
psychotics, and proton pump inhibitors may be causative. Among
drugs of abuse, alcohol and anabolic steroids may be associated with
gynecomastia, but very little evidence supports an association with
marijuana, opiates, or amphetamines.

Other breast pathology in males is uncommon. Benign masses such
as neurofibromas, lipomas, and dermoid cysts have been reported in
the male breast. Males with Klinefelter syndrome have an elevated risk
of breast cancer (see Chapter 583), but this malignancy is otherwise
exceedingly rare in adolescents.

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Bibliography
Menstrual problems vary in presentation. For adolescents with minor variations from normal (Table 116-1), an explanation of symptoms and reassurance of reproductive health may be all that is needed. Severe dysmenorrhea or prolonged menstrual bleeding can be not only frightening, but a cause of persistent morbidity requiring more aggressive management, potentially including referral to a specialist in adolescent gynecology.

NORMAL MENSTRUATION

The average age of menarche, or first menses, varies according to the racial/ethnic background of the population and (possibly) socioeconomic status. There is often a close concordance of the age at menarche between mother and daughter, suggesting that genetic factors are determinants, as well as individual factors such as weight, exercise level, and chronic medical conditions. In the United States, the age of menarche has been relatively stable over the last few decades. The average age at menarche is 12.6 yr for non-Hispanic whites, 12.1 yr for non-Hispanic blacks, and 12.3 yr for Hispanic Americans. Age of menarche has declined in countries and populations experiencing improved nutritional standards and other living conditions. For example, in South Africa, average menarcheal age for blacks has been decreasing at a rate of approximately 0.50 yr/decade compared to an average decline of 0.22 yr/decade for whites.

Menarche typically occurs within 2.5 yr (range: 0.5-3 yr) of the onset of breast budding (thearche), which is the first sign of puberty in most females. Menarche usually occurs during breast sexual maturity rating (SMR; i.e., Tanner) stage 4. Periods gradually become more regular, and by 3 yr after menarche, 90% of females have an average cycle length of between 21 and 45 days. The older the age at which menarche occurs, the longer it takes for consistently ovulatory cycles to be established. However, for most adolescents, by 5-6 yr after menarche, menstrual cycles are similar to that of adults: between 21 and 35 days long with 75% of cycles being ovulatory.

MENSTRUAL IRREGULARITIES

In young adolescents, many variations in menstruation are explained by anovulation that results from immaturity of the hypothalamic-pituitary-ovarian axis that governs menstrual cyclicity. However, organic pathology should be considered and excluded in a logical and cost-effective manner. An accurate menstrual history is an important, but often lacking, first step toward a diagnosis. At the time of menarche, all patients should be encouraged to track their periods, something several free smart phone and tablet applications can facilitate.

Previously, a range of terms have been used to describe abnormal menstrual bleeding. These include menorrhagia to indicate regularly occurring bleeding that was excessive in amount or duration, and metrorrhagia to indicate irregular bleeding between periods. Such terms are imprecise, confusing, and not linked to any specific underlying pathology. Abnormal uterine bleeding (AUB) is the preferred term for uterine bleeding that is abnormal in regularity, volume, frequency, or duration. AUB is further specified by adding terms that describe the bleeding as heavy menstrual bleeding, or intermenstrual bleeding. A qualifying letter is added to indicate the etiology of the abnormal bleeding. Of the nine categories of etiologies, the three most relevant to adolescents are ovulatory dysfunction (AUB-O), previously referred to as dysfunctional uterine bleeding, discussed in Chapter 116.2, coagulopathy (AUB-C), and not yet classified (AUB-N).

In addition to a standard medical history noting hospitalizations, chronic illness, and medication use, a complete history for evaluating a patient with menstrual irregularity should include: the timing of pubertal milestones, such as onset of pubic and axillary hair and breast development; a detailed patient menstrual history; age of menarche and overall menstrual pattern of mother and sisters; and a family history of gynecologic problems. The complete review of systems should elicit any changes in headache pattern or vision; the presence of galactorrhea; and any changes in skin, hair, or bowel patterns. Changes in diet, level of exercise, and sports participation are also important factors when generating a differential diagnosis. As with all adolescent visits, the patient should be interviewed alone and the confidential history should assess substance use, consensual sexual activity, forced sexual behavior, abuse, and other psychosocial stressors.

In addition to the basic growth parameters of weight, height, blood pressure, heart rate, and body mass index, a careful review of the patient’s growth chart is indicated. Physical exam should document SMR; signs of androgen excess, such as hirsutism or severe acne; and signs suggestive of an eating disorder (see Chapter 28), such as lanugo or knuckle calluses. A careful external genital examination should be performed, but in the absence of sexual activity, an internal pelvic examination is rarely necessary. If being considered for the young adolescent, an internal exam should be performed by someone with expertise in this age group using proper equipment and technique. Trans-abdominal pelvic ultrasound can be a useful adjunct for evaluating anatomic abnormalities in the adolescent.

Bibliography is available at Expert Consult.

116.1 Amenorrhea

Gina S. Sucato and Gale R. Burstein

Amenorrhea, the absence of menstruation, generally requires evaluation if there has been no menstruation within 4 yr of the onset of

### Table 116-1 Characteristics of Normal Menses

<table>
<thead>
<tr>
<th>Description</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cycle length</td>
<td>21-35 days from the 1st day of one period to the 1st day of the next (during 1st 3 yr after menarche can be 21-45 days)</td>
</tr>
<tr>
<td>Duration of menses</td>
<td>7 or fewer days</td>
</tr>
<tr>
<td>Blood flow</td>
<td>6 or fewer (soaked) pads or tampons per day</td>
</tr>
</tbody>
</table>

*Adolescents with 2 or more cycles outside this range or who skip their period for 3 consecutive mo warrant more thorough evaluation.*
Bibliography
puberty (primary amenorrhea), or for the length of 3 previous cycles in a postmenarchal patient (secondary amenorrhea). However the following caveats exist: Lack of any pubertal signs by age 13 yr in a girl should prompt evaluation for pubertal delay, and in sexually active patients, or those with other symptoms suggesting pathology, evaluation should be initiated without waiting for 3 missed cycles. The evaluation of a patient presenting with amenorrhea should begin by ascertaining whether she has ever had any previous menstrual bleeding. Some aspects of the evaluation of both primary and secondary amenorrhea are identical; entities that can interrupt the menstrual cycle can also prevent menarche. However, in females with primary amenorrhea consideration must also be given to the possibility of genetic and anatomic conditions.

The differential diagnosis of amenorrhea is broad (Table 116-2) and requires a careful history and physical exam to guide any necessary diagnostic studies. Key to the evaluation is understanding the timing and tempo of the patient's pubertal milestones. Age 15 yr is commonly considered the age at which an evaluation for primary amenorrhea should be undertaken. Evaluation should begin sooner if 4 yr have elapsed since the onset of puberty (breast development in most females). Conversely, expectant management with close follow-up can be considered in a patient whose history, physical (showing some signs of pubertal development), and family history suggest constitutional delay of puberty. When a patient presents with primary amenorrhea, genetic and anatomic conditions are added to the differential diagnosis (Table 116-3).

**HISTORY AND PHYSICAL EXAMINATION**

Important elements of the history include dietary intake, exercise level, and a thorough review of any ongoing symptoms, including fever, headache, vision changes, chronic respiratory or gastrointestinal complaints, changes in bowel history, galactorrhea, changes in hair or nails, excessive body hair, severe acne, unexplained musculoskeletal complaints, and changes in vaginal discharge (which can disappear in females who are hypoestrogenic for reasons such as poor caloric intake). Any underlying medical conditions and the adequacy of their control should be noted, as well as the presence of any known renal or skeletal anomalies, which can be associated with reproductive system anomalies. Medications, particularly those for psychiatric conditions, should be documented. Family history of menarchal age, eating disorders (see Chapter 28), and polycystic ovary syndrome (PCOS; see Chapter 552) should be elicited. A thorough social history is necessary, especially concerning the presence or absence of sexual activity or abuse (see Chapter 40).

Physical examination should begin with careful attention to growth chart trajectories. In addition to a search for undiagnosed systemic disease, clues to an eating disorder, thyroid disease, or hyperandrogenism should be sought. The exam should assess for body mass index, orthostatic pulses, blood pressure, abnormal dentition, anosmia or hyposmia (suggestive of Kallmann syndrome; see Chapter 583.2), parotid enlargement, thyroid gland palpation, hepatosplenomegaly or other abdominal mass, lymphadenopathy, presence or absence of breast tissue (by palpation not inspection) and SMR (see Chapter 110). Skin exam should note any lanugo, dry or doughy skin, loss of hair from scalp or eyebrows, striae, acne, or the presence of other stigmata associated with PCOS (rapid pubertal development, hirsutism, or physical stigmata). The genital exam should note SMR and appearance of the vagina which should be pink and moist; thin, dry and reddened mucosa suggests estrogen deficiency. The clitoral width should be < 1 cm. In the patient with primary amenorrhea, vaginal patency can be assessed painlessly using a slender saline-moist swab (e.g., a urethral swab) and careful avoidance of the hymen. If physical exam assessment of the cervix and uterus is not tolerated, a pelvic ultrasound is advisable in patients with primary amenorrhea.

**LABORATORY STUDIES**

Diagnostic tests in the patient presenting with amenorrhea should be tailored to her history and physical exam (Table 116-4). However, a urine pregnancy test, serum levels of prolactin, thyroid-stimulating hormone, and follicle-stimulating hormone (FSH) are reasonable to measure in all patients (Fig. 116-1). Elevation of FSH (> 30 mIU/mL) in an amenorrheic female suggests ovarian insufficiency, and, if confirmed with repeat testing, should be followed with a pelvic ultrasound, karyotype, and specialist referral.

In patients with signs of androgen excess (e.g., severe acne or hirsutism) or physical stigmata associated with PCOS (rapid pubertal weight gain, acanthosis nigricans) consider measuring levels of 17-hydroxyprogesterone (17-OHP) (morning, in the follicular/preovulatory phase), free and total testosterone, dehydroepiandrosterone sulfate (DHEAS), and androstenedione. PCOS affects approximately 5% of premenopausal females; diagnostic criteria for adolescents are controversial but include variations of menstrual irregularity (ranging from amenorrhea to dysfunctional uterine bleeding), polycystic ovarian morphology identified on ultrasound, and physical or biochemical evidence of androgen excess.

With the exceptions of pregnancy, constitutional delay and imperforate hymen, conditions that cause primary amenorrhea limit fertility and diagnosis may cause profound emotional responses in patients and

<table>
<thead>
<tr>
<th>Table 116-2 Causes of Amenorrhea (Primary or Secondary)</th>
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</thead>
<tbody>
<tr>
<td>Pregnancy (regardless of history can cause primary or secondary amenorrhea)</td>
</tr>
<tr>
<td>Functional hypothalamic causes (stress, weight loss, undereating, high levels of exercise, energy deficit even at normal weight)</td>
</tr>
<tr>
<td>Female athlete triad (low energy availability, amenorrhea, and low bone density)</td>
</tr>
<tr>
<td>Eating disorders</td>
</tr>
<tr>
<td>Premature ovarian insufficiency (autoimmune, idiopathic, galactosemia, or secondary to radiation or chemotherapy)</td>
</tr>
<tr>
<td>Hypothalamic and/or pituitary damage (e.g., irradiation, tumor, traumatic brain injury, surgery, hemochromatosis, midline central nervous system defects such as septo-optic dysplasia, and autoimmune pituitary hypophysitis)</td>
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<tr>
<td>Thyroid disease (hyper- or hypo-, although the latter usually associated with increased bleeding)</td>
</tr>
<tr>
<td>Prolactinoma</td>
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<tr>
<td>Systemic disease (e.g., inflammatory bowel disease, cyanotic congenital heart disease, sickle cell disease, cystic fibrosis, celiac disease)</td>
</tr>
<tr>
<td>Hyperandrogenism (polycystic ovary syndrome, nonclassic congenital adrenal hyperplasia, adrenal tumor or dysfunction)</td>
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<td>Drugs and medications (e.g., illicit drugs, atypical antipsychotics, hormones)</td>
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<td>Turner syndrome mosaicism</td>
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<table>
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<tr>
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<tr>
<td>Physiologic/constitutional delay</td>
</tr>
<tr>
<td>Anatomic abnormalities</td>
</tr>
<tr>
<td>Müllerian agenesis</td>
</tr>
<tr>
<td>Imperforate hymen</td>
</tr>
<tr>
<td>Transverse vaginal septum</td>
</tr>
<tr>
<td>Genetic disorders</td>
</tr>
<tr>
<td>46 XY disorders of sexual development (e.g., androgen insensitivity syndrome, 5α-reductase deficiency and 17α-hydroxylase deficiency)</td>
</tr>
<tr>
<td>Mixed gonadal dysgenesis (associated with a number of different chromosome patterns)</td>
</tr>
<tr>
<td>Turner syndrome (resulting from 45X or a variety of mosaic or other abnormal karyotypes)</td>
</tr>
<tr>
<td>Genetic hypogonadotropic hypogonadism (e.g., X-linked Kallmann syndrome)</td>
</tr>
</tbody>
</table>
families. Thus, before ordering studies to confirm these diagnoses (e.g., karyotype, MRI of reproductive anatomy) the clinician should carefully consider the implications and be prepared to refer to specialists with experience managing the long term treatment of such diagnoses with families.

In patients presumed to have hypothalamic amenorrhea on the basis of a low FSH and prepubertal baseline ultrasensitive assay for lutetizing hormone, and consistent history and physical, MRI of the brain is not necessary in all patients. However, MRI should be considered for patients presenting with a headache history that is a change from baseline; persistent emesis; change in thirst, urination, or vision; elevated prolactin or galactorrhea; or other neurologic symptoms.

**TREATMENT**

Treatment for amenorrhea varies widely depending upon the underlying cause. Many diagnoses require referral to clinicians in specialties such as endocrinology, adolescent medicine, gynecology, and other surgical subspecialists, and often collaboration with other disciplines such as psychology or nutrition is indicated. For patients with PCOS, the mainstay of treatment is lifestyle modifications and suppression of ovarian androgens (typically with combined oral contraceptive [COC] pills, i.e., estrogen and progestin). Many patients benefit from the addition of metformin and spironolactone as an androgen receptor blocker; all require ongoing monitoring of lipids and periodic screening with an oral glucose tolerance test as a result of the high prevalence of metabolic syndrome in PCOS. For patients with eating disorders or other conditions of energy imbalance that render them hypoestrogenic, normalizing weight and improving nutritional status are the keys to treatment; whether exogenous hormones will adequately protect bone health in these patients is unproven. For females with amenorrhea based on ovarian insufficiency (or absence) exogenous hormones are required for all pubertal development. Experts recommend starting at age 10-12 yr with low-dose transdermal estrogen, progressing to increased doses of estrogen and cyclic progestin, and then continuing maintenance therapy with higher dose combination products such as those found in typical combined hormone contraceptive pills, patches and rings.

For patients with secondary amenorrhea, use of hormones to bring on monthly bleeding (for example with combined hormonal contraception) in the absence of a clear indication (such as PCOS or contraception) is not recommended as doing so will mask the patient’s subsequent menstrual pattern. However, in those patients with normal postpubertal estrogen levels progesterone can be useful to periodically (every 4-12 wk) induce shedding of the endometrial lining to avoid build up and subsequent heavy menses. One commonly used regimen is medroxyprogesterone 10 mg daily for the 1st 12 days of the month.

**116.2 Abnormal Uterine Bleeding (AUB)**

AUB is a broad term used to describe any pattern that is outside what is considered physiologic. Clinicians are encouraged to categorize the abnormal pattern based on the patient’s complaint, which will usually be menses that are irregular (AUB/IMB: intermenstrual bleeding) or heavy (AUB/HMB: heavy menstrual bleeding).

**IRREGULAR MENSTRUAL BLEEDING**

The American Academy of Pediatrics advocates treating menstrual status as a vital sign at routine visits. Although menses are frequently irregular in the early postmenarchal years, further evaluation is necessary when menstrual patterns vary too widely from what is normal for age. Even in the first postmenarchal year, menses should not be less frequent than every 45 days. Menses become increasingly regular with age, and by 3 yr postmenarche are typically 21-35 days long, lasting 3-7 days. An adolescent’s personal cycle duration is usually established by age 19 or 20 yr.

Adolescents rarely present with complaints of unusually short or light menses. However, those females, along with those with infrequent menses, should be evaluated similarly to females presenting with secondary amenorrhea. Females whose menses are excessive are much more likely to come to attention for AUB.

In the early postmenarchal years, the most common cause of AUB in adolescents is anovulation because of immaturity of the hypothalamic-pituitary-ovarian axis. In the absence of a midcycle surge of lutetizing hormone to stimulate ovulation, there is no corpus luteum production of progesterone. Without the stabilizing effects of progesterone on the endometrial lining there is increased risk of irregular bleeding. Irregular bleeding because of anovulation, in the absence

**Figure 116-1 Initial diagnostic testing to evaluate amenorrhea**

**Table 116-4 Laboratory Tests to Evaluate Patients with Abnormal Uterine Bleeding**

<table>
<thead>
<tr>
<th>Test</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete blood count with platelets</td>
<td>Urine pregnancy test (regardless of history)</td>
</tr>
<tr>
<td>Complete blood count with platelets</td>
<td>Sexually transmitted infections testing</td>
</tr>
<tr>
<td>Prothrombin and partial thromboplastin times</td>
<td>von Willebrand factor antigen, ristocetin cofactor, factor VIII* activities</td>
</tr>
<tr>
<td>Liver, kidney, and thyroid function studies</td>
<td>Liver, kidney, and thyroid function studies</td>
</tr>
<tr>
<td>Total and free testosterone</td>
<td>Pelvic ultrasound (if diagnosis is elusive or anatomic abnormality suspected)</td>
</tr>
</tbody>
</table>

*A Any abnormalities should be followed with a ristocetin-induced platelet aggregation and von Willebrand factor multimers. Testing in the 1st 3 days of menses and before any estrogen treatment is started minimizes the chances of false-negative tests. Repeat testing can be warranted in patients for whom there is a high pretest suspicion.

† In patients with signs or symptoms suggestive of PCOS, such as acne, hirsutism, obesity, acanthosis nigricans, and a history of infrequent menses.
Bibliography


HEAVY AND PROLONGED MENSTRUAL BLEEDING

Irregular bleeding (Table 116-5), particularly that resulting from anovulation, can be long and heavy. However, in patients who have regular, cyclic menses that are long and/or heavy, a hematologic cause should be strongly considered, particularly if menses are heavy from the onset of menarche, or if bleeding is severe enough to warrant hospitalization. In such patients, prevalence estimates for von Willebrand disease (see Chapter 477) and platelet functions disorders (see Chapter 484) range as high as 36% and 44%, respectively. These patients may also report flooding (changing a pad or tampon more than hourly), passing clots larger than an inch in diameter, menses longer than 7 days, a history of hemorrhagic ovarian cysts, excessive bleeding from wounds or postoperatively, and 1st-degree relatives with heavy menses or epistaxis requiring medical treatment.

LABORATORY FINDINGS

Table 116-4 lists laboratory tests to be considered in patients with long heavy bleeding. Females with persistent heavy bleeding despite negative testing should be referred to a hematologist for testing for platelet function disorders, factor deficiencies and other less common disorders. In the initial evaluation, the hemoglobin is the key element as it establishes the severity of the bleeding: mild (hemoglobin > 10 g/dL), moderate (hemoglobin 8-10 g/dL), or severe (hemoglobin < 8 g/dL).

TREATMENT

In mild cases, iron supplementation is recommended, and the patient should keep a menstrual calendar to follow the subsequent flow patterns. Nonsteroidal antiinflammatory drugs (e.g., naproxen) are more effective than placebo in treating heavy bleeding and also would help any concurrent dysmenorrhea. Active bleeding typically responds well to cycling with any COC (i.e., estrogen and progestin) starting with twice-daily dosing if needed until bleeding stops. Patients with estrogen contraindications can be treated with progestins alone, for example, medroxyprogesterone or norethindrone acetate 10 mg orally per day, either continuously or for 12 days per month. The latter regimen will be followed by monthly bleeding.

Table 116-5 Causes of Irregular Menstrual Bleeding

<table>
<thead>
<tr>
<th>CAUSES OF AUB</th>
<th>EXAMPLES</th>
<th>FEATURES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immature hypothalamic-pituitary-ovarian axis (AUB-O)</td>
<td>Patient within 2 yr of menarche; patient more than 2 yr postmenarche but with history of later menarche</td>
<td>Painless, responds to hormonal treatment</td>
</tr>
<tr>
<td>Weight changes, disordered eating, or excessive exercise</td>
<td>Anorexia nervosa, bulimia, weight gain or loss of more than 10 pounds from any etiology</td>
<td>Weight loss more commonly results in lighter, less frequent menses</td>
</tr>
<tr>
<td>Endocrinologic causes</td>
<td>Thyroid disease, PCOS</td>
<td>Bleeding typically increases with hypothyroidism and decreases with PCOS and hyperthyroidism</td>
</tr>
<tr>
<td>Complication of pregnancy</td>
<td>Threatened abortion, postpartum or postabortal endometritis</td>
<td>History of sexual activity and/or pregnancy</td>
</tr>
<tr>
<td>Infection</td>
<td>Cervicitis, condyloma, pelvic inflammatory disease</td>
<td>Bleeding usually not heavy, may occur with sexual intercourse</td>
</tr>
<tr>
<td>Trauma</td>
<td>Sexual assault, bicycle accidents</td>
<td>History will be evident in patients of menstruating age unless there is cognitive disability</td>
</tr>
<tr>
<td>Vaginal foreign body</td>
<td>Toilet paper, broken condoms, tampons</td>
<td>Associated with odor and vaginal discharge, but usually not heavy bleeding</td>
</tr>
<tr>
<td>Hematologic causes</td>
<td>von Willebrand disease, platelet function disorder, thrombocytopenia (idiopathic thrombocytopenic purpura, drug induced) hemophilia carriage, clotting factor deficiency, leukemia</td>
<td>Bleeding is heavy and/or long and frequently regular, may present at menarche, may be accompanied by a suggestive family history (hysterectomies or uterine ablation, or cautery for epistaxis) or physical exam (ecchymoses, petechiae)</td>
</tr>
<tr>
<td>Medications</td>
<td>Estrogens, progestins, (in pills, patches, rings, injections, implants, and intrauterine devices) androgens, drugs that cause prolactin release (estrogens, phenothiazines, tricyclic antidepressants, metoclopramide), and anticoagulants (heparin, warfarin, aspirin, and nonsteroidal antiinflammatory drugs), and selective serotonin reuptake inhibitors</td>
<td>Affect the hypothalamic-pituitary-ovarian axis, endometrial lining, platelets, or coagulation pathway</td>
</tr>
<tr>
<td>Anatomic</td>
<td>Partial obstruction of vagina or uterus causing asynchronous bleeding, cervical or endometrial polyps or myomas, hemangioma, uterine vascular malformation, genital/reproductive tract cancer</td>
<td>Most of these entities are extremely rare, especially reproductive tract cancers</td>
</tr>
<tr>
<td>Systemic disease</td>
<td>Celiac disease, rheumatoid arthritis, Ehlers-Danlos syndrome</td>
<td>Accompanied by other signs of the condition</td>
</tr>
</tbody>
</table>
With moderate anemia, any of the hormonal regimens above can be used. However, it may be necessary to start with 3-4 COC (or 3-4 doses of medroxyprogesterone 10 mg) per day and taper to daily dosing over the next 2 wk. Patients with ongoing rapid bleeding, syncope or lightheadedness, or hemodynamic instability should be treated in the hospital, as should patients with a hemoglobin of <7-8 g/dL.

Patients with severe anemia should be treated with 1 of the hormone tapers described above, in addition to fluid or blood products as indicated; it is advisable to draw necessary laboratory studies prior to transfusion. Patients with emesis or other significant symptoms may be treated initially with conjugated estrogens 25 mg intravenously every 4-6 hr for 1-2 days. A COC or progestin regimen should be added within the 1st day as progestin is needed to stabilize the endometrial lining and can be used as maintenance therapy after hospital discharge. In the exceptionally rare case of a patient whose bleeding cannot be controlled hormonally, options for gynecologic interventions include intrauterine Foley balloon placement or uterine packing to tamponade the uterus mechanically. Dilation and curettage, performed frequently in adult women, is almost never indicated in adolescents.

Hormonal treatment for AUB should continue for at least 3-6 mo—depending on the patient’s age, prior menstural history, and severity of presentation—before reassessing the need for ongoing therapy. Additional options for maintenance therapy include combined hormonal transdermal patches and vaginal rings, depomedroxyprogesterone acetate 150 mg IM every 3 mo, and placement of a levonorgestrel intrauterine device, depending on the patient’s concurrent need for long-term contraception. For those patients who choose to avoid (or augment) hormonal therapy, tranexamic acid 1,300 mg orally 3 times daily can be used for up to the 1st 5 days of menses. This medication, new to the United States, has been available in other countries for years. Nonetheless, published data in young adolescents remain sparse, and the clinical significance of the theoretic increased risk of thrombosis when used in conjunction with hormonal treatment is yet to be determined.

For young women with bleeding disorders, formulation of a long-term treatment plan is best done in collaboration with the patient’s hematologist. Females with a known bleeding disorder may be up to 5 times more likely to develop heavy menstrual bleeding. Therefore, it can be helpful while the patient is still premenarchal to proactively put a plan in place in the event of acute heavy menstrual bleeding which can occur with a patient’s first menstrual period.

Bibliography is available at Expert Consult.

116.3 Dysmenorrhea

Gina S. Sucato and Gale R. Burstein

Dysmenorrhea, painful uterine cramps that precede and accompany menses, occur in up to 93% of adolescent females based on studies from around the world. Dysmenorrhea is severe enough to interfere with school and other activities in approximately 10% of adolescents in the United States. Yet many adolescents undertreat their symptoms, and fewer still seek medical care for relief.

Dysmenorrhea may be primary or secondary. Primary dysmenorrhea, characterized by the absence of any specific pelvic pathologic condition, is by far the more commonly occurring form, accounting for approximately 90% of cases. After ovulation, withdrawal of progesterone results in synthesis of prostaglandins by the endometrium, which stimulate local vasoconstriction, uterine ischemia and pain, and smooth muscle contraction, explaining both uterine and gastrointestinal symptoms. Because of the association with ovulation, primary dysmenorrhea typically presents at least 12 mo after menarche.

Secondary dysmenorrhea results from underlying pathology such as anatomic abnormality, or infection such as pelvic inflammatory disease. However, the most common cause of secondary dysmenorrhea in adolescents is endometriosis, a condition in which implants of endometrial tissue are found outside the uterus, most commonly near the fallopian tubes and ovaries. Often there are other family members with endometriosis. Although characteristically there is severe pain at the time of menses, adolescents can present with noncyclic pain as well.

Although primary dysmenorrhea is almost always the cause, a careful history and physical examination is required for adolescents who present with pelvic pain. An internal pelvic exam is not required in females who are not sexually active and whose presentation is consistent with primary dysmenorrhea. Constipation can vary cyclically in many females, especially those with irritable bowel syndrome, and often significantly contributes to the pain. Mittelschmerz, brief severe

| Table 116-6 Differential Diagnosis of Dysmenorrhea in Adolescents (Red Flags Indicated in Bold) |
|-----------------------------------------------|---------------------------------------------------------------|
| **PRESENTATION**                               | **DIAGNOSIS**                                                  |
| Primary                                       | Normal physical exam; internal exam only for sexually active adolescents. Ultrasound can be reserved for those patients with atypical presentations (e.g., onset at menarche) or those whose pain does not respond to NSAIDs and hormonal therapy |
| Endometriosis and adenomyosis                 | Increased risk in patients with obstructive anomalies and possibly bleeding disorders; however, most teenagers with endometriosis have normal anatomy and bleeding indices; diagnosis is made visually during surgery. Found in up to 69% of adolescents who underwent laparoscopy for persistent pelvic pain |
| Mullerian anomalies with partial outflow obstruction | Pelvic ultrasound will demonstrate uterine anomalies (e.g., rudimentary uterine horn); MRI may be required to identify some lesions (e.g., obstructed hemivagina). Found in 8% of adolescents who underwent laparoscopy for persistent pelvic pain |
| Pelvic inflammatory disease                   | Clinical diagnosis made by findings of uterus or adnexal tenderness on bimanual pelvic examination (see Chapter 120); supporting features include dysuria, vaginal discharge, fever, and increased white blood cell count |
| Pregnancy complication                       | Urine hCG-positive                                             |

hCG, human chorionic gonadotropin; NSAIDs, nonsteroidal antiinflammatory drugs.
Bibliography


Table 116-7  Treatment for Dysmenorrhea

<table>
<thead>
<tr>
<th>MEDICATION</th>
<th>REGIMEN</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSAIDs for up to 5 days</td>
<td>Ibuprofen, 200 mg Naproxen sodium, 275 mg Celecoxib (cylooxygenase [COX]-2 inhibitor)*</td>
<td>2 tablets PO q 4-6 hr 550 mg loading dose then 275 mg PO q 6 hr 400 mg then 200 mg PO q 12 hr pm pain</td>
</tr>
<tr>
<td>Hormonal contraception</td>
<td>Combined oral contraceptive pills or vaginal ring Progestin-only methods</td>
<td>Continuous hormone regimens (as opposed to the standard 21 hormone days followed by 7 placebo days) may offer better relief but increase the risk of intermenstrual bleeding DMPA 150 mg IM or 104 mg SC q 3 mo, levonorgestrel intrauterine device for up to 5 yr, etonogestrel implant for up to 3 yr</td>
</tr>
<tr>
<td>Gonadotropin-releasing hormone agonist</td>
<td>Depot leuprolide</td>
<td>11.25 mg IM q 3 mo</td>
</tr>
</tbody>
</table>

*FDA-approved for patients older than 18 yr. Should be used with caution in patient with impaired renal or liver dysfunction, heart failure, a history of gastrointestinal bleeding or ulcer. Full prescribing information can be found at: [http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/020998s033,021156s003lbl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/020998s033,021156s003lbl.pdf). DMPA, depomedroxyprogesterone acetate; IM, intramuscular; LARC, long-acting reversible contraceptive; NSAIDs, nonsteroidal antiinflammatory drugs.

Pain with ovulation, occurs at midcycle and can explain what initially appeared to be noncyclic pelvic pain. Table 116-6 lists the red flags for secondary dysmenorrhea. Ovarian cysts, a frequent concern of families, are usually transient and painless.

Treatment for primary dysmenorrhea is aimed at decreasing levels of prostaglandins, preferably before they are produced. Thus, the mainstay of treatment is with prostaglandin synthetase inhibition by either nonsteroidal antiinflammatory drugs, hormonal contraception, or a gonadotropin-releasing hormone agonist (Table 116-7) beginning at, or preferably the day prior to, menstruation. The high doses of around the clock treatment are rarely needed for more than the 1st 2 days. More data are needed to make specific treatment recommendations regarding exercise, but females should be reassured that participation in usual sports and extracurricular activities is not only permissible but a benchmark of adequate treatment.

For those adolescents whose pain does not respond to optimally dosed nonsteroidal antiinflammatory drugs, or who also require contraception, all of the currently available forms of hormonal contraception will improve dysmenorrhea. A number of trials have investigated adjuvant treatments including heat, aromatherapy, acupressure, acupuncture, transcutaneous nerve stimulation, herbal remedies, yoga, and dietary supplements; however, the mainstay second-line treatment is hormones. The mechanisms are not fully delineated but are presumed to include elimination of progestosterone production from the corpus luteum for those methods that prevent ovulation, and decreased prostaglandin production from the diminished endometrial lining. Up to 3 cycles may be required to appreciate the full benefit. Methods and regimens that eliminate a placebo interval may provide better relief. Females whose pain persists despite more than 3 mo of adequate hormonal therapy require further evaluation and treatment.

_Bibliography is available at Expert Consult._

### 116.4 Premenstrual Syndrome and Premenstrual Dysphoric Disorder

_Gina S. Sucato and Gale R. Burstein_

Premenstrual dysphoric disorder (PMDD) is a depressive disorder that is distinguished from other depressive disorders by its timing. Symptoms of anxiety and depressed mood begin in the luteal phase of the menstrual cycle (i.e., in the second half, after ovulation) and improve within a few days after the onset of menses. PMDD causes significant distress and functional impairment and may be accompanied by physical and behavioral symptoms. PMDD occurs in 2-6% of menstruating females worldwide. Based on a large body of scientific evidence, it has been included in the _Diagnostic and Statistical Manual of Mental Disorders_ (DSM) V (Table 116-8) as a distinct, treatment-responsive, depressive disorder. It is distinguished from premenstrual syndrome (PMS), which has similar timing and occurs in up to 30% of adolescents, by the severity and consequences of the affective symptoms. Premenstrual symptoms are precipitated by ovulation; symptoms recur in the luteal phase and should disappear at the end of menstruation.

Validated tools to screen for severe PMS and PMDD exist; up to half of females who report PMS do not meet diagnostic criteria when symptoms are rated prospectively. Consequently, use of a menstrual calendar to prospectively document symptoms is necessary, as it is important to distinguish PMDD from anxiety, depression, or another mental health disorder the symptoms of which are exacerbated cyclically but occur throughout the cycle.

Treatment success is gauged by improvement in patient symptoms. In mild cases of PMS, adolescents may have adequate relief following education about the relationship of symptoms to the menstrual cycle and instruction on stress management techniques, including exercise. There is not strong evidence supporting the effectiveness of most COC pills for PMS, particularly in adolescents. However, some experts suggest this treatment option for those patients who also have dysmenorrhea or contraceptive needs.

The treatment option with the most supportive evidence is use of selective serotonin reuptake inhibitors, which are first-line therapy for adult women with severe PMS and PMDD. In contrast to the treatment of depression, selective serotonin reuptake inhibitors can be rapidly effective for PMDD, and thus can be prescribed either continuously or intermittently, beginning at ovulation (or whenever in the luteal phase symptoms begin) and ending when symptoms resolve. Adolescents can be prescribed the standard doses used for adults, for example, fluoxetine 10-20 mg orally daily. Among the many dietary supplements that have been studied, the best evidence is for supplementation with calcium 1,200 mg in 3 divided doses to treat both mood and pain symptoms.

_Bibliography is available at Expert Consult._
Bibliography


Bibliography


Table 116-8  Criteria for Premenstrual Dysphoric Disorder

A. In the majority of menstrual cycles, at least 5 symptoms must be present in the final week before the onset of menses, start to improve with a few days after the onset of menses, and become minimal or absent in the week postmenses.

B. One (or more) of the following symptoms must be present:
   1. Marked affective lability (e.g., mood swings; feeling suddenly sad or tearful, or increased sensitivity to rejection).
   2. Marked irritability or anger or increased interpersonal conflicts.
   3. Marked depressed mood; feelings of hopelessness, or self-deprecating thoughts.
   4. Marked anxiety, tension, and/or feelings of being keyed up or on edge.

C. One (or more) of the following symptoms must additionally be present, to reach a total of 5 symptoms when combined with symptoms from criterion B above.
   1. Decreased interest in usual activities (e.g., work, school, friends, hobbies).
   2. Subjective difficulty in concentration.
   3. Lethargy, easy fatigability, or marked lack of energy.
   4. Marked change in appetite; overeating; or specific food cravings.
   5. Hypersomnia or insomnia.
   6. A sense of being overwhelmed or out of control.
   7. Physical symptoms such as breast tenderness or swelling, joint or muscle pain, a sensation of “bloating,” or weight gain.

*Note:* The symptoms in criteria A-C must have been met for most menstrual cycles that occurred in the preceding year.

D. The symptoms are associated with clinically significant distress or interference with work, school, usual social activities, or relationships with others (e.g., avoidance of social activities; decreased productivity and efficiency at work, school, or home).

E. The disturbance is not merely an exacerbation of the symptoms of another disorder, such as major depressive disorder, panic disorder, persistent depressive disorder (dysthymia), or a personality disorder (although it may co-occur with any of these disorders).

F. Criterion A should be confirmed by prospective daily ratings during at least two symptomatic cycles. (*Note:* The diagnosis may be made provisionally prior to this confirmation).

G. The symptoms are not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication, other treatment) or another medical condition (e.g., hyperthyroidism).

*From the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (Copyright 2013). American Psychiatric Association, pp. 171-172.*
The untoward consequences of sexual activity (sexually transmitted infections [STIs; see Chapter 120], and early, unintended pregnancy [see Chapter 118]) all too often are experienced by adolescents. Adolescents often do not seek reproductive healthcare for 6-12 mo after initiating sex; many will become pregnant and/or acquire an STI during this interval. Appropriate counseling and educational interventions with adolescents, including the healthcare provider raising the topic of prevention, can decrease sexual risk behavior; youth who plan sexual initiation (as opposed to "it just happened") are 75% more likely to use contraception at sexual debut.

**Epidemiology**

**Sexual Activity**

According to the Youth Risk Behavior Surveillance System 2011, almost half (47.4%) of U.S. high school students had ever had sexual intercourse and one-third reported being currently sexually active (had sexual intercourse with at least 1 person during the 3 mo before the survey).

Although U.S. teens and European teens have similar levels of sexual activity and ages of sexual debut, U.S. teens are less likely to use contraception and less likely to use the most effective methods. Teen pregnancy rates have been declining worldwide as a result of delayed initiation of sexual activity and increased contraceptive use. Despite declines, the U.S. still had the highest 2010 teen birth rate in the Western industrialized world with 34 live births per 1,000 females 15-19 yr old (Fig. 117-1). That is nearly 2 times higher than the 2010 teen birth rate in Ireland, which has the highest rate in Western Europe, and almost 10 times higher than the lowest rate in Switzerland. Of the 750,000 teen pregnancies in the United States in 2008, 31% ended in abortion. More than 80% of these pregnancies are unintended, indicating a remaining unmet need for reliable, effective contraception that teens will consistently use.

**Contraceptive Use**

According to the National Survey of Family Growth, 2006-2010, virtually all sexually experienced teens have used some method of contraception in the past. The most commonly used method is the condom, followed by withdrawal and then the pill. Use of contraception at first sex has greatly increased over the last 50 yr and the condom is currently the most common method used at first sex, as reported by more than 75% of males and females. Factors increasing contraception use at first sex include increasing age among teens up to age 17 yr; time in college; and planning their sexual debut (75% more likely to have used contraception than those who did not plan it).

To decrease rates of unintended pregnancy, more teens must use most or moderately effective contraception consistently and correctly.
Effectiveness of Family Planning Methods

The CDC Effectiveness of Contraceptive Methods Chart illustrates a tiered system of most effective (Tier 1), moderately effective (Tier 2), and least effective (Tier 3) methods (Fig. 117-2). Tier 1 methods include those with failure rates of less than 1 pregnancy per 100 women in a year of typical use. Tier 2 methods have failure rates of 6-12 pregnancies per 100 women in a year of typical use, and Tier 3 methods have failure rates of 18 or more pregnancies per 100 women per year of typical use.

More than half of sexually experienced female teens are currently using most effective or moderately effective contraceptive methods, such as an intrauterine device (IUD) or contraceptive implant, oral contraceptive pills, the contraceptive patch, the vaginal ring, an injectable contraception, or, rarely, sterilization. U.S. teens’ use of hormonal methods at last intercourse is less frequent compared to teens in other developed countries; 52% of U.S. teens, 56% of Swedish 18-19 yr olds, 67% of French 15-19 yr olds, 72% of British 16-19 yr olds, and 73% of Canadian 15-19 yr olds use hormonal methods. A higher likelihood of female current contraceptive use is associated with older age at sexual initiation, aspirations for higher academic achievement, acceptance of one’s own sexuality, and a positive attitude toward contraception. Condom use should also be encouraged along with effective contraception, preferably Tier 1 or 2, for dual protection against pregnancy and STIs. Only 12% of sexually active female teens who are using a most effective or moderately effective method are using condoms as well.

Contraceptive Counseling

The health screening interview during the adolescent preventive visit offers opportunities to identify and discuss unsafe sexual practices among sexually active adolescents and to identify and reinforce safe sexual behaviors including abstinence (see Chapter 112). Adolescents with medical conditions, either chronic or acute, are particularly vulnerable to having sexual and reproductive health omitted from their visits (see Chapters 42 and 717). Their comorbidities or concurrent medication use may make unintended pregnancy an increased health risk; therefore addressing sexuality and contraceptive issues at visits is imperative.

The goals of counseling with adolescents are to (1) understand adolescent perceptions and misperceptions about pregnancy and use of...
contraceptives; (2) help adolescents put unprotected intercourse risk in a personal perspective; (3) educate adolescents regarding the true risks and benefits for the various methods available; and (4) help adolescents choose a safe and effective method that can either be provided on site or be easily obtained by referral. Counseling should include a review of all contraceptive methods available, starting with the most effective methods. The adolescent should be counseled using “typical use” failure rates, which reflect the effectiveness of a method for the average person who may not always use the method or use the method correctly (see Fig. 117-2). For example, for oral contraceptive pills, the typical use failure rate is 9% whereas perfect use failure rate is <1%. It is important to ask about use of withdrawal as more than half (58%) of teens have used it for contraception and it has a typical use failure rate of 22%. Abstinence should also be discussed as an option even if teens have engaged in sexual intercourse in the past. Situational abstinence may be the best option if they do not have another method available at a particular time.

Necessary concepts to address while discussing individual methods include how effective the method is, how long the method works, what behaviors are required for correct and consistent use, what side effects may be seen, and what signs or symptoms of complications should prompt a return visit. Reviewing common side effects allows teens to anticipate and cope with any changes with reassurance. Weighing the possibility of certain side effects with the possibility of an unintended pregnancy may also help with the conversation. It is also important to address any specific misperceptions teens may have for certain contraceptives regarding side effects or effectiveness.

Once an adolescent chooses a method, the provider and teen should discuss clear plans on correct and consistent use of the chosen method and strategies for appropriate follow-up (Table 117-1). Providers

### Table 117-1: Contraceptive Methods

<table>
<thead>
<tr>
<th>METHOD</th>
<th>FAILURE RATE (%)</th>
<th>DOSING</th>
<th>MECHANISM OF ACTION</th>
<th>POTENTIAL SIDE EFFECTS</th>
<th>ADVANTAGES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hormonal Contraceptives</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Implant (Implanon or Nexplanon)</td>
<td>0.05</td>
<td>0.05</td>
<td>Insertion of implant into upper arm once every 3 yr</td>
<td>Progestin effects: thickening of cervical mucus, inhibition of ovulation, endometrial atrophy</td>
<td>Rare insertion complications, possible weight gain, uterine bleeding changes including amenorrhea</td>
</tr>
<tr>
<td>Progestin-releasing IUD (Skyla and Mirena)</td>
<td>0.2</td>
<td>0.2</td>
<td>Releases 14 or 20 µg/day levonorgestrel</td>
<td>Progestin effects (see above) and IUD effect of preventing sperm from fertilizing ovum</td>
<td>Breakthrough bleeding in 1st 3-6 mo, then hypo-, or amenorrhea</td>
</tr>
<tr>
<td>Progestin-only injection (Depo-Provera)</td>
<td>6</td>
<td>0.2</td>
<td>3 mo (13 wk) 150 mg depot medroxyprogesterone IM</td>
<td>Progestin effects (see above)</td>
<td>Irregular bleeding or amenorrhea, weight gain, breast tenderness, acne, depression, possible decrease in bone density</td>
</tr>
<tr>
<td>The patch</td>
<td>9</td>
<td>0.3</td>
<td>Weekly for 3 wk (off on 4th wk) 20 µg ethinyl estradiol 150 µg norelgestromin released daily</td>
<td>Combined hormonal method: thickens cervical mucus, inhibits ovulation, inhibits sperm’s ability to fertilize egg, slows tubal mobility, disrupts ovum transport, induces endometrial atrophy</td>
<td>Breakthrough bleeding, nausea, headaches, breast tenderness, skin site reaction, less effective if patient weighs &gt;90 kg (198 lb)</td>
</tr>
<tr>
<td>Vaginal ring (NuvaRing)</td>
<td>9</td>
<td>0.3</td>
<td>Monthly (insert for 3 wk of each mo) Serum levels of 15 µg ethinyl estradiol Releases 150 µg norelgestromin daily</td>
<td>Combined hormonal method (see above)</td>
<td>Vaginal irritation, vaginal discharge, headache</td>
</tr>
<tr>
<td>Combined Oral Contraceptives (OCPs)</td>
<td>9</td>
<td>0.3</td>
<td>Daily Varies 20-50 µg estrogen Varies 0.15-1 µg progestogen</td>
<td>Combined hormonal method (see above)</td>
<td>Breakthrough bleeding, nausea, headaches, breast tenderness</td>
</tr>
<tr>
<td>Progestin-only pills (POPs)</td>
<td>9</td>
<td>0.3</td>
<td>Daily (within 3-hr period) 0.35 mg norethindrone or 0.075 mg norgestrel</td>
<td>Progestin-only hormonal method: inhibits ovulation, thickens and decreases cervical mucus, atrophies endometrium</td>
<td>Irregular bleeding, breast tenderness, depression</td>
</tr>
</tbody>
</table>
Table 117-1  Contraceptive Methods—cont’d

<table>
<thead>
<tr>
<th>METHOD</th>
<th>FAILURE RATE (%)</th>
<th>MECHANISM OF ACTION</th>
<th>POTENTIAL SIDE EFFECTS</th>
<th>ADVANTAGES</th>
</tr>
</thead>
<tbody>
<tr>
<td>NONHORMONAL CONTRACEPTIVES</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IUD copper-containing (ParaGard)</td>
<td>Typical Use: 0.8 Perfect Use: 0.6</td>
<td>IUD: prevents sperm from fertilizing ova and copper ions may act as spermicide</td>
<td>Heavier menses</td>
<td>Easy to use, long-acting nonhormonal</td>
</tr>
<tr>
<td>Male condom</td>
<td>18 2 Every act of intercourse</td>
<td>Barrier method: blocks passage of semen</td>
<td>Latex allergy</td>
<td>Recommended to be used in addition to another contraceptive; only method that decreased STD, HIV risk</td>
</tr>
<tr>
<td>Female condom</td>
<td>21 5 Every act of intercourse</td>
<td>Barrier method: lines the vagina fully and penis partially</td>
<td>Vaginal discomfort, partner penile irritation</td>
<td>Provides some protection against STD, HIV; polyurethane can be used with latex allergy Recommended to be used in addition to another barrier contraceptive</td>
</tr>
<tr>
<td>Spermicides</td>
<td>28 18 Every act of intercourse</td>
<td>Kills sperm by destroying sperm cell membrane</td>
<td>Allergy or sensitivity to ingredients, recurrent urinary tract infections</td>
<td></td>
</tr>
</tbody>
</table>

Bibliography is available at Expert Consult.

117.1 Long-Acting Reversible Contraception

Tara Jatlaoui and Gale R. Burstein

Long-acting reversible contraception (LARC) includes 2 levonorgestrel IUDs, the Copper IUD and the etonogestrel subdermal implant; LARCs are the only Tier 1 methods that are reversible (see Fig. 117-2). Considered forgettable contraception, LARCs do not require frequent office or pharmacy visits and do not depend on user compliance for effectiveness. In the CHOICE project in St. Louis, more than 9,000 women were given the contraception of their choice at no cost and were followed for 2-3 yr. The failure rates among women who use oral contraceptive pills, transdermal patch or vaginal ring was more than 20 times higher than the failure rate for women using a LARC method according to this study. Acceptance, continuation, and satisfaction in this study were also higher among teens using LARC compared to those using non-LARC methods. The ACOG recommends LARC methods as first-line contraceptives for all females. The US Medical Eligibility Criteria, 2010, supports safe use of both IUDs and implants in this population. Implants are considered category 1 for all ages, and IUDs are considered category 2 for women <20 years old and for nulliparous women (see Table 117-2 for explanation of categories of eligibility).

Intrauterine Devices

Intrauterine devices (IUDs) are small, flexible, plastic objects introduced into the uterine cavity through the cervix. They differ in size, shape, and the presence or absence of pharmacologically active substances. In the United States, 3 IUDs are currently available: the Copper T380A and 2 levonorgestrel IUDs. The effectiveness of the copper IUD is enhanced by the copper ions released into the uterine cavity with possible mechanisms including inhibition of sperm transport and prevention of implantation; this IUD is effective for at least 10 yr.

The levonorgestrel IUDs also have various actions, from thickening of cervical mucus and inhibiting sperm survival to suppressing the endometrium; these IUDs are effective for at least 3 and 5 yr. All 3 IUDs have typical use failure rates of less than 1% (see Fig. 117-2).

Common misconceptions of IUDs among healthcare providers are that IUDs cause infections, infertility, and generally are not safe for teens or nulliparous women to use; these misconceptions are a barrier.
Bibliography


to teens accessing these highly effective and acceptable methods. These IUDs do not increase risk of infertility, and the IUD may be inserted safely in teens as well as nulliparous women (see Table 117-2).

Although early studies suggested an increased risk for upper genital tract infection, theoretically as a result of the presence of a foreign body in the cervix, newer work has refuted these earlier concerns. Therefore, clinicians are encouraged to consider use of IUDs in adolescents despite relatively high prevalence rates of STIs in this population. Teens should be screened for gonorrhea and chlamydia at the time of or before IUD placement, although placement should not be delayed if results have not returned and there are no signs of infection. If STI testing returns positive with an IUD in place, the patient may be treated without removing the IUD if she wishes to continue the method.

**Implants**

There is currently 1 contraceptive implant available in the United States. Originally FDA-approved in 2006, the single rod that releases 60 µg/day of etonogestrel has been updated to a radiopaque rod with a new inserter. This progestin-only method keeps etonogestrel at steady serum levels for 3 yr and primarily works to inhibit ovulation. Similarly to the levonorgestrel IUD, the progestin acts on the uterus to cause an atrophic endometrium and thickening cervical mucus to block sperm penetration; its typical use failure rate is also <1% (see Fig. 117-2). Unlike the IUD, no pelvic exam is required for insertion. A trained provider can quickly place or remove the implant in the upper arm under local anesthesia. Common side effects include amenorrhea, irregular bleeding, or infrequent bleeding, and, less often, prolonged or frequent bleeding. One potential unique complication of this method relates to localized infection and other side effects after implantation, such as bleeding, hematoma, or scarring, and, if inserted too deeply into the muscle, neural damage or migration; however, these events are rare, occurring in <1% of patients. Minor side effects, such as bruising or skin irritation, are more common but tend to resolve without treatment.

**Bibliography is available at Expert Consult.**

### Chapter 117: Contraception

#### Table 117-3: Conditions Classified as U.S. MEC

<table>
<thead>
<tr>
<th>Category</th>
<th>Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Category 1</td>
<td>Complicated valvular heart disease</td>
</tr>
<tr>
<td>Category 2</td>
<td>Current breast cancer</td>
</tr>
<tr>
<td>Category 3</td>
<td>Severe decompensated cirrhosis</td>
</tr>
<tr>
<td>Category 4</td>
<td>Deep venous thrombosis/Pulmonary embolism (acute)</td>
</tr>
<tr>
<td>Category 5</td>
<td>Malignant liver tumor</td>
</tr>
<tr>
<td>Category 6</td>
<td>Peripartum cardiomyopathy (diagnosed &lt;6 mo prior or with moderately or severely impaired cardiac function)</td>
</tr>
<tr>
<td>Category 7</td>
<td>Postpartum ≤21 days</td>
</tr>
<tr>
<td>Category 8</td>
<td>History of cerebrovascular accident</td>
</tr>
<tr>
<td>Category 9</td>
<td>Systemic lupus erythematosus with positive antiphospholipid antibodies</td>
</tr>
<tr>
<td>Category 10</td>
<td>Thrombogenic mutations</td>
</tr>
<tr>
<td>Category 11</td>
<td>Viral hepatitis (acute or flare)</td>
</tr>
</tbody>
</table>

#### 117.2 Other Progestin-Only Methods

*Tara Jatlaoui and Gale R. Burstein*

Several progestin-only methods are available and include the levonorgestrel IUDs and implant (see Chapter 117.1), as well as an injectable and progestin-only pills. These methods do not contain estrogen and may be useful for teens with contraindications to estrogen (Table 117-3) and are considered generally safe for use in teens (see Table 117-2). Progestins thicken cervical mucus to block sperm entry into the uterine cavity as well as induce an atrophic endometrium leading to either amenorrhea or less menstrual blood loss; the implant and injectable additionally suppress ovulation. Teens should be provided anticipatory counseling regarding bleeding irregularities that may normally occur in the 1st 3-6 mo of hormonal contraceptive use.

**DEPO-PROVERA**

An injectable progestin, medroxyprogesterone acetate (Depo-Provera, DMPA), is a Tier 2 contraceptive method available as a deep intramuscular injection (150 mg), or as a subcutaneous injection (104 mg) with typical-use failure rates of 6% (see Fig. 117-2). Both preparations must be readministered every 3 mo (13 wk) and act to inhibit ovulation. DMPA is particularly attractive for adolescents who have difficulty with compliance, are intellectually or physically impaired, and are chronically ill or have a condition for which estrogen use is not recommended. After 1 yr of use, 50% of DMPA users develop amenorrhea, which may be an added advantage for teens with heavy menstrual bleeding, dysmenorrhea, anemias, or blood dyscrasias; or for those with impairments that make hygiene difficult. Although concern has been directed toward the potential for loss in bone mineral density in adolescents, thereby potentially increasing their risk for osteoporosis later in life, subsequent studies have found that bone density is recovered after discontinuation of the method and is considered safe for use in this population (see Table 117-2). Healthcare providers may want to consider a contraceptive containing estrogen in teens who are already at high risk for low bone density, such as those on chronic corticosteroids or those with eating disorders (see Chapter 707). Although a black box warning was issued in 2004, the American Academy of Pediatrics and ACOG do not recommend limiting DMPA use to 2 yr for all women and do not recommend routine bone mineral density screening for females using DMPA. There is also concern for weight gain in women using DMPA. A systematic review found 2 studies indicating early weight gain may be predictive of progressive gain over time; thus, those teens gaining weight in the 1st 3-6 mo should consider another method.

**PROGESTIN-ONLY PILLS**

Progestin-only oral contraceptives are available for the adolescent in whom the use of estrogen is potentially deleterious, such those with active liver disease, replaced cardiac valves, or hypercoagulable states (see Table 117-3). These agents (“mini-pills”) are less reliable in inhibiting ovulation, are associated with a typical use failure rate of 9%, and
Bibliography


Product Information

are considered Tier 2 or moderately effective contraceptives (see Fig. 117-2). Acceptance by adolescents is limited by the necessity of taking the pill daily and bleeding irregularities, including amenorrhea and breakthrough bleeding. Progestin-only pills are quickly effective after 2 days of initiation in thickening cervical mucus. Effects, however, are short-lived and pill-taking must be punctual, which may be difficult for teens. If a pill is more >3 hr late from normal time, an unintended pregnancy may occur.

Bibliography is available at Expert Consult.

117.3 Combined Hormonal Contraceptives
Tara Jatlaoui and Gale R. Burstein

Combined hormonal contraceptives (CHCs) are methods that include an estrogenic substance in combination with a progestin; methods available in the United States include several formulations of combined oral contraceptives (COCs), a transdermal patch and a vaginal ring. The major mechanism of action of the estrogen-progestin combination is to prevent the surge of luteinizing hormone and, as a result, to inhibit ovulation. Additional effects to the reproductive tract include thickening of the cervical mucus in such a way that prevents sperm penetration and thinning of the endometrial lining, which may decrease menstrual blood loss. Typical use failure rates for all CHCs are the same at 9%.

CHCs are also considered similarly in the U.S. Medical Eligibility Criteria, and recommendations mostly are concerned with estrogen exposure for a given condition or characteristic (see Table 117-3). Thrombophlebitis, hepatic adenomas, myocardial infarction, and carbohydrate intolerance are some of the more serious potential complications of exogenous estrogen use. These disorders are exceedingly rare in adolescents. Even though teenage smokers who use oral contraceptives have more than twice the risk of myocardial infarction, the likelihood of its occurrence is very small, and thus clinically insignificant, compared to the risk of dying from other pregnancy-related complications.

COMBINED ORAL CONTRACEPTIVES

Oral contraceptive pills can be either COCs or progestin-only pills and are commonly referred to as “the pill.” The pill is one of the most common contraceptive methods used among women of all ages. To decrease risk of pregnancy and increase continuation, providers are encouraged to provide oral contraceptive pills at the time of patient presentation to start immediately rather than waiting for next menses, as long as the provider is reasonably sure that the patient is not pregnant. Providers are also encouraged to provide up to 13 pill packs at a time, based on evidence that more pill packs given is associated with higher continuation rates. However, most health plans will not cover costs for more than 3 pill packs dispensed at 1 time. Advanced provision of emergency contraceptive pills is also recommended should patients miss pills and have unprotected sex. The effectiveness of COCs is dependent on compliance, and unfortunately adolescents may forget to take a pill each day. Figures 117-3 and 117-4 list the rules for missed pills or following vomiting or diarrhea.

COCs contain 50, 35, 30, 25, or 20 µg of estrogenic substance, typically ethinyl estradiol, and as many as 10 progestins have been available

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Figure 117-3 Recommended actions after late or missed combined oral contraceptives. (From Centers for Disease Control and Prevention: US Selected Practice Recommendations for Contraceptive Use, 2013, MMWR Recomm Rep 2013;62(RR-5):1–60, Fig. 2, p. 27.)
Bibliography
in the United States for combined pills. Multiple preparations are available to help select the formulation with which an individual patient will be satisfied with minimal side effects.

COCs can be packaged as 28-day monophasic pills, which contain the same dose of active pills for 21 or 24 days followed by 7 or 4 days of placebo pills, respectively. Monophasic formulations are also available for extended-cycles of 91 days or 1 yr such that withdrawal bleeding does not occur each month but at the end of each extended cycle. Extended cycling of monophasic COCs for adolescents has some anticipated benefits associated with increased ovarian activity suppression and may decrease failure rates. Other advantages include diminished frequency of hormonal withdrawal (premenstrual) effects including headaches and migraines, mood changes, and heavy monthly bleeding. The most common side effect of extended-cycle oral contraceptive pills is intermenstrual bleeding and/or spotting with the total days of bleeding over the 1st yr of treatment being similar for extended-cycle users and users following a 28-day cycle regimen. The unscheduled bleeding pattern diminishes over time. Multiphasic pill packs contain various levels of estrogen and progestin for 21 active pills and contains 7 placebo pills. Multiphasic formulations are not available for extended cycle use.

The short-term adverse effects of COCs, such as nausea and weight gain, often interfere with compliance in adolescent patients. These effects are usually transient and may be overshadowed by the beneficial effects of a shortened menses and the relief of dysmenorrhea. The inhibition of ovulation or the suppressant effect of estrogens on prostaglandin production by the endometrium makes COCs effective in preventing dysmenorrhea (see Chapter 116). Acne (see Chapter 669) may be worsened by some and improved by other oral contraceptive preparations. The pills with nonandrogenic progestins are particularly effective in reducing acne and hirsutism. Drospirenone, a progestin with antimineralocorticoid activity, has been shown to reduce premenstrual symptomatology, but the potential for hyperkalemia as a side effect eliminates patients with renal, liver, or adrenal diseases and patients on certain medications.

As of 2011, the FDA has concluded that drospirenone-containing oral contraceptives may be associated with a higher risk of blood clots compared to other progestin-containing pills. Although no studies have provided consistent estimates of the comparative risk of blood clots between birth control pills that contain drospirenone and those that do not, nor have studies accounted for patient characteristics that may affect blood clot risk, there has been a 3-fold increased risk of blood clots reported for drospirenone, as compared to products containing levonorgestrel or other progestins. As a result, the FDA is requiring that labeling be revised for the oral contraceptives marketed under the Beyaz, Safyral, Yasmin, and Yaz brands. Despite the risk of blood clots with all oral contraceptives, the risk still remains lower than the risk of developing blood clots during pregnancy or the postpartum period.

**Transdermal Patch**

The transdermal patch (Ortho Evra) releases 20 µg ethinyl estradiol and 150 µg norelgestromin daily and is applied to the lower abdomen, buttocks, or upper body. It is worn continuously for 1 wk and changed weekly for a total of 3 wk; then no patch is worn for the fourth wk at which time bleeding occurs (see Table 117-1). It should not be applied to the breast. Limited studies in adolescents suggest higher rates of partial or full detachment compared to adults, with high patient satisfaction and 50-83% continuation rates from 3-18 mo of use (Fig. 117-5). Like other combined hormonal methods, the patch is a Tier 2 or moderately effective contraceptive.

**Vaginal Ring**

The vaginal contraceptive ring (NuvaRing) is a flexible, transparent, colorless vaginal ring that measures about 2.1 inches in diameter and

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**Figure 117-4 Recommended steps after vomiting or diarrhea while using combined oral contraceptives.** (From Centers for Disease Control and Prevention: US Selected Practice Recommendations for Contraceptive Use, 2013, MMWR Recomm Rep 2013;62(RR-5):1–60, Fig. 5, p. 30.)
Delayed application or detachment* for <48 hours since a patch should have been applied or reattached.

- Apply a new patch as soon as possible. (If detachment occurred <24 hours since the patch was applied, try to reapply the patch or replace with a new patch.)
- Keep the same patch change day.
- No additional contraceptive protection is needed.
- Emergency contraception is not usually needed but can be considered if delayed application or detachment occurred earlier in the cycle or in the last week of the previous cycle.

Delayed application or detachment* for ≥48 hours since a patch should have been applied or reattached.

- Apply a new patch as soon as possible.
- Keep the same patch change day.
- Use back-up contraception (e.g., condoms) or avoid sexual intercourse until a patch has been worn for 7 consecutive days.
- If the delayed application or detachment occurred in the third patch week:
  - Omit the hormone-free week by finishing the third week of patch use (keeping the same patch change day) and starting a new patch immediately.
  - If unable to start a new patch immediately, use back-up contraception (e.g., condoms) or avoid sexual intercourse until a new patch has been worn for 7 consecutive days.
- Emergency contraception should be considered if the delayed application or detachment occurred within the first week of patch use and unprotected sexual intercourse occurred in the previous 5 days.
- Emergency contraception may also be considered at other times as appropriate.

*If detachment takes place but the woman is unsure when the detachment occurred, consider the patch to have been detached for ≥48 hours since a patch should have been applied or reattached.

Figure 117-5 Recommended actions after delayed application or detachment with combined hormonal patch. (From Centers for Disease Control and Prevention: US Selected Practice Recommendations for Contraceptive Use, 2013, MMWR Recomm Rep 2013;62(RR-5):1–60, Fig. 3, p. 28).

Delayed insertion of a new ring or delayed reinsertion* of a current ring for <48 hours since a ring should have been inserted.

- Insert ring as soon as possible.
- Keep the ring in until the scheduled ring removal day.
- No additional contraceptive protection is needed.
- Emergency contraception is not usually needed but can be considered if delayed insertion or reinsertion occurred earlier in the cycle or in the last week of the previous cycle.

Delayed insertion of a new ring or delayed reinsertion* for ≥48 hours since a ring should have been inserted.

- Insert ring as soon as possible.
- Keep the ring in until the scheduled ring removal day.
- Use back-up contraception (e.g., condoms) or avoid sexual intercourse until a ring has been worn for 7 consecutive days.
- If the ring removal occurred in the third week of ring use:
  - Omit the hormone-free week by finishing the third week of ring use and starting a new ring immediately.
  - If unable to start a new ring immediately, use back-up contraception (e.g., condoms) or avoid sexual intercourse until a new ring has been worn for 7 consecutive days.
- Emergency contraception should be considered if the delayed insertion or reinsertion occurred within the first week of ring use and unprotected sexual intercourse occurred in the previous 5 days.
- Emergency contraception may also be considered at other times as appropriate.

*If removal takes place but the woman is unsure of how long the ring has been removed, consider the ring to have been removed for ≥48 hours since a ring should have been inserted or reinserted.

Figure 117-6 Recommended actions after delayed insertion or reinsertion with combined vaginal ring. (From Centers for Disease Control and Prevention: US Selected Practice Recommendations for Contraceptive Use, 2013, MMWR Recomm Rep 2013;62(RR-5):1–60, Fig. 4, p. 29).
Potential Indications for Use of Contraception

Unprotected intercourse at midcycle carries a pregnancy risk of 20–30%. At other times during the cycle, the risk is 2–4%. The risk may be reduced or eliminated by interventions known collectively as emergency contraception (EC) as soon as possible after unprotected intercourse or contraceptive failure with a “window” up to 120 hr. Table 117-4 lists the indications for use of EC. Methods that can be used after unprotected intercourse for EC include the Copper IUD and various emergency contraceptive pills, which include ulipristal acetate, levonorgestrel and COCs following the Yuzpe method. Although the mechanism of action of the Copper IUD as EC is unclear, all emergency contraceptive pills work to delay ovulation and are effective only for intercourse that occurs prior to administration. Initiation of a regular contraceptive method is necessary to prevent pregnancy for any intercourse that occurs for the remainder of the cycle and for future cycles. If pregnancy has already occurred, emergency contraceptive pills will not cause an abortion or have teratogenic effects on the fetus.

 Teens can access EC information through a hotline at 1-888-NOT-2-LATE to obtain EC pills over the counter. The American Academy of Pediatrics recommends advance provision of EC pills for teens who are or may become sexually active. A follow-up appointment is also recommended to determine the effectiveness of treatment and to diagnose a possible early pregnancy. The visit also provides an opportunity to counsel the adolescent, explore the situation leading up to the unprotected intercourse or contraceptive failure, test for STIs, offer HIV testing, and initiate continuing contraception when appropriate. Pap smear screening is not initiated until 21 yr of age.

**COPPER IUD**

The Copper T380A is FDA approved for EC and has been shown to be more than 99% effective if used within 5 days (120 hr) after unprotected sex. The additional benefit of using the Copper IUD for EC is it also provides long-term reversible contraception.

**ULIPRISTAL ACETATE**

This is the newest formulation available for EC and was FDA approved in 2010 for use up to 120 hr after unprotected sex. It is available only by prescription regardless of age. It has been shown in a few studies to be more effective than levonorgestrel at and beyond 72 hr.

**LEVONORGESTREL**

In 2009, the FDA approved the emergency contraceptive drug Plan B as an over-the-counter option for women age 17 yr and older. Experience in adolescent women demonstrates more effective use of EC with advance provision and is not associated with more frequent unprotected intercourse or less condom or pill use. Nausea and vomiting are uncommon side effects, and in a recent comparison, levonorgestrel proved more effective at preventing pregnancy than the Yuzpe method.

The Yuzpe method has been replaced by the more effective levonorgestrel pills but may be useful for women who already have COCs at home and are in need of EC. For EC, pills consist of COCs totaling 200 µg ethinyl estradiol and 2.0 mg norgestrel or 1.0 mg levonorgestrel. This method is effective in reducing the risk of pregnancy by 75%. The most common side effects are nausea (50%) and vomiting (20%), prompting some clinicians to prescribe or recommend emetics along with the oral contraceptives.

**117.5 Dual Protection**

Dual protection is the protection against STIs/HIV as well as effective contraception. Although condoms can provide both, providers should encourage more highly effective contraceptive methods along with condoms for each act of intercourse.

**CONDOMS**

This method prevents sperm from being deposited in the vagina. There are no major side effects associated with the use of a condom. The risk of HIV may have increased the use of condoms among adolescents, with 46.2% of high school students in 1981 reporting using a condom at last sexual intercourse increasing to 60.2% in 2011. The main advantages of condoms are their low price, availability without prescription, little need for advance planning, and, most important for this age
Bibliography

Bibliography


group, their effectiveness in preventing transmission of STIs, including HIV and human papillomavirus. The typical use failure rate for male condoms is 18%. For most effective dual protection, male latex condoms are recommended as protection against STIs, and should be used with an effective contraceptive method for adolescents such as a LARC. According to the National Survey of Family Growth, only 12% of females used a highly effective method along with a condom in the month that they were interviewed.

A female condom is available over-the-counter in single-size disposable units. It is a second choice over the male latex condom because of the complexity of properly using the device, its high typical use failure rate of 21%, and the lack of studies in humans demonstrating its effectiveness against STIs. Most adolescents would require intensive education and hands-on practice to use it effectively.

Bibliography is available at Expert Consult.

117.6 Other Barrier Methods
Tara Jatlaoui and Gale R. Burstein

DIAPHRAGM, CERVICAL CAP, AND SPONGE
These methods have few side effects but are much less likely to be used by teenagers. Typical use failure rates exceed 12%. The cervical cap and sponge have lower failure rates in nulliparous women while the diaphragm has similar rates among nulliparous or parous women. Adolescents tend to object to the messiness of the jelly or to the fact that the insertion of a diaphragm may interrupt the spontaneity of sex, or they may express discomfort about touching their genitals.

117.7 Other Methods
Tara Jatlaoui and Gale R. Burstein

SPERMICIDES
A variety of agents containing the spermicide nonoxynol-9 are available as foams, jellies, creams, films, or effervescent vaginal suppositories. They must be placed in the vaginal cavity shortly before intercourse and reinserted before each subsequent ejaculation in order to be effective. Rare side effects consist of contact vaginitis. There has been some concern regarding the vaginal and cervical mucosal damage observed with nonoxynol-9, and the overall impact on HIV transmission is unknown. The finding that nonoxynol-9 is gonococcicidal and spirocheticidal has not been substantiated in randomized clinical trials. Spermicides should be used in combination with other barrier methods as their typical use failure rate alone is 28%.

WITHDRAWAL
The pregnancy risk for use of withdrawal as a contraceptive method is probably underestimated in adolescents, and high typical use failure rate of 22% should be specifically addressed with young adolescents; especially since over half (58%) of teens have used withdrawal for contraception.

FERTILITY AWARENESS–BASED METHODS
These include the standard days method, basal body temperature method, billings method and may also include combinations as well. Since these are based on regular ovulatory cycles, which are less common in teens, these should be used with caution.

LACTATIONAL AMENORRHEA METHOD
The lactational amenorrhea method may be a highly effective temporary contraceptive method if all of the following criteria are met: (a) no return of menses, (b) the infant is < 6 mo old, and (c) exclusively breastfeeding.

Bibliography is available at Expert Consult.
Bibliography

Bibliography
Chapter 118
Adolescent Pregnancy
Dianne S. Elfenbein and Marianne E. Felice

Epidemiology
In 1960, the teen birth rate in the United States was recorded as 89.1 births per 1,000 females 15-19 yr of age; by 2011, the rate had decreased to 31.3 births per 1,000 females 15-19 yr of age. Despite increases in the rates in 1990 and 2006, there has been a steady decline over the last half century (Fig. 118-1). The most dramatic decreases have been in African-American and Hispanic adolescents. Pregnancy rates, which include births, miscarriages, stillbirths, and induced abortions, have also decreased since the 1990s. In 1990, the pregnancy rate was 116.9 per 1,000 females age 15-19 yr of age; in 2008, the pregnancy rate was 67.8, indicating that the decline in birthrates was not attributable to an increase in pregnancy terminations. The improvement in U.S. female teen birth rates is attributed to 3 factors: more teens are delaying the onset of sexual intercourse, are using some form of contraception when they begin to have sexual intercourse, and are using long-lasting contraceptive agents such as injections, implants, and intrauterine devices.

In spite of the decrease in female teen births in the last 2 decades, the United States continues to have female teen birth rates markedly higher than those in most other industrialized nations. For comparison, in 2009 the United States birth rate to female teens age 15-19 yr was 37.9 per 1,000 compared to a rate of 22 among all industrialized nations. The Russian Federation reported a rate of 30.2, the UK a rate of 25.0, and Australia a rate of 16.5. Japan's rate was 5.1 births per 1,000 female teens. Among developing countries the estimated rate was 56 and among the least-developed nations, 123. Globally, the estimated rate was 52 births per 1,000 female teens. Globally, teen pregnancy rates declined from 1990 to 2000 but have leveled off since then.

Etiology
In industrialized countries with policies supporting access to protection against pregnancy and sexually transmitted infections (STIs), older adolescents are more likely to use hormonal contraceptives and condoms, resulting in a lowered risk of unplanned pregnancy. Younger teenagers are likely to be less deliberate and logical about their sexual decisions and their sexual activity is likely to be sporadic or even coercive, contributing to inconsistent contraceptive use and a greater risk of unplanned pregnancy. Better hopes for employment and higher educational goals are associated with lowered probability of childbearing in most groups. In nonindustrialized countries, laws permitting marriage of young and mid-adolescents, poverty, and limited female education are associated with increased adolescent pregnancy rates.

Clinical Manifestations
Adolescents may experience the traditional symptoms of pregnancy: morning sickness (vomiting, nausea that may also occur any time of the day), swollen tender breasts, weight gain, and amenorrhea. Often the presentation is less classic. Headache, fatigue, abdominal pain, dizziness, and scanty or irregular menses are common presenting complaints.

In the pediatric office, some teens are reluctant to divulge concerns of pregnancy. Denial of sexual activity and menstrual irregularity should not preclude the diagnosis in face of other clinical or historical information. An unanticipated request for a complete checkup or a visit for contraception may uncover a suspected pregnancy. Pregnancy is still the most common diagnosis when an adolescent presents with secondary amenorrhea.
DIAGNOSIS

Table 118-1 provides information regarding the diagnosis of pregnancy.

On physical examination, the findings of an enlarged uterus, cervical cyanosis (Chadwick sign), a soft uterus (Hegar sign), or a soft cervix (Goodell sign) are highly suggestive of an intrauterine pregnancy. A confirmatory pregnancy test is always recommended, either qualitative or quantitative. Modern qualitative urinary detection methods are efficient at detecting pregnancy, whether performed at home or in the office. These tests are based on detection of the beta subunit of human chorionic gonadotropin (hCG). Although claims for nonprescription home pregnancy tests may indicate 98% detection on the day of the first missed menstrual period, sensitivity and accuracy vary considerably. Office or point-of-care tests have increased standardization and generally have increased sensitivity, with the possibility of detecting a pregnancy within 3-4 days after implantation. However, in any menstrual cycle, ovulation may be delayed, and in any pregnancy, the day of implantation may vary considerably, as may rate of production of hCG. This variability, along with variation of urinary concentration, may affect test sensitivity. Consequently, each negative test should be repeated in 1-4 wk if there is a heightened suspicion of pregnancy. The most sensitive pregnancy detection test is a serum quantitative βhCG radioimmunoassay in which results are reliable within 7 days after fertilization. This more expensive test is used primarily during evaluations for ectopic pregnancy, to detect retained placenta after pregnancy termination, or in the management of a molar pregnancy. It is generally used when serial measurements are necessary in clinical management.

Although not generally used for primary diagnosis of pregnancy, pelvic or vaginal ultrasound can be used to detect and date a pregnancy. Pelvic ultrasound will detect a gestational sac at about 5-6 wk (dated from last menstrual period) and vaginal ultrasound at 4.5-5 wk.


<table>
<thead>
<tr>
<th>Year</th>
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<th>Non-Hispanic black</th>
<th>Hispanic</th>
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<tr>
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<tr>
<td>2011</td>
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</tr>
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This tool may also be used to distinguish diagnostically between intrauterine and ectopic pregnancies.

**PREGNANCY COUNSELING AND INITIAL MANAGEMENT**

After the diagnosis of pregnancy is made, it is important to begin addressing the psychosocial, as well as the medical, aspects of the pregnancy. The patient’s response to the pregnancy should be assessed and her emotional issues addressed. It should not be assumed that the
pregnancy was unintended. Discussion of the patient’s options should be initiated. These options include (a) releasing the child to an adoptive family, (b) electively terminating the pregnancy, and (c) raising the child herself with the help of family, father of the baby, friends, and/or other social resources. Options should be presented in a supportive, informative, nonjudgmental fashion; for some young women, they may need to be discussed over several visits. Physicians who are uncomfortable in presenting options to their young patients should refer their patients to a provider who can provide this service expedi-
tiously. Pregnancy terminations implemented early in the pregnancy are generally less risky and less expensive than those initiated later. Other issues that may need discussion are how to inform and involve the patient’s parents and the father of the infant; implementing strategies for insuring continuation of the young mother’s education; discontinuation of tobacco, alcohol, and illicit drug use; discontinuation and avoidance of any medications that may be considered teratogenic; starting folic acid, calcium, and iron supplements; proper nutrition; and testing for STIs. Especially in younger adolescents, the possibility of coercive sex (see Chapter 119) should be considered and appropriated social work/legal referrals made if abuse has occurred, although most pregnancies are not a result of coercive sex. Patients who elect to continue their pregnancies should be referred as soon as possible to an adolescent-friendly obstetric provider.

CHARACTERISTICS OF TEEN PARENTS

Young women who become parents as teenagers often come from economically disadvantaged families. Although birthrates among African-American and Hispanic teens have decreased in the past 2 decades, their rates are more than double those for non-Hispanic whites. Parenting teens frequently have poor school performance prior to becoming pregnant, and they often have a family history of low educational attainment. Learning disabilities are not uncommon. Teen mothers frequently come from single-parent families where their own mother gave birth during adolescence. A large majority (84%) of teen mothers have a baby outside of marriage. They may view pregnancy as having a positive social value and as not interfering with their long-term goals.

Teenage men who become fathers as adolescents also have poorer educational achievement than their age-matched peers. They are more likely than peers to have been involved with illegal activities and with the use of illegal substances. Adult men who father the children of teen mothers are poorer and educationally less advanced than their age-matched peers and tend to be 2-3 yr older than the mother; any combination of age differences may exist. Younger teen mothers are more likely to have a greater age difference between themselves and the father of their child, raising the issue of coercive sex or statutory rape (see Chapter 119).

Male partners have a significant influence on the young woman’s decision/desire to become pregnant and to parent her child. Sensitively and appropriately including the male partner in discussions of family planning, contraception, and pregnancy options may be a useful strategy in improving outcomes for all. This can only be successful if the young female patient is willing to have her partner involved in such discussions.

MEDICAL COMPLICATIONS OF MOTHERS AND BABIES

Although pregnant teens are at higher-than-average risk for some complications of pregnancy, most teenagers have pregnancies that are without major medical complications, delivering healthy infants. The miscarriage/stillbirth risk for adolescents is estimated at 15-20%. In the United States, elective pregnancy termination rates peaked from 1985-1988 at 41-46%, decreasing since then to approximately 30% in 2008. As expected, teen mothers have lower rates of age-related chronic disease (diabetes or hypertension) that might affect the outcomes of a pregnancy. They also have lower rates of twin pregnancies than older women. They tolerate childbirth well with few operative interventions. However, as compared with 20-39 yr old mothers, teens have higher incidences of low birthweight infants, preterm infants, neonatal deaths, passage of moderate to heavy fetal meconium during parturition, and infant deaths within 1 yr after birth. The highest rates of these poor outcomes occur in the youngest and most economically deprived mothers. Gastrochisis, although very rare, has a markedly higher incidence in infants of teen mothers for reasons that are unclear. Teen mothers also have higher rates of anemia, pregnancy-associated hypertension, and eclampsia, with the youngest teens having rates of pregnancy-associated hypertension higher than the rates of women in their 20s and 30s. The youngest teens also have a higher incidence of poor weight gain (<16 lb) during their pregnancy. This correlates with a decrease in the birth weights of their infants. Poor maternal weight gain also has correlated strongly with teens’ late entrance into prenatal care and with inadequate utilization of prenatal care. Sexually active teens have higher rates of STIs than older sexually active women.

Globally, many young women who become pregnant have been exposed to violence or abuse in some form during their lives. There is some evidence that teenage women have the highest rates of violence during pregnancy of any group. Violence has been associated with injuries and death as well as preterm births, low birthweight, bleeding, substance abuse, and late entrance into prenatal care. An analysis of the Pregnancy Mortality Surveillance System indicates that in the United States from 1991 to 1999, homicide was the second leading cause of injury-related deaths in pregnant and postpartum women. Women ages 19 yr and younger had the highest pregnancy-related homicide rate (see Chapter 113).

Ectopic pregnancy occurs in 1-2% of conceptions and is more common in women with a previous history of an ectopic pregnancy, pelvic inflammatory disease, prior appendicitis, infertility, in utero exposure to diethylstilbestrol, and possibly the presence of an intrauterine contraceptive device. Most ectopic pregnancies are in the fallopian tube (tubal pregnancy). Manifestations include vaginal spotting after a missed menstrual period that may progress to more intense vaginal bleeding (which may be suggestive of a spontaneous abortion); vaginal bleeding is absent in 10-20%. Abdominal pain is associated with distention of the fallopian tube; tubal rupture results in more intense pain, hemorrhagic shock, and peritonitis. Some women have nonspecific abdominal complaints and are misdiagnosed with gastro- enteritis. Cervical motion and adnexal tenderness (and adnexal mass) may be present. Transvaginal sonography (not transabdominal) is the diagnostic test of choice to detect an ectopic pregnancy and reveals an adnexal mass and no uterine pregnancy. Nonetheless, some women will have pregnancy of unknown location by transvaginal sonography; approximately 20% of these will have an ectopic pregnancy. Measurement of sensitive quantitative serum βhCG levels together with transvaginal sonography has value in diagnosing an ectopic pregnancy. If the initial βhCG is above the discriminatory zone (level at which one expects an intrauterine pregnancy), but on transvaginal sonography there is no intrauterine pregnancy, there may be an ectopic pregnancy or an abnormal uterine pregnancy. In addition, if the βhCG is below the discriminatory level (usually <3000 mIU/mL) with no definitive diagnosis by sonography, serial βhCG testing should be performed every 48 hr. In a normal uterine pregnancy, βhCG levels should increase approximately 50% every 48 hr; declining levels may suggest a miscarriage or an ectopic pregnancy. Some would perform a dilation and curettage and check for products of conception or follow serial βhCG levels. If there are no products of conception or if βhCG levels plateau or increase, an ectopic pregnancy is present. Treatment of unstable or advanced patients is usually by laparoscopic surgery or by laparotomy. Because of early detection, many patients remain stable (unruptured). Stable patients with an unruptured ectopic pregnancy may be treated with single-, or more often multiple-, dose methotrexate to induce abortion. Contraindications to methotrexate in a stable patient include size of the ectopic mass (>3.5 cm) and embryonic cardiac motion.

Prematurity and low birthweight increase the perinatal morbidity and mortality for infants of teen mothers. These infants also have higher-than-average rates of sudden infant death syndrome (see Chapter 375), possibly because of less use of the supine sleep position, and are at higher risk of both intentional and unintentional injury (see Chapter 40). One study shows the risk of homicide to be 9-10 times
higher if a child born to a teen mother is not the mother’s firstborn as compared with the risk to a firstborn of a woman age 25 yr or older. The perpetrator is often the father, stepfather, or boyfriend of the mother.

After childbirth, depressive symptoms may occur in as many as 50% of teenaged mothers. Depression seems to be greater with additional social stressors and with decreased social supports. Support from the infant’s father and the teen’s mother seems to be especially important in preventing depression. Pediatricians who care for parenting teens should be sensitive to the possibility of depression, as well as to inflicted injury to mother or child; appropriate diagnosis, treatment, and referral to mental health or social agencies should be offered and facilitated.

PSYCHOSOCIAL OUTCOMES/RISKS FOR MOTHER AND CHILD

Educational
Teenage mothers often do poorly in school and drop out prior to becoming pregnant. After childbirth many choose to defer completion of their education for some time. High school graduation or an equivalency degree is generally achieved eventually. Mothers who have given birth as teens generally remain 2 yr behind their age-matched peers in formal educational attainment at least through their 3rd decade. Maternal lack of education limits the income of many of these young families (see Chapter 1).

Substance Use
See also Chapter 114.

Teenagers who abuse drugs, alcohol, and tobacco have higher pregnancy rates than their peers. Most substance-abusing mothers appear to decrease or stop their substance use while pregnant. Use begins to increase again about 6 mo postpartum, complicating the parenting process and the mother’s return to school.

Repeat Pregnancy
In the United States, approximately 20% of all births to adolescent mothers (age 15-19 yr) are second order or higher. Prenatal care is begun even later with a second pregnancy, and the second infant is at higher risk of poor outcome than the first birth. Mothers at risk of early repeat pregnancy include those who do not initiate long-acting contraceptives after the index birth, those who do not return to school within 6 mo of the index birth, those who are married or living with the infant’s father, and those who are no longer involved with the baby’s father and who meet a new boyfriend who wants to have a child. To reduce repeat pregnancy rates in these teens, programs must be tailored for this population, preferably offering comprehensive healthcare for both the young mother and her child (Table 118-2). Healthcare providers should remember to provide positive reinforcement for teen parenting successes (i.e., compliment teen parents when they are doing a good job).

Behavioral, Educational, and Social Outcomes of Children Born to Teen Mothers
Many children born to teen mothers have behavioral problems that may be seen as early as the preschool period. Many drop out of school early (33%), become adolescent parents (25%), or, if male, are incarcerated (16%). Explanations for these poor outcomes include poverty, parental learning difficulties, negative parenting styles of teen parents, maternal depression, parental immaturity, poor parental modeling, social stress, exposure to surrounding violence, and conflicts with grandparents, especially grandmothers. Continued positive paternal involvement throughout the child’s life may be somewhat protective against negative outcomes. Many of these poor outcomes appear to be attributable to the socioeconomic/demographic situation in which the teen pregnancy has occurred, not solely to maternal age. Even when socioeconomic status and demographics are controlled, infants of teen mothers have lower achievement scores, lower high school graduation rates, increased risk of teen births themselves, and, at least in Illinois (where records include age of birth mother), a higher probability of abuse and neglect.

Comprehensive programs focused on supporting adolescent mothers and infants utilizing life skills training, medical care, and psychosocial support demonstrate higher employment rates, higher income, and less welfare dependency in adolescents exposed to the programs.

Prevention of Teen Pregnancies
Adolescent pregnancy is a multifaceted problem that requires multifactorial solutions. The provision of contraception and education about fertility risk from the primary care physician is important, but
insufficient to address the problem fully. Family and community involvement are essential elements for teen pregnancy prevention. Strategies for primary prevention (preventing first births) are different from the strategies needed for secondary prevention (preventing second or more births). Over the last 30 yr, many models of teen pregnancy prevention programs have been implemented and evaluated. Table 118-3 lists the common components of many successful evidence-based programs.

Abstinence-only sexual education aims to teach adolescents to wait until marriage to initiate sexual activity but, unfortunately, does not mention contraception. Abstinence education is sometimes coupled with “virginity pledges” in which teenagers pledge to remain abstinent until they marry. Other educational programs emphasize HIV and STI prevention and in the process prevent pregnancy, whereas others include both abstinence and contraception in their curricula. Sex education and teaching about contraception do not lead to an increase in sexual activity. Teenagers who participate in programs that have comprehensive sex education components generally have lower rates of pregnancy than those teenagers who have exposure solely to abstinence-only programs or no sex education at all.

In many U.S. communities, programs that engage youth in community service and/or combine sex education and youth development are also successful in deterring pregnancy. Programs vary in their sites of service from schools, to social agencies, to health clinics, to youth organizations, to churches. Programs must be tailored to the cultural background, ethnicity, age group, and gender of the group being targeted for the prevention services.

Secondary prevention programs are fewer in number. In the United States, some communities have tried to “pay” young mothers to not become pregnant again, but these efforts have not always been fruitful. Home visiting by nurses has been successful in some areas, and many communities have developed “Teen Tot” Clinics that provide a “one-stop shopping model” for healthcare for both the teen mother and the baby in the same site at the same time. Both of these latter types of programs have reported some successes.

In the practice setting, the identification of the sexually active adolescent through a confidential clinical interview is a first step in pregnancy prevention. The primary care physician should provide the teenager with factual information in a nonjudgmental manner and then guide the teenager in the decision-making process of choosing a contraceptive (see Chapter 117). The practice setting is an ideal setting to support the teenager who chooses to remain abstinent. When a teenager does become pregnant and requires prenatal care services, healthcare providers should remember that the pregnant teenager is an adolescent who has become pregnant, not a pregnant woman who happens to be an adolescent.

Bibliography is available at Expert Consult.

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<tr>
<th>Table 118-3</th>
<th>Common Components of Most Successful Evidence-Based Programs to Prevent Teen Pregnancy</th>
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<tr>
<td>• Information is provided about the benefits of abstinence.</td>
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<tr>
<td>• Information is provided about contraception for those who are already sexually active.</td>
<td></td>
</tr>
<tr>
<td>• Information is provided about the signs and symptoms of STIs and how to prevent STIs.</td>
<td></td>
</tr>
<tr>
<td>• Interactive sessions on peer pressure are presented.</td>
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<tr>
<td>• Teenagers are taught communication skills.</td>
<td></td>
</tr>
<tr>
<td>• Programs are tailored to meet the needs of specific groups of young people (young men or young women; cultural groups; younger or older teens; etc.).</td>
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**Bibliography**


Rape is an act of violence, not an act of sex. Rape is coercive sexual intercourse involving physical force or psychological manipulation of a female or a male. Rape is defined as penetration of any genital, oral, or anal orifice by a part of the assailant’s body or any object.

EPIDEMIOLOGY

Exact figures on the incidence of rape are unavailable because many rapes are not reported. Females exceed males as reported rape victims by 8:1 to 10:1, but male rape may be more underreported than female rape. In the United States, the annual rates of sexual victimization per 1,000 persons were reported in 2010 by the U.S. Department of Justice, National Crime Victimization Survey to be 4.1 for ages 12-17 yr, and 3.7 for ages 18-34 yr. The highest annual rate of sexual victimization has continued to be among 16-19 yr old adolescents. Rape occurs worldwide and is especially prevalent in war and armed conflicts. The World Health Organization estimates that rape and domestic violence are responsible for 5-16% of healthy years of life lost by females of reproductive age.

Female adolescents and young adults account for the highest rates of rape compared to any other age group. The normal developmental growth tasks of adolescence may contribute to this vulnerability in the following ways: (1) the emergence of independence from parents and the establishment of relationships outside the family may expose adolescents to environments with which they are unfamiliar and situations that they are unprepared to handle; (2) dating and becoming comfortable with one's sexuality may result in activities that are unwanted, but the adolescent is too inexperienced to stop the unwanted actions; and (3) young adolescents may be naïve and more trusting than they should be (see Chapter 110). Many teens are computer competent, which gives sexual perpetrators access to unsuspecting vulnerable populations who were previously beyond their reach. Chat rooms and online dating sites represent a major risk for adolescents, resulting in correspondence with individuals unknown to them or protective family members, while simultaneously providing a false sense of security because of remote electronic communications. A determined perpetrator can obtain specific information to identify the adolescent and arrange for a meeting that is primed for sexual victimization.

Some adolescents are at higher risk of being victims of rape than others (Table 119-1).

TYPES OF RAPE

Acquaintance rape (by a person known to the victim) is the most common form of rape for victims 16-24 yr of age. The acquaintance may be a neighbor, classmate, or friend of the family. The victim-assailant relationship may cause conflicting loyalties in families, and the teen's report may be received with disbelief and/or skepticism by the teen's family. Adolescent acquaintance rape differs from adult acquaintance rape because weapons are less-often used, and victims are less likely to sustain physical injuries. Victims of acquaintance rape are also more likely to delay seeking medical care, may never report the crime (males greater than females), and are less likely to proceed with criminal prosecution even after reporting the incident(s).

Date rape (by a person dating the victim) is often drug facilitated and is prevalent in adolescent populations. Date rape drugs are pharmaceuticals administered in a clandestine manner to potential victims. γ-Hydroxybutyric acid (GHB), Flunitrazepam (Rohypnol), and ketamine hydrochloride are the leading agents used for these illegal purposes, but may also include alcohol, benzodiazepines, stimulants, barbiturates, opiates, and other drugs (see Chapter 114). The pharmacologic properties of these drugs make them suitable for this use as they have simple modes of administration, are easily concealed...
Adolescents at High Risk of Rape Victimization

**MALE AND FEMALE ADOLESCENTS**
- Drug and alcohol users
- Runaways
- Those with intellectual disability or developmental delay
- Street youths
- Transgender youth
- Youths with a parental history of sexual abuse

**PRIMARILY FEMALES**
- Survivors of prior sexual assault
- Newcomers to a town or college

**PRIMARILY MALES**
- Those in institutionalized settings (detention centers, prison)
- Young male homosexuals

(colorless, odorless, tasteless), have rapid onsets of action with resulting induction of anterograde amnesia, and have rapid eliminations as a result of short half-lives. Detection of these drugs requires a high index of suspicion and medical evaluation within 8-12 hr, prompting specific testing because routine toxicology screening is insufficient.

Date rape victims are often new to a specific environment (college freshman, newcomer to a town) and lack strong social support. Victims may not be assertive in establishing boundaries or limits with their dates and may be intoxicated when the incident takes place. The date rape assailant may engage in more sexual activities than other men his age and often has a history of aggressive behavior toward women. He may interpret passivity as assent and deny the charge of coercion or force; he may also be intoxicated at the time of the assault.

A date rape victim often experiences long-term issues of trust, self-blame, and guilt. She may lose confidence in her judgment concerning men in the future. She is nearly always ashamed of the incident and is less likely to report the rape. She is reluctant to talk about the rape to family, friends, or a counselor and may never heal from the psychological scars that ensue.

Male rape generally refers to same-sex rape of male teens by other males. Specific subgroups of young men are at high risk of being victims of rape (see Table 119-1). Male rape is most prevalent within institutional settings. Male rape that occurs outside of institutional settings typically involves coercion of the male teen by someone considered an authority figure, either male or female. Male rape victims often experience conflicted sexual identity about whether or not they are homosexual. Issues of loss of control and powerlessness are particularly bothersome for male rape victims, and these young men commonly have symptoms of anxiety, depression, sleep disturbance, and suicidal ideation. Males are less likely than females to report rape and less likely to seek professional help.

Gang rape usually occurs when a group of young men rape a solitary female victim. This type of rape may be part of a ritualistic activity or rite of passage for some male group (gangs, college fraternity) or be displaced rape on the part of the assailants.

Female victims of gang rape may find it difficult to return to the environment in which the rape occurred for fear of confrontation with the assailants (college setting or place of employment) and may insist on moving away from the locale entirely.

Statutory rape refers to sexual activity between an adult and an adolescent under the age of legal consent, as defined by individual state law. Statutory rape laws are based on the premise that below a certain age, an individual is not legally capable of giving consent to engage in sexual intercourse. In some states in the United States, statutory rape laws apply to sexual contact or intercourse occurring between a minor and another individual with a specific age difference even when both are minors and both assert that the sexual act was voluntary (an 18 yr old male who has sexual intercourse with a 14 yr old female). The intent of such laws is to protect youths from being victimized, but they may inadvertently lead a teenager to withhold pertinent sexual information from a clinician for fear that her sexual partner will be reported to the law. A clinician must be familiar with the laws of the state or province in which the clinician is practicing medicine.

**Stranger rape** occurs less frequently within the adolescent population and is most similar to adult rape. Such rapes frequently occur with an abduction, use of weapons, and increased risk of physical injuries. These rapes are more likely to be reported and prosecuted.

**CLINICAL MANIFESTATIONS**

The adolescent’s acute presentation following a rape may vary considerably, from histrionics to near-mute withdrawal. Even if they do not seem to be afraid, most victims are extremely fearful and very anxious about the incident, the rape report, examination, and the entire process including potential repercussions. Because adolescents are between the developmental lines of childhood and adulthood, their responses to rape may have elements of both child and adult behaviors. Many teens, particularly young adolescents, may experience some level of cognitive disorganization.

Adolescents may be reluctant to report rape for a variety of reasons, including self-blame, fear, embarrassment, or in the circumstances of drug-facilitated rape, uncertainty of event details. Adolescent victims, unlike child victims who elicit sympathy and support, are often faced with intense scrutiny regarding their credibility and inappropriately misplaced societal blame for the assault. This view is baseless and should not be used during an evaluation of any teenage victim, including acquaintance rape.

When adolescents do not report a rape, they may present at a future date with symptoms of posttraumatic stress disorder (see Chapters 25 and 39), such as sleep disturbances, nightmares, mood swings, and flashbacks. Other teens may present with psychosomatic complaints or difficulties with schoolwork; all adolescents should be screened for the possibility of sexual abuse at nearly all health examination visits.

**INTERVIEW AND PHYSICAL EXAMINATION**

Although many teens delay seeking medical care, others present to a medical facility within 72 hr (or up to 96 hr depending on the protocol used) of the rape, at which time forensic evidence collection should be completed. Experienced clinicians with training and knowledge of forensic evidence collection and medical-legal procedures should complete the rape evaluation or supervise the evaluation when possible.

The clinician’s responsibilities are to provide support, to obtain the history in a nonjudgmental manner, to conduct a complete examination without retraumatizing the victim, and to collect forensic evidence. The clinician must complete laboratory testing, administer prophylaxis treatment for sexually transmitted infections (STIs) and emergency contraception, arrange for counseling services, and file a report to appropriate authorities. It is not the clinician’s responsibility to decide whether a rape has occurred; the legal system will make that determination.

Ideally, a clinician trained in forensic interviewing should obtain the history. In all cases, the history should be obtained by asking only open-ended questions to obtain information about: (1) what happened; (2) where did it happen; (3) when did it happen; and (4) who did it. After obtaining a concise history including details of the physical contact that occurred between the victim and the assailant, the clinician should conduct a thorough and complete physical examination and document all injuries. Clinicians should provide sensitive, nonjudgmental support during the entire evaluation, as the adolescent victim has experienced a major trauma and is susceptible to retraumatization during this process. Each component of the evaluation should be explained in detail to the victim, allowing the adolescent as much control as possible, including refusal to complete any part or all of the forensic evidence collection process. It is often useful to permit a trusted supportive person, such as a family member, friend or rape crisis advocate, to be present during the evaluation if that is the adolescent’s wish.

The examining clinician should be familiar with the forensic evidence collection kit prior to initiating the examination. In the United States, each state’s forensic evidence kit is different, but most include
some or all of the following components: forensic evidence of semen deposits detected by a fluorescent lamp with a wavelength near 490 nm (many Woods lamps are inadequate); swabs of bite mark impressions to collect genetic markers (DNA, ABO group); swabs of any penetrated orifice; and documentation of acute cutaneous injuries using body diagram charts and/or photographs with visible standard measurements. Areas of restraint should be carefully inspected for injuries; these areas include extremities, neck, and the inner aspect of the oral mucosa where a dentition impression may be seen.

The genital examination of a female rape victim should be undertaken with the patient in the lithotomy position. The genital examination of a male rape victim should be undertaken with the patient in supine position. The clinician’s examination should include careful inspection of the entire pelvic, genital, and perianal areas. The clinician should document any acute injuries such as edema, erythema, petechiae, hemorrhage, or tearing. Aqueous solution of toluidine blue (1%), which adheres to nucleated cells, may be used during the acute examination to improve visualization of microtrauma in the perianal area. Additionally, a colposcope may be used to provide magnification and photodocumentation of injuries.

LABORATORY DATA

The forensic evidence kit should be completed when clinically indicated and if the patient is evaluated within 72-92 hr of sexual assault. Table 119-2 lists additional laboratory studies required during initial evaluation. Follow-up evaluations should be scheduled to repeat these laboratory studies.

TREATMENT

Medical treatment includes prophylaxis treatment for STIs (see Chapter 120) and emergency contraception (see Chapter 117). The Centers for Disease Control and Prevention estimates that the risk for acquiring STIs following a sexual assault in adults is 6-12% for Neisseria gonorrhoeae, 4-17% for Chlamydia trachomatis, and 0.5-3.0% for syphilis. Antimicrobial prophylaxis is recommended for adolescent rape victims because of the risk of acquiring an STI and the risk of pelvic inflammatory disease (Table 119-3). HIV postexposure prophylaxis should be considered and consultation with an infectious disease specialist sought if higher transmission risk factors are identified (e.g., knowing that the perpetrator is HIV-positive, significant mucosal injury of the victim) to prescribe a triple antiretroviral regimen. Clinicians should review the importance for patient’s compliance with medical and psychological treatment and follow-up.

<table>
<thead>
<tr>
<th>Table 119-2</th>
<th>Laboratory Data for Evaluation of Rape Victims</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>WITHIN 8-12 HR (IF INDICATED BY HISTORY)</strong></td>
<td>Urine and blood for date rape drugs (GHB, Rohypnol, and ketamine)</td>
</tr>
<tr>
<td></td>
<td>Comprehensive toxicology screen (for other classes of drugs)</td>
</tr>
<tr>
<td><strong>WITHIN 72 HR (OR UP TO 96 HR DEPENDING ON THE PROTOCOL USED)</strong></td>
<td>Forensic evidence kit</td>
</tr>
<tr>
<td></td>
<td>Urinalysis</td>
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<tr>
<td></td>
<td>Pregnancy test</td>
</tr>
<tr>
<td></td>
<td>Hepatitis B screen</td>
</tr>
<tr>
<td></td>
<td>Syphilis (rapid plasma reagin [RPR], Venereal Disease Research Laboratory [VDRL])</td>
</tr>
<tr>
<td></td>
<td>Herpes simplex virus titer (I and II)</td>
</tr>
<tr>
<td></td>
<td>HIV</td>
</tr>
<tr>
<td></td>
<td>Wet mount for the detection of spermatozoa, Trichomonas vaginalis, and bacterial vaginosis</td>
</tr>
<tr>
<td></td>
<td>Cultures obtained based on history of physical contact for:</td>
</tr>
<tr>
<td></td>
<td>Oropharynx: Neisseria gonorrhoeae</td>
</tr>
<tr>
<td></td>
<td>Rectal: N. gonorrhoeae and Chlamydia</td>
</tr>
<tr>
<td></td>
<td>Urethral (male): N. gonorrhoeae and Chlamydia</td>
</tr>
<tr>
<td></td>
<td>Endocervical (female): N. gonorrhoeae and Chlamydia</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 119-3</th>
<th>Prophylaxis Treatment for Rape Victims</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Neisseria gonorrhoeae</strong></td>
<td>Ceftriaxone 250 mg IM x 1 dose</td>
</tr>
<tr>
<td></td>
<td>If positive for gonorrhea, treatment is:</td>
</tr>
<tr>
<td></td>
<td>Ceftriaxone 20 mg IM x 1 dose plus</td>
</tr>
<tr>
<td></td>
<td>Azithromycin 1 g PO x 1 dose or</td>
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<tr>
<td></td>
<td>doxycycline 10 mg PO bid x 7 days</td>
</tr>
<tr>
<td><strong>Chlamydia trachomatis</strong></td>
<td>Azithromycin 1 g PO x 1 dose</td>
</tr>
<tr>
<td></td>
<td>or Doxycycline 100 mg PO bid x 7 days</td>
</tr>
<tr>
<td><strong>Trichomonas vaginalis and bacterial vaginosis</strong></td>
<td>Metronidazole 2 g PO x 1 dose</td>
</tr>
<tr>
<td><strong>HIV</strong></td>
<td>Combivir 1 tab PO bid x 28 days or</td>
</tr>
<tr>
<td></td>
<td>Truvada 1 tab PO qd x 28 days</td>
</tr>
<tr>
<td><strong>Hepatitis B</strong></td>
<td>Complete immunizations</td>
</tr>
<tr>
<td><strong>Human papillomavirus</strong></td>
<td>Complete immunizations</td>
</tr>
<tr>
<td><strong>Emergency contraception</strong></td>
<td>Oral 2 tabs (0.05 mg ethinyl estradiol, 0.50 mg norgestrel) and 2nd dose in 12 hr</td>
</tr>
<tr>
<td></td>
<td>Plan B 1 tab (0.75 mg levonorgestrel) and 2nd dose in 12 hr, or both pills together as 1 dose</td>
</tr>
</tbody>
</table>

*Prophylaxis is recommended for all 3 STIs.
†HIV postexposure prophylaxis is provided for patients with penetration and when the assailant is known to be HIV-positive or at high risk because of a history of incarceration, intravenous drug use, or multiple sexual partners. If provided, follow-up must be arranged.
‡Provided for patients with negative urine pregnancy screen for patients receiving emergency contraception medication other than Plan B. In addition, provide antiemetic (Compazine, Zofran) for patients receiving emergency contraception medication other than Plan B.

At the time of presentation, the clinician should address the need for follow-up care, including psychological counseling. Adolescent victims are at increased risk of posttraumatic stress disorder, depression, self-abusive behaviors, suicidal ideation, delinquency, substance abuse, eating disorders, and sexual revictimization. It is important for the adolescent victim and parents to understand the value of timely counseling services to decrease these potential long-term sequelae. Counseling services should be arranged during the initial evaluation, with follow-up arranged with the primary care physician to improve compliance. Counseling services for family members of the victim may improve their ability to provide appropriate support to the adolescent victim. Caution parents not to use the assault as a validation of their parental guidance, as it will only serve to place blame inappropriately on the adolescent victim.

PREVENTION

Primary prevention may be accomplished through education of preadolescents and adolescents on the issues of rape, healthy relationships, Internet dangers, and drug-facilitated rape. Prevention messages should be targeted to both males and females at high schools and colleges. Particular emphasis on prevention efforts during college orientation is highly recommended. High-risk situations that may increase the likelihood of a sexual assault (use of drugs or alcohol) should be discouraged. Secondary prevention includes informing adolescents of the benefits of timely medical evaluations when rape has occurred. Individual clinicians should ask adolescents about past experiences of forced and unwanted sexual behaviors and offer help in dealing with those experiences. The importance of prevention cannot be overstated because adolescents are disproportionately affected by rape and they are particularly vulnerable to long-term consequences.

Bibliography is available at Expert Consult.
Age-specific rates of many sexually transmitted infections (STIs) are highest among sexually experienced adolescents and young adults, after controlling for sexual activity. Although some STI pathogens present as STI syndromes with a specific constellation of symptoms, most are asymptomatic and only detected by a laboratory test. The approach to prevention and control of these infections lies in education, screening, and early diagnosis and treatment.

ETIOLOGY
Any adolescent who has had oral, vaginal, or anal sexual intercourse is at-risk for acquiring an STI. Not all adolescents are at equal risk; physical, behavioral, and social factors contribute to the adolescent’s higher risk (Table 120-1). Adolescents who initiate sex at a younger age, youth residing in detention facilities, youth attending sexually transmitted disease clinics, young men having sex with men, and youth who are injecting-drug users are at higher risk for STIs. Risky behaviors, such as sex with multiple concurrent partners or multiple sequential partners of limited duration, failure to use barrier protection consistently and correctly, and increased biologic susceptibility to infection, also contribute to risk. Although all 50 states and the District of Columbia explicitly allow minors to consent for their own sexual health services, many adolescents encounter multiple obstacles to accessing this care. Adolescents who are victims of sexual assault may not consider themselves “sexually active,” given the context of the encounter, and need reassurance, protection, and appropriate intervention when these circumstances are uncovered (see Chapter 119).

EPIDEMIOLOGY
STI prevalence varies by age, gender, and race/ethnicity. In the United States, although adolescents and young adults ages 15-24 yr represent 25% of the sexually experienced population, this age group accounts for nearly 50% of all incident STIs each year. Adolescents and young adults < 25 yr of age have the highest reported prevalence of gonorrhea (see Chapter 192) and chlamydial (see Chapter 226) infection; among females and males, rates are highest in the 15-24 yr old age groups (Fig. 120-1). In 2012, females 20-24 yr of age had the highest reported chlamydia rate (3,696 per 100,000 population), followed by females 15-19 yr of age (3,293 per 100,000 population). The reported 2012 chlamydia rate for 15-19 yr old females was more than 4 times higher than for 15-19 yr old males. Chlamydia is common among all races and ethnic groups; Blacks, Native American/Alaska Native, and Hispanic females are disproportionately affected. In 2011, non-Hispanic black females 20-24 yr of age had the highest chlamydia rate of any group (7,863), followed by black females 15-19 yr of age (7,719). Data from the 2007-2008 National Health and Nutrition Examination Survey estimated the prevalence of chlamydia among the U.S. population was highest among African-Americans (Fig. 120-2).

Reported rates of other bacterial STIs are also high among adolescents and young adults. In 2012, 20-24 yr old females had the highest (579 per 100,000 population) and 15-19 yr old females had the second highest gonorrhea rates (521 per 100,000 population) compared to any other age/sex group (see Chapter 192). Following a period of decreasing gonorrhea rates among 20-24 yr old, rates have increased for the past 3 yr. Primary and secondary syphilis rates among 15-19 yr old

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**Table 120-1** Circumstances Contributing to Adolescents’ Susceptibility to Sexually Transmitted Infections

<table>
<thead>
<tr>
<th>PHYSICAL</th>
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</thead>
<tbody>
<tr>
<td>Younger age at puberty</td>
<td>Cervical ectopy</td>
<td>Smaller introitus leading to traumatic sex</td>
</tr>
<tr>
<td>Asymptomatic nature of sexually transmitted infection</td>
<td>Uncircumcised penis</td>
<td></td>
</tr>
</tbody>
</table>

**BEHAVIOR LIMITED BY COGNITIVE STAGE OF DEVELOPMENT**

Early adolescence: have not developed ability to think abstractly
Middle adolescence: develop belief of uniqueness and invulnerability

**SOCIAL FACTORS**

Poverty
Limited access to “adolescent friendly” healthcare services
Adolescent health-seeking behaviors (focusing care because of confidentiality concerns or denial of health problem)
Sexual abuse and violence
Homelessness
Young adolescent females with older male partners

females have decreased annually since 2009 from 3.5 cases per 100,000 population to 2.3 per 100,000 population in 2012 (see Chapter 218). Rates among females have been the highest each year in the 20-24 yr age group (3.9 cases per 100,000 population in 2012). Primary and secondary syphilis rates among 15-19 yr old males are much lower than those in older males, although rates among males age 20-24 yr have increased consecutively since 2002, from 5.2 cases per 100,000 males to 23.4 cases in 2011. Males age 20-24 yr also have had the highest rate of primary and secondary syphilis among males of any age group since 2008. Pelvic inflammatory disease (PID) rates are highest in females age 15-24 yr when compared to older women.

Adolescents also suffer from a large burden of viral STIs. Young people in the United States are at persistent risk for HIV infection (see Chapter 278). In 2009, youths age 13-24 yr, who represented 21% of the U.S. population, comprised 7% of persons living with HIV. In 2010, 26% of the estimated 47,500 new HIV infections were among 13-24 yr olds. Of those new infections, 57% were among blacks, 20% among Hispanic/Latinos, and 20% among whites. Nearly 75% of the 12,200 new HIV infections among youths were attributable to male-to-male sexual contact. Only a low percentage of youths have been tested for HIV, and 60% of youths with HIV are unaware of their infection.

The STI with the highest estimated incidence in the United States is human papillomavirus (HPV). The 2003-2006 National Health and Nutrition Examination Survey (NHANES) found a third of females age 14-24 yr old were actively infected with HPV. The highest HPV infection prevalence was among females age 20-24 yr (54%; 95% confidence interval [CI], 46-62%; see Chapter 266). Although HPV infection is common, studies suggest approximately 90% of infections clear within 2 yr.

Herpes simplex virus-2 (HSV-2) is the most prevalent viral STI (see Chapter 252). HSV-2 prevalence rates among adolescents in the United States and young adults appear to be decreasing. The 2005-2008 NHANES estimated that 1.4% (95% CI, 1.0-2.0) of adolescents age 14-19 yr were infected with HSV-2, which is about a 76% decrease observed from the 1988-1994 NHANES and 10.5% (95% CI, 9.0-12.3) of 20-29 yr olds are HSV-2 seropositive, which is a 39% decrease compared to the 1988-1994 NHANES.

Pathogenesis
During puberty, increasing levels of estrogen cause the vaginal epithelium to thicken and cornify and the cellular glycogen content to rise, the latter causing the vaginal pH to fall. These changes increase the resistance of the vaginal epithelium to penetration by certain organisms (including Neisseria gonorrhoeae) and increase the susceptibility to others (Candida albicans and Trichomonas; see Chapter 284). The transformation of the vaginal cells leaves columnar cells on the ectocervix, forming a border of the 2 cell types on the ectocervix, known as the squamocolumnar junction. The appearance is referred to as ectopy (Fig. 120-3). With maturation, this tissue involutes. Prior to involution, it represents a unique vulnerability to infection for adolescent females. A 15 yr old sexually active female with endocervical colonization has a 1:8 chance of developing PID compared to the 1:80 chance for a 24 yr old. As a result of these physiologic changes, gonococcal infection becomes primarily cervical and susceptibility to ascending infection is greatest during menses, when the pH is 6.8-7.0. The association of early sexual debut and younger gynecologic age with increased risk of STIs supports this explanation of the pathogenesis of infection in young adolescents.

Sexually Transmitted Infection Screening
Early detection and treatment are the primary STI control strategies. Some of the most common STIs in adolescents, including HPV, HSV, chlamydia, and gonorrhea, are usually asymptomatic and if undetected can be spread inadvertently by the infected host. Screening initiatives for chlamydial infections have demonstrated reductions in PID cases by up to 40%. Although federal and professional medical organizations recommend annual chlamydia screening for sexually active females 25 yr and younger, according to the National Center for Quality Assurance, in 2012 approximately 40% of commercially insured and 54% of Medicaid insured 16-20 yr old sexually active females were tested for chlamydia during the previous year. The lack of a dialog about STIs or the provision of STI services at annual preventive service visits to adolescents who are sexually experienced are missed opportunities for screening and education. Comprehensive, confidential, reproductive health services, including STI screening, should be offered to all sexually experienced adolescents (Table 120-2).

Definitions, Etiology, and Clinical Manifestations
STI syndromes are generally characterized by the location of the manifestation (vaginitis) or the type of lesion (genital ulcer). Certain constellations of presenting symptoms suggest the inclusion of a possible STI in the differential diagnosis.

Urethritis
Urethritis is an STI syndrome characterized by inflammation of the urethra, usually caused by an infectious etiology. Urethritis may present with urethral discharge, dysuria, urethral irritation, or meatal pruritus. Urgency, frequency of urination, erythema of the urethral meatus, and urethral pain or burning are less common clinical presentations. Approximately 30-50% of males are asymptomatic but may have signs of discharge on diagnosis. On examination, the classic finding is mucoid or purulent discharge from the urethral meatus (Fig. 120-4). If no discharge is evident on exam, providers may attempt to express discharge by applying gentle pressure to the urethra from the base distally to the meatus 3-4 times. Chlamydia trachomatis and N. gonorrhoeae are the most commonly identified pathogens. Mycoplasma genitalium has been associated with urethritis, but data supporting Ureaplasma urealyticum have been inconsistent. Trichomonas vaginalis can cause NGU, but the prevalence varies. HSV-1, HSV-2, and Epstein-Barr virus are also potential urethritis pathogens in some cases. Sensitive diagnostic C. trachomatis and N. gonorrhoeae tests are available for the evaluation of urethritis. However, other pathogens can be considered when NGU is not responsive to treatment, although commercial diagnostic tests are not available for males. Noninfectious causes of urethritis include urethral trauma or foreign body. Unlike in females, urinary tract infections are rare in males who have no genitourinary medical history. In the typical sexually active adolescent male, dysuria and urethral discharge suggest the presence of an STI unless proven otherwise.

Epididymitis
The inflammation of the epididymis in adolescent males is most often associated with an STI, most frequently C. trachomatis or N. gonorrhoeae. The presentation of unilateral scrotal swelling and tenderness, often accompanied by a hydrocele and palpable swelling of the epididymis, associated with the history of urethral discharge, constitute the presumptive diagnosis of epididymitis. Males who practice insertive
anal intercourse are also vulnerable to *Escherichia coli* infection. Testicular torsion, a surgical emergency usually presenting with sudden onset of severe testicular pain, should be considered in the differential diagnosis (see Chapter 545). The evaluation for epididymitis should include obtaining evidence of urethral inflammation by physical exam, Gram stain of urethral secretions, urine leukocyte esterase test, or urine microscopy. A *C. trachomatis* and *N. gonorrhoeae* nucleic acid amplification test (NAAT) should be performed.

### Vaginitis

Vaginitis is a superficial infection of the vaginal mucosa frequently presenting as a vaginal discharge, with or without vulvar involvement (see Chapter 549). **Bacterial vaginosis, vulvovaginal candidiasis,** and trichomoniasis are the predominant infections associated with vaginal discharge. Bacterial vaginosis is replacement of the normal H<sub>2</sub>O<sub>2</sub>–producing *Lactobacillus* sp. vaginal flora by an overgrowth of anaerobic microorganisms as well as *Gardnerella vaginalis*, *Ureaplasma*, and *Mycoplasma*. Although bacterial vaginosis is not categorized as an STI, sexual activity is associated with increased frequency of vaginosis. Vulvovaginal candidiasis, usually caused by *C. albicans*, can trigger vulvar pruritus, pain, swelling, and redness and dysuria. Findings on vaginal exam include vulvar edema, fissures, excoriations, or thick curdy vaginal discharge. Trichomoniasis is caused by the protozoan *T. vaginalis*. Infected females may present with symptoms characterized by a diffuse, malodorous, yellow-green vaginal discharge with vulvar irritation or may be diagnosed by screening an asymptomatic patient. Cervicitis can sometimes cause a vaginal discharge. Laboratory confirmation is recommended because clinical presentations may vary and patients may be infected with more than 1 pathogen.

### Cervicitis

The inflammatory process in cervicitis involves the deeper structures in the mucous membrane of the cervix uteri. Vaginal discharge can be a manifestation of cervicitis, however, cervicitis frequently is asymptomatic. Patients also commonly present with complaints of irregular or postcoital bleeding. Two major diagnostic signs characterize cervicitis: (1) a purulent or mucopurulent endocervical exudate visible in the endocervical canal or on an endocervical swab specimen (e.g., swab sign, Fig. 120-5), commonly referred to as mucopurulent cervicitis or cervicitis, and (2) sustained endocervical bleeding easily induced by gentle passage of a cotton swab through the cervical os signifying friability. Cervical changes associated with cervicitis must be distinguished from cervical ectopy in the younger adolescent to avoid the over diagnosis of inflammation (Fig. 120-6; see Fig. 120-3). The pathogens identified most commonly with cervicitis are *C. trachomatis* and *N. gonorrhoeae*, although no pathogen is identified in the majority of cases. HSV is a less-common pathogen associated with ulcerative and necrotic lesions on the cervix.
Pelvic Inflammatory Disease

PID encompasses a spectrum of inflammatory disorders of the female upper genital tract, including endometritis, salpingitis, tuboovarian abscess, and pelvic peritonitis, usually in combination rather than as separate entities. N. gonorrhoeae and C. trachomatis predominate as the involved pathogenic organisms in younger adolescents, although PID should be approached as multiorganism etiology, including pathogens such as anaerobes, G. vaginalis, Haemophilus influenzae, enteric Gram-negative rods, and Streptococcus agalactiae. In addition, cytomegalovirus (see Chapter 255), Mycoplasma hominis, U. urealyticum, and M. genitalium (see Chapter 224) may be associated with PID.

PID is difficult to diagnose because of the wide variation in the symptoms and signs. Many females with PID have subtle or mild symptoms resulting in many unrecognized cases. Healthcare providers should consider the possibility of PID in young sexually active females presenting with vaginal discharge and/or abdominal pain.

The clinical diagnosis of PID is based on the presence of at least 1 of the minimal criteria, either cervical motion tenderness, uterine tenderness, or adnexal tenderness, to increase the diagnostic sensitivity and reduce the likelihood of missed or delayed diagnosis. Providers should also consider that adolescents are the population in which PID is typically diagnosed and thus should have a low threshold for initiating empiric treatment. In addition, the majority of females with PID have either mucopurulent cervical discharge or evidence of white blood cell (WBC) on a microscopic evaluation of a vaginal fluid saline preparation. If the cervical discharge appears normal and no WBCs are observed on the wet prep of vaginal fluid, the diagnosis of PID is unlikely, and alternative causes of pain should be investigated. Specific, but not always practical, criteria for PID include evidence of endometritis on biopsy, transvaginal sonography or MRI evidence of thickened, fluid-filled tubes, or Doppler evidence of tubal hyperemia or laparoscopic evidence of PID.

Genital Lesions and Ectoparasites

Lesions that present as outgrowths on the surface of the epithelium and other limited epidermal lesions are included under this categorization of syndromes. HPV can cause genital warts and genital cervical abnormalities that can lead to cancer. Genital HPV types are classified according to their association with cervical cancer. Infections with low-risk types, such as HPV types 6 and 11, can cause benign or low-grade changes in cells of the cervix, genital warts, and recurrent...
HIV Disease and Hepatitis B

HIV and hepatitis B present as an asymptomatic, unexpected occurrences in most infected adolescents. High vaccination coverage rates among infants and adolescents have resulted in substantial declines in acute hepatitis B incidence among U.S.-born adolescents. Risk factors identified in the history or routine screening during prenatal care are much more likely to result in suspicion of infection, leading to the appropriate laboratory screening, than are clinical manifestations in this age group (see Chapters 276 and 358).
Diagnosis
Most commonly, adolescents infected with viral and bacterial STI pathogens do not report symptoms suggestive of infection. With the increased use of very sensitive, noninvasive chlamydia and gonorrhea NAATs, providers are finding that most genital infections in females as well as many males are asymptomatic. A thorough sexual history is key to identifying adolescents who should be screened for STIs and for identifying those who require a laboratory diagnostic evaluation for a sexually transmitted disease syndrome.

When eliciting a sexual health history, discussions should be appropriate for the patient's developmental level. In addition to questions regarding vaginal or urethral discharge, genital lesions, and lower abdominal pain among females, one should ask about prior treatment of any STI symptoms, including self-treatment using nonprescription medications. Dyspareunia is a consistent symptom in adolescents with PID. Providers must ask about oral or anal sexual activity to determine sites for specimen collection.

Urethritis should be objectively documented by evidence of inflammation or infectious etiology. Patient complaint without objective clinical or laboratory evidence does not fulfill diagnostic criteria. Inflammation can be documented by (a) observing urethral mucopurulent discharge, (b) ≥2 WBC per high-power field on microscopic examination Gram stain urethral secretions, (c) urine microscopic findings of ≥10 WBCs per high power field of first-void urine specimen, or (d) a positive urine leukocyte esterase test of a (first-void urine) specimen. Laboratory evaluation is essential to identify the involved pathogens to determine treatment, partner notification, and disease control. C. trachomatis and N. gonorrhoeae NAATs of a urine specimen are recommended. The presence of Gram-negative intracellular diplococci on microscopy obtained from a male urethral specimen confirms the diagnosis of gonococcal urethritis.

An essential component of the diagnostic evaluation of vaginal, cervical or urethral discharge is a chlamydia and gonorrhea NAAT. NAATs are the most sensitive chlamydia and gonorrhea tests available and are licensed for use with urine, urethral, vaginal, and cervical specimens. Many of the chlamydia NAATs are approved by the Food and Drug Administration (FDA) to test patient-collected vaginal swabs in the clinical setting and liquid cytology specimens. Female vaginal swab specimens and male first-void urine are considered the optimal specimen types. Female urine remains an acceptable chlamydia and gonorrhea NAAT specimen, but may have slightly reduced performance when compared with cervical or vaginal swab specimens. Urine is the recommended specimen for male urethral infection. Gonorrhea and chlamydia NAATs perform well on rectal and oropharyngeal specimens and can be performed by clinical laboratories that have completed the appropriate verification studies to obtain Clinical Laboratory Improvement Amendments (CLIA)-approval, which include most commercial laboratories.

Evaluation of adolescent females with vaginitis includes laboratory data. Traditionally, the cause of vaginal symptoms was determined by pH and microscopic examination of the discharge. However, newer CLIA-waived point-of-care vaginitis tests are available. Using pH paper, an elevated pH (i.e., >4.5) is common with bacterial vaginosis or trichomoniasis. For microscopic exam, a slide can be made with the discharge diluted in 1-2 drops of 0.9% normal saline solution and another slide with discharge diluted in 10% potassium hydroxide (KOH) solution. Examining the saline specimen slide under a microscope may reveal motile or dead T. vaginalis or clue cells (epithelial cells with borders obscured by small bacteria), which are characteristic of bacterial vaginosis. WBCs without evidence of trichomonads or yeast are usually suggestive of cervicitis. The yeast or pseudohyphae of Candida species are more easily identified in the KOH specimen (Fig. 120-8). The
sensitivity of microscopy is approximately 50% and requires immediate evaluation of the slide for optimal results. Therefore, lack of findings does not eliminate the possibility of infection. More sensitive, point-of-care vaginitis tests include the OSOM Trichomonas Rapid Test (Sekisui Diagnostics, Lexington, MA), an immunochromatographic capillary flow dipstick technology that reports an 83% sensitivity; and the OSOM BVBLUE Test (Sekisui Diagnostics, Lexington, MA), which detects elevated vaginal fluid sialidase activity, an enzyme produced by bacterial pathogens associated with bacterial vaginosis including Gardnerella, Bacteroides, Prevotella, and Mobiluncus, that reports a 90% sensitivity. Both of these tests are CLIA-waived with results are available within 10 minutes.

Clinical laboratory-based vaginitis tests are also available. The Affirm VP III (Becton Dickinson, San Jose, CA), a nucleic acid probe test that evaluates for T. vaginalis, G. vaginalis, and C. albicans, is a moderate complexity laboratory test, has a sensitivity >83% and a specificity >97%, with results are available within 45 min. Some gonorrhea and chlamydia NAA Ts also offer an assay for T. vaginalis testing of female specimens tested for N. gonorrhoeae and C. trachomatis, which are considered the gold standard for trichomonas testing.

Objective signs of vulvar inflammation in the absence of vaginal pathogens, along with a minimal amount of discharge, suggest the possibility of mechanical, chemical, allergic, or other noninfectious irritation of the vulva (Table 120-4).

The definitive diagnosis of PID is difficult based on clinical findings alone. Clinical diagnosis is imprecise and no single historical, physical, or laboratory finding is both sensitive and specific for the diagnosis of acute PID. Clinical criteria have a positive predictive value of only 65-90% compared with laparoscopy. Although healthcare providers should maintain a low threshold for the diagnosis of PID, additional criteria to enhance specificity of diagnosis, such as transvaginal ultrasonography, can be considered (Table 120-5).

Cell culture and PCR are the preferred HSV tests. Viral culture sensitivity is low and false negatives do occur as a consequence of intermittent viral shedding. NAA Ts, including PCR assays for HSV DNA, are more sensitive and increasingly available for diagnosing genital HSV. The Tzanck test is insensitive and nonspecific and should not be relied on.

Accurate type-specific HSV serologic assays are based on the HSV-specific glycoprotein G2 (HSV-2) and glycoprotein G1 (HSV-1). Both laboratory-based and point-of-care tests are available. Because nearly all HSV-2 infections are sexually acquired, the presence of type-specific HSV-2 antibody implies anogenital infection. The presence of HSV-1 antibody alone is more difficult to interpret because of the frequency of oral HSV infection acquired during childhood. Type-specific HSV serologic assays might be useful in the following scenarios: (1) recurrent genital symptoms or atypical symptoms with negative HSV cultures; (2) a clinical diagnosis of genital herpes without laboratory confirmation; and (3) a patient with a partner with genital herpes, especially if considering suppressive antiviral therapy to prevent transmission.

For syphilis testing, nontreponemal tests, such as the rapid plasma reagin (RPR) or Venereal Disease Research Laboratory (VDRL), and treponemal testing, such as fluorescent treponemal antibody absorbed tests, the T. pallidum passive particle agglutination (TP-PA) assay, various enzyme and chemiluminescence immunoassays (EIA/CIA) are recommended. However, many clinical laboratories have adopted a reverse sequence of screening in which a treponemal EIA/CIA is performed first, followed by testing of reactive sera with a nontreponemal test (e.g., RPR). A positive treponemal EIA or CIA test can identify both previously treated and untreated or incompletely treated syphilis. False-positive results can occur, particularly among populations with low syphilis prevalence. Persons with a positive treponemal screening test should have a standard nontreponemal test with titer, such as an RPR or VDRL to guide patient management decisions. If EIA/CIA and nontreponemal test (e.g., RPR or VDRL) test results are discordant, the laboratory should perform a different treponemal test to confirm the results of the initial test. Patients with discordant serologic results by EIA/CIA and RPR/VDRL testing whose sera are reactive by TP-PA testing are considered to have past or present syphilis; if sera is TP-PA nonreactive, syphilis is unlikely (Fig. 120-9).

### Table 120-5 Evaluation for Pelvic Inflammatory Disease

<table>
<thead>
<tr>
<th>2014 CENTERS FOR DISEASE CONTROL AND PREVENTION DIAGNOSTIC CRITERIA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimal Criteria</td>
</tr>
<tr>
<td>• Cervical motion tenderness</td>
</tr>
<tr>
<td>• or</td>
</tr>
<tr>
<td>• Uterine tenderness</td>
</tr>
<tr>
<td>• or</td>
</tr>
<tr>
<td>• Adnexal tenderness</td>
</tr>
<tr>
<td>Additional Criteria to Enhance Specificity of the Minimal Criteria</td>
</tr>
<tr>
<td>• Oral temperature &gt;38.3°C (&gt;101°F)</td>
</tr>
<tr>
<td>• Abnormal cervical or vaginal mucopurulent discharge*</td>
</tr>
<tr>
<td>• Presence of abundant numbers of white blood cells on saline microscopy of vaginal secretions*</td>
</tr>
<tr>
<td>• Elevated ESR or C-reactive protein</td>
</tr>
<tr>
<td>• Laboratory documentation of cervical Neisseria gonorrhoeae or Chlamydia trachomatis infection</td>
</tr>
<tr>
<td>Most Specific Criteria to Enhance the Specificity of the Minimal Criteria</td>
</tr>
<tr>
<td>• Transvaginal sonography or MRI techniques showing thickened, fluid-filled tubes, with or without free pelvic fluid or tuboovarian complex, or Doppler studies suggesting pelvic infection (e.g., tubal hyperemia)</td>
</tr>
<tr>
<td>• Endometrial biopsy with histopathologic evidence of endometritis</td>
</tr>
<tr>
<td>• Laparoscopic abnormalities consistent with PID</td>
</tr>
</tbody>
</table>

### Table 120-4 Pathologic Vaginal Discharge

<table>
<thead>
<tr>
<th>INFECTIVE DISCHARGE</th>
<th>OTHER REASONS FOR DISCHARGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>COMMON CAUSES</td>
<td></td>
</tr>
<tr>
<td>Organisms</td>
<td></td>
</tr>
<tr>
<td>Candida albicans</td>
<td></td>
</tr>
<tr>
<td>Trichomonas vaginalis</td>
<td></td>
</tr>
<tr>
<td>Chlamydia trachomatis</td>
<td></td>
</tr>
<tr>
<td>Neisseria gonorrhoeae</td>
<td></td>
</tr>
<tr>
<td>Mycoplasma genitalium</td>
<td></td>
</tr>
<tr>
<td>Conditions</td>
<td></td>
</tr>
<tr>
<td>Bacterial vaginosis</td>
<td></td>
</tr>
<tr>
<td>Acute pelvic inflammatory disease</td>
<td></td>
</tr>
<tr>
<td>Postoperative pelvic infection</td>
<td></td>
</tr>
<tr>
<td>Postabortal sepsis</td>
<td></td>
</tr>
<tr>
<td>PER OPERAL SEPSIS</td>
<td></td>
</tr>
<tr>
<td>LESS COMMON CAUSES</td>
<td></td>
</tr>
<tr>
<td>Ureaplasma urealyticum</td>
<td></td>
</tr>
<tr>
<td>Syphilis</td>
<td></td>
</tr>
<tr>
<td>Escherichia coli</td>
<td></td>
</tr>
</tbody>
</table>


*If the cervical discharge appears normal and no WBCs are observed on the wet prep of vaginal fluid, the diagnosis of PID is unlikely and alternative causes of pain should be investigated.

ESR, erythrocyte sedimentation rate; GI, gastrointestinal; GYN, gynecologic; WBC, white blood cell.

HIV screening should be discussed and offered in healthcare settings to all adolescents >15 yr and to younger adolescents with HIV risk factors. Rapid HIV testing with the availability of results in 10-20 min can be useful in settings in which the likelihood of adolescents returning for their results is low. Point-of-care, CLIA-waived tests for whole blood fingerstick and oral fluid specimen testing are available. Clinical studies have demonstrated that the rapid HIV test performance is comparable to those of EIAIs. Because some reactive test results may be false-positive, every reactive rapid test must be confirmed.

**Treatment**

See Part XVII for chapters on the treatment of specific microorganisms and Tables 120-6 to 120-8. Treatment regimens using nonprescription products for candida vaginitis and pediculosis reduce financial and access barriers to rapid treatment for adolescents, but there are potential risks for inappropriate self-treatment and complications from untreated more serious infections that must be considered before using this approach. Minimizing noncompliance with treatment, finding and treating the sexual partners, addressing prevention and contraceptive issues, offering available vaccines to prevent STIs and making every effort to preserve fertility are additional physician responsibilities.

Chlamydia and gonorrhea-infected males and females should be retested approximately 3 mo after treatment, regardless of whether they believe that their sex partners were treated or whenever persons next present for medical care in the 12 mo following initial treatment. Once an infection is diagnosed, partner evaluation, testing, and treatment are recommended for sexual contacts within 60 days of symptoms or diagnosis or the most recent partner if sexual contact was >60 days, even if the partner is asymptomatic. Abstinence is recommended for at least 7 days after both patient and partner are treated. A test for pregnancy should be performed for all females with suspected PID as the test outcome will affect management. Repeat testing 3 mo after treatment is recommended for *Trichomonas* infection.

Diagnosis and therapy are often necessarily carried out within the context of a confidential relationship between the physician and the patient. Therefore, the need to report certain STIs to health department authorities should be clarified at the outset. Health departments are HIPAA-exempt and will not violate confidentiality. The health department's role is to assure that treatment and case finding have been accomplished and that sexual partners have been notified of their STI exposure. Expedited partner therapy (EPT), where the patient, preferably, delivers the medication, or a prescription for the medication if medication itself is not possible to the partner for treatment without a

![Figure 120-9](http://www.cdc.gov/std/treatment/update.htm). Figure 120-9 This figure shows the recommended algorithm for reverse sequence syphilis screening (treponemal test screening followed by nontreponemal test confirmation). The CDC recommends that a specimen with reactive EIA/CIA results be tested reflexively with a quantitative nontreponemal test (e.g., RPR or VDRL). If test results are discordant, the specimen should be tested reflexively using the TP-PA test as a confirmatory treponemal test. EIA/CIA, enzyme immunosassay/chemiluminescence immunoassay; RPR, rapid plasma reagin; TP-PA, Treponema pallidum particle agglutination. *Despite these recommendations for reverse sequence screening, CDC continues to recommend the traditional algorithm with reactive nontreponemal tests confirmed by treponemal testing. †If incubating or primary syphilis is suspected, treat with benzathine penicillin G 2.4 million units intramuscularly in a single dose. ‡Evaluate clinically, determine whether treated for syphilis in the past, assess risk for infection, and administer therapy according to CDC's STD Treatment Guidelines (available at http://www.cdc.gov/std/treatment/update.htm). ¶If at risk for syphilis, repeat RPR in several weeks. (Adapted from CDC: Discordant results from reverse sequence syphilis screening—five laboratories, United States, 2006-2010, MMWR Morb Mortal Wkly Rep 60:133–137, 2011.)

### Table 120-6 Management Guidelines for Uncomplicated Bacterial STIs in Adolescents and Adults

<table>
<thead>
<tr>
<th>PATHOGEN</th>
<th>RECOMMENDED REGIMENS</th>
<th>ALTERNATIVE REGIMENS AND SPECIAL CONSIDERATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlamydia trachomatis</td>
<td>Azithromycin 1 g orally once</td>
<td>For pregnancy:</td>
</tr>
<tr>
<td></td>
<td>or Doxycycline 100 mg orally twice daily for 7 days</td>
<td>Azithromycin 1 g orally once</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Alternative regimens:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Erythromycin base 500 mg orally 4 times a day for 7 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>or Erythromycin ethylsuccinate 800 mg orally 4 times a day for 7 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>or Levofloxacin 500 mg orally once daily for 7 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>or Ofloxacin 300 mg orally twice a day for 7 days</td>
</tr>
<tr>
<td>Neisseria gonorrhoeae (cervix, urethra, and rectum)</td>
<td>Ceftriaxone 250 mg IM in a single dose or Single-dose injectable cephalosporin plus Azithromycin 1 g orally once</td>
<td>Alternative if unable to offer IM: Cefixime 400 mg orally in a single dose plus Azithromycin 1 g orally once</td>
</tr>
<tr>
<td></td>
<td></td>
<td>If azithromycin is not available or if patient is allergic to azithromycin, doxycycline 100 mg orally twice daily for 7 days may be substituted for azithromycin as the second antimicrobial</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Severe cephalosporin allergy: contact infectious disease specialist</td>
</tr>
</tbody>
</table>
clinical assessment, is a strategy to reduce further transmission of infection, particularly for male partners of women with gonorrhea and/or chlamydia who are otherwise unlikely to seek care for STI exposure. In randomized trials, EPT has reduced the rates of persistent or recurrent gonorrhea and chlamydia infection. Serious adverse reactions are rare with recommended chlamydia and gonorrhea treatment regimens, such as doxycycline, azithromycin, and cefixime. Transient gastrointestinal side effects are more common but rarely result in severe morbidity. Many states expressly permit EPT or may potentially allow its practice. Resources for information regarding EPT and state laws are available at the Centers for Disease Control and Prevention website (http://www.cdc.gov/std/ept/).

Prevention
Healthcare providers should integrate sexuality education into clinical practice with children from early childhood through adolescence. Providers should counsel adolescents regarding sexual behaviors associated with risk of STI acquisition and should educate using evidence-based prevention strategies, which include a discussion of abstinence and other risk reduction strategies, such as consistent and correct condom use. The U.S. Preventative Task Force recommends high-intensity behavioral counseling to prevent STIs for all sexually active adolescents. The HPV vaccine, either bivalent or quadrivalent, is recommended for 11 and 12 yr old female routine immunization. Catch-up vaccination is recommended for females age 13-26 yr who

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### Table 120-6 Management Guidelines for Uncomplicated Bacterial STIs in Adolescents and Adults—cont’d

<table>
<thead>
<tr>
<th>PATHOGEN</th>
<th>RECOMMENDED REGIMENS</th>
<th>ALTERNATIVE REGIMENS AND SPECIAL CONSIDERATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neisseria gonorrhoeae (pharynx)</td>
<td>Ceftriaxone 250 mg IM in a single dose plus Azithromycin 1 g orally once</td>
<td>No alternative therapy available Patients treated with an alternative regimen should return 14 days after treatment for a test of cure using either culture or NAAT. If the NAAT is positive, every effort should be made to perform a confirmatory culture</td>
</tr>
<tr>
<td>Treponema pallidum (primary and secondary syphilis or early latent syphilis, i.e., infection &lt;12 mo)</td>
<td>Benzathine penicillin G 2.4 million units IM in 1 dose</td>
<td>Penicillin allergy: doxycycline 100 mg orally twice daily for 14 days. Limited data suggest ceftriaxone 1-2 g daily either IM or IV for 10-14 days.</td>
</tr>
<tr>
<td>Treponema pallidum (late latent syphilis or syphilis of unknown duration)</td>
<td>Benzathine penicillin G 7.2 million units total, administered as 3 doses of 2.4 million units IM each at 1 wk intervals</td>
<td>Penicillin allergy: doxycycline 100 mg orally twice daily for 28 days with close serologic and clinical follow-up</td>
</tr>
<tr>
<td>Haemophilus ducreyi (chancroid: genital ulcers, lymphadenopathy)</td>
<td>Azithromycin 1 g orally in a single dose or Ceftriaxone 250 mg IM in a single dose or Ciprofloxacin 500 mg orally twice a day for 3 days or Erythromycin base 500 mg orally 3 times a day for 7 days</td>
<td></td>
</tr>
<tr>
<td>Chlamydia trachomatis (lymphogranuloma venereum)</td>
<td>Doxycycline 100 mg orally twice daily for 21 days</td>
<td>Alternative: erythromycin base 500 mg orally 4 times a day for 21 days or Azithromycin 1 g orally once a week for 3 wk</td>
</tr>
</tbody>
</table>

IM, intramuscular; IV, intravenous; NAAT, nucleic acid amplification test.


### Table 120-7 Management Guidelines for Uncomplicated Miscellaneous Sexually Transmitted Infections in Adolescents and Adults

<table>
<thead>
<tr>
<th>PATHOGEN</th>
<th>RECOMMENDED REGIMENS</th>
<th>ALTERNATIVE REGIMENS AND SPECIAL CONSIDERATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trichomonas vaginalis</td>
<td>Metronidazole 2 g orally in a single dose or Tinidazole 2 g orally in a single dose</td>
<td>Metronidazole 500 mg orally twice daily for 7 days</td>
</tr>
<tr>
<td>Phthirus pubis (pubic lice)</td>
<td>Permethrin 1% cream rinse applied to affected areas and washed off after 10 min or Pyrethrins with piperonyl butoxide applied to affected areas and washed off after 10 min Lauder clothing and bedding</td>
<td>Malathion 0.5% lotion applied for 8-12 hr and washed off or Ivermectin 250 µg/kg PO, repeat in 2 wk</td>
</tr>
<tr>
<td>Sarcoptes scabiei (scabies)</td>
<td>Permethrin 5% cream applied to all areas from the neck down, washed off after 8-14 hr or Ivermectin 200 µg/kg orally, repeated in 2 wk Lauder clothing and bedding</td>
<td>Lindane (1%) 1 oz of lotion or 30 g of cream in thin layer to all areas of body from neck down; wash off in 8 hr</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PATHOGEN</th>
<th>RECOMMENDED REGIMENS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human papillomaviruses external</td>
<td>Patient-applied:</td>
</tr>
<tr>
<td>genital warts</td>
<td>Podofilox 0.5% solution or gel self-applied twice daily for 3 consecutive days each wk followed by 4 days of no therapy. May be repeated for up to 4 cycles.</td>
</tr>
<tr>
<td></td>
<td>or Imiquimod 3.75% cream or 5% cream self-applied to warts at bedtime 3 times wkly for up to 16 wk; wash off after 6-10 hr</td>
</tr>
<tr>
<td></td>
<td>or Sinecatechins 15% ointment self-applied 3 times daily for up to 16 wk. Do not wash off after use</td>
</tr>
<tr>
<td></td>
<td>Provider-administered:</td>
</tr>
<tr>
<td></td>
<td>Cryotherapy with liquid nitrogen or cryoprobe. Repeat applications every 1-2 wk</td>
</tr>
<tr>
<td></td>
<td>or Trichloroacetic acid (TCA) or bichloracetic acid (BCA) 80-90%. A small amount should be applied only to the warts and allowed to dry, at which time a white “frosting” develops. Can be repeated weekly</td>
</tr>
<tr>
<td></td>
<td>or Surgical removal by tangential scissor excision, tangential shave excision, curettage, or electrosurgery</td>
</tr>
<tr>
<td></td>
<td>Refer to specialist for oncologic evaluation</td>
</tr>
<tr>
<td>Human papillomaviruses</td>
<td></td>
</tr>
<tr>
<td>Cervical warts</td>
<td></td>
</tr>
<tr>
<td>Human papillomaviruses</td>
<td>Cryotherapy with liquid nitrogen. Avoid cryoprobe use</td>
</tr>
<tr>
<td>Vaginal warts</td>
<td>or TCA or BCA 80-90% applied to warts. A small amount should be applied only to warts and allowed to dry, at which time a white “frosting” develops. Can be repeated weekly</td>
</tr>
<tr>
<td></td>
<td>or Surgical removal</td>
</tr>
<tr>
<td>Human papillomaviruses</td>
<td>Cryotherapy with liquid nitrogen or Surgical removal</td>
</tr>
<tr>
<td>Urethral meatal warts</td>
<td>Warts on the rectal mucosa should be managed in consultation with a specialist. Persons with anal warts should have rectal mucosa inspected by digital examination, standard anoscopy, or high-resolution anoscopy</td>
</tr>
<tr>
<td>Human papillomaviruses</td>
<td>Cryotherapy with liquid nitrogen or TCA or BCA 80-90% applied to warts. A small amount should be applied only to warts and allowed to dry, at which time a white “frosting” develops. Can be repeated weekly</td>
</tr>
<tr>
<td>Anal warts</td>
<td>or Surgical removal</td>
</tr>
<tr>
<td></td>
<td>Herpes simplex virus (genital herpes): First clinical episode</td>
</tr>
<tr>
<td></td>
<td>Treat for 7-10 days with 1 of the following:</td>
</tr>
<tr>
<td></td>
<td>Acyclovir 400 mg orally 3 times daily</td>
</tr>
<tr>
<td></td>
<td>or Acyclovir 200 mg orally 5 times daily</td>
</tr>
<tr>
<td></td>
<td>or Valacyclovir 1 g orally twice daily</td>
</tr>
<tr>
<td></td>
<td>or Famciclovir 250 mg orally 3 times daily</td>
</tr>
<tr>
<td></td>
<td>Consider extending treatment if healing is incomplete after 10 days of therapy</td>
</tr>
<tr>
<td>PATHOGEN</td>
<td>RECOMMENDED REGIMENS</td>
</tr>
<tr>
<td>----------</td>
<td>---------------------</td>
</tr>
<tr>
<td>Herpes simplex virus (genital herpes): Episodic therapy for recurrences</td>
<td>Acyclovir 400 mg orally 3 times daily for 5 days or Acyclovir 800 mg orally twice daily for 5 days or Acyclovir 800 mg orally 3 times daily for 2 days or Valacyclovir 500 mg orally twice daily for 3 days or Valacyclovir 1,000 mg orally once daily for 5 days or Famciclovir 125 mg orally twice daily for 5 days or Famciclovir 1,000 mg orally twice daily for 1 day or Famciclovir 500 mg orally once then 250 mg twice daily for 2 days</td>
</tr>
<tr>
<td>Herpes simplex virus (genital herpes): Suppressive therapy to reduce frequency of recurrences</td>
<td>Acyclovir 400 mg orally twice daily or Valacyclovir 500 mg orally once daily or 1 g orally once daily or Famciclovir 250 mg orally twice daily</td>
</tr>
</tbody>
</table>

Adapted from Centers for Disease Control and Prevention: STD Treatment Guidelines 2014, MMWR 59 In press.

have not yet received or completed the vaccine series. The routine use of quadrivalent HPV vaccine is recommended in males age 11 or 12 yr. The CDC’s Advisory Committee on Immunization Practices also recommends vaccination with quadrivalent HPV vaccine for males age 13 through 21 yr who have not yet received or completed the vaccine series; males age 22 through 26 yr may be vaccinated.

Bibliography is available at Expert Consult.
Chronic fatigue syndrome (CFS) describes a complex, diverse, and debilitating illness characterized by chronic or intermittent fatigue accompanied by selected symptoms of $>3$ mo (young children) or $>6$ mo duration (adolescents or adults). The combination of fatigue and symptoms interferes significantly with usual daily activities and has no apparent medical explanation. The fatigue does not require exertion by the patient, nor does rest relieve it. Post-exertion malaise (i.e., worsening of fatigue and sickness symptoms after mental or physical exertion lasting more than 24 hr) is considered by some to be characteristic of CFS. A definitive causal agent or process has not been identified, although the differential diagnosis includes many infectious and inflammatory diseases. The understanding of this condition is largely from studies among adults and adolescents, with limited descriptions of chronic fatiguing illness among younger children.

This illness was formally defined in 1988 as chronic fatigue syndrome because persistent and unexplained fatigue was considered the principal and invariable physical symptom. A variety of names have been used to describe the syndrome (chronic mononucleosis, chronic Epstein-Barr virus infection, myalgic encephalomyelitis, post-infection syndrome, immune dysfunction syndrome), and several case definitions are in use in both clinical and research settings. Some of the more widely used definitions are the 1994 International Research Case Definition (an update of the 1988 version), the Oxford (UK) Guidelines for research, the Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Clinical working case definition, diagnostic and treatments protocols, also commonly referred to as the Canadian Consensus Criteria for CFS/ME (2003), and the 2011 International Consensus Criteria for Myalgic Encephalomyelitis (ME). In 2006, the International Association of Chronic Fatigue Syndrome Pediatric Case Definition Working group developed a case definition specifically for children and adolescents with ME/CFS, utilizing the 3-mo duration of fatigue. In the UK, pediatric practitioners adhere to guidelines in the National Institute for Health and Clinical Excellence (NICE); Chronic fatigue syndrome/Myalgic encephalomyelitis (or encephalopathy); Diagnosis and Management (2007), which includes the 3-mo duration criterion.

The Institute of Medicine (IOM) of the National Academy of Science was commissioned by the Department of Health and Human Services (HHS) to conduct a study to evaluate existing diagnostic criteria and to develop evidence-based diagnostic criteria for use by clinicians. Their recommendations were published in February 2015. The IOM case definition is intended to apply to all ages, and the report includes a special focus on pediatrics. The IOM suggested new diagnostic criteria and a new name, systemic exertion intolerance disease, in part to emphasize the post-exertion malaise criterion and bring greater understanding about the illness.

**Epidemiology**

Between 0.2% and 2.3% of children or adolescents suffer from CFS based on worldwide studies. Most epidemiology studies utilize the 1994 definition. CFS is more prevalent in adolescents than in younger children. The large variation in the CFS prevalence estimates may be
due to variation in study methodology, such as the study population composition (special clinic versus general practice or general population) and data collection procedures (parent/self-reporting vs. clinical evaluation; the choice of case definition and method of applying case definition). Sex/gender distribution differs from that in adults with a more equal distribution in children less than 15 yr of age, while remaining 2- to 3-fold higher in females ages 15-18 yr. Few studies have reported the incidence of CFS among children <10 yr of age, leading to uncertainty in this age group. In adolescents in the Netherlands, the pediatrician-diagnosed incidence of CFS/ME was reported to be 0.01%, while in the UK the incidence was 0.5%.

PATHOGENESIS

Although the cause of CFS is unknown, some patients correlate the onset with a recent episode of a viruslike illness such as infectious mononucleosis (10-12%) (see Chapter 254). A potentially pathophysiologic relationship of CFS to infection is suggested because the sickness or illness behaviors elicited by the nonspecific or innate host responses in infections in general are present in CFS. CFS-like illness after infectious mononucleosis is not predicted by viremia or an altered host response to Epstein-Barr virus infection, but is associated with the severity of the primary infection. There have been a wide variety of other candidate infections associated with postinfection fatigue syndromes, particularly in adults or teenagers older than 16 yr. Efforts continue to determine if infections with these or other agents may produce the illness.

Similarities between CFS symptoms and those experienced by patients with autoimmune and other inflammatory disorders raises the issue of primary perturbations in the immune system in the pathogenesis of CFS. Immunologic alterations (hypogammaglobulinemia or hypergammaglobulinemia, immunoglobulin subclass deficiencies, elevated levels of circulating immune complexes, mild increased helper/suppressor lymphocyte ratios, natural killer cell dysfunction, and monocye dysfunction) have been reported in adult patients with CFS. These findings have not been consistent among studies. While CFS patients as a group appear to differ from healthy controls, in most studies the laboratory values of the immune parameters are not outside the normal range.

Autonomic nervous system changes are suggested by the orthostatic intolerance experienced by some CFS patients. Orthostatic intolerance (OI) syndromes with circulatory dysfunction including neurally mediated hypotension, instantaneous orthostatic hypotension, and postural tachycardia syndrome have been observed in some patients with CFS and could contribute to the syndrome. The pathophysiology of these manifestations among adolescents with CFS is unclear; but in postinfection states, they could be associated with failure to replenish mineral and fluid losses that accompany infections or to immune-mediated injury (auto-antibodies directed against the autonomic nervous system).

Because the widespread musculoskeletal pain in CFS is similar to that in fibromyalgia (Chapter 168.3), and fibromyalgia and CFS are often considered overlapping syndromes, they may share similarities in pathogenesis. Fibromyalgia pain is thought to be due to neurochemical imbalances in the central nervous system. Neurochemical changes represent another area for research into the origins of development and persistence of CFS.

A variety of other hypotheses for the biologic basis of this illness are being investigated. These include alterations in energy metabolism (particularly as related to exercise and post-exertional malaise), in sleep, as well as in stress response and the hypothalamic-pituitary-axis. Understanding CFS has proved so challenging because it represents more than one underlying pathophysiology. Current studies are attempting to stratify or subgroup patients to address this possibility.

CLINICAL MANIFESTATIONS

The dominant symptoms expressed by adolescents are similar to those observed in adults and include fatigue and an increased level of illness after physical or mental activity. In younger children, who frequently do not spontaneously describe symptoms, exertion induces behavioral changes manifested by a lack of their usual energy. In adolescents, the fatigue and post-exertional malaise may lead to reduced participation in school activities and time spent with friends. Cognitive problems and difficulties in concentrating are common and are indicated by a decreased ability to keep up with homework and a drop in grades. Sleep complaints include difficulty falling or staying asleep, daytime sleepiness, frequent awakening, and intense and vivid dreaming. While nonrestorative nighttime sleeping is common, diagnosed sleep disorders, such as restless legs or sleep apnea, are not. Myalgias and arthralgias may accompany fatigue and altered sleep. Sore throat and lymph node tenderness occur in some children but may be part of an inciting illness. Adolescents also have increased complaints of headaches, abdominal pain, nausea, and hypersensitivity to touch and noise.

Patients diagnosed with CFS in primary care practices are more likely to report an abrupt onset to their symptoms, often as part of an initial virus-like illness, whereas gradual onset is more common in those identified in population-based studies. School absenteeism is a major problem. In one study two thirds of adolescents missed >2 wk of school over a 6-week observation period and one third required a home tutor. Unlike school phobia, inactivity due to CFS persists on the weekends and during holidays as it does during the school week.

Although fatigue and accompanying symptoms are subjective, the magnitude of impairment of each component can be measured by questionnaires addressing pain and function or, in the case of suspected orthostatic instability, by recording routine or supine/standing heart rate and blood pressure. Fatigue should not be dismissed as a minor ailment. It is generally manifested as lassitude, profound tiredness, intolerance of exertion with easy fatigability, and general malaise.

Abnormal physical examination findings are conspicuously absent, providing reassurance and consternation to both the patient and the physician. The presence of unusual symptoms such as chest palpitations, visual blurring, paresthesias, dry eyes and mouth, diarrhea, cough, night sweats, and rash should suggest a diagnosis other than CFS. Weight loss, as seen in chronic infections or inflammatory conditions, is uncommon in CFS.

DIAGNOSIS

There are no pathognomonic signs or diagnostic tests for CFS. The diagnosis is clinically defined based on inclusion and exclusion criteria (Fig. 121-1). The diagnostic criteria are applicable to adults and adolescents >11 yr of age because of the current requirement for a self-generated history. The 3- or 6-mo criterion in CFS case definitions does not mean that evaluation and symptom management should wait until that criterion is met before intervention can begin.

CFS is difficult to diagnose in children, who have trouble describing their symptoms and articulating their concerns. Sole reliance on parental history for diagnosis is fraught with confusion because of the inaccuracy of the historical information. A combination of child and parent reports is most effective. It is important to document the child’s activity levels and worsening symptoms after physical or mental endeavors. Changes in participation in hobbies and social activities can help identify illness effects on daily activities.

The diagnosis of CFS can be established only after alternative medical and psychiatric causes of fatigue and illness, many of which are treatable, have been excluded. These include any medical condition that may explain the presence of a chronic illness, such as untreated hypothyroidism, respiratory and/or food allergies, sleep apnea, narcolepsy, drug abuse, an adverse effect of medication, or severe obesity. A previously diagnosed medical condition with uncertain resolution that may explain chronic fatigue should be clarified, such as unresolved cases of hepatitis B or C virus infection.

Certain illnesses, for example, fibromyalgia and depression, share similar symptoms with CFS, but are not exclusionary diagnoses. They should be considered in the differential diagnosis in selected cases. There is concern that CFS might be mistaken for readily identifiable psychiatric disorders, but evidence supports differences in clinical
Clinical Evaluation and Classification of Chronic Fatigue

I. Clinically evaluate cases of chronic fatigue by:
   A. History and physical examination
   B. Mental status examination (abnormalities require appropriate psychiatric, psychologic, or neurologic examination)
   C. Tests (abnormal results that strongly suggest an exclusionary condition must be resolved)
      1. Screening lab tests: complete blood count, erythrocyte sedimentation rate, alanine aminotransferase, total protein, albumin, globulin, alkaline phosphatase, calcium, phosphorus, glucose, blood urea nitrogen, electrolytes, creatinine, thyroid stimulating hormone, and urinalysis
      2. Additional tests as clinically indicated to exclude other diagnosis

II. Classify as either chronic fatigue syndrome or idiopathic chronic fatigue
   A. Classify as chronic fatigue syndrome if both of the following criteria are met:
      a. Unexplained persistent or relapsing fatigue of new or definite onset that is not due to ongoing exertion, is not relieved by rest, and results in a substantial reduction in previous levels of activity.
      b. Four or more of the following symptoms are concurrently present for 6 months or longer:
         1. Impaired memory or concentration (severe enough to reduce levels of occupational, social, or personal activities)
         2. Sore throat
         3. Tender cervical or axillary lymph nodes
         4. Muscle pain
         5. Multijoint pain (without joint swelling or redness)
         6. New headaches
         7. Unrefreshing sleep
         8. Postexertion malaise (lasting more than 24 hr)

   B. Classify as idiopathic chronic fatigue if fatigue severity or symptom criteria for chronic fatigue syndrome are not met.

 Exclude if another cause for chronic fatigue is found


Presentation between CFS and mood/anxiety disorders. CFS should not be diagnosed in persons with prior diagnoses of a major depressive disorder with psychotic or melancholic features, bipolar affective disorders, schizophrenia of any subtype, delusional disorders of any subtype, anorexia nervosa, bulimia nervosa, or alcohol or other substance abuse within 2 yr before the onset of the chronic fatigue or at any time afterward.

Although evaluation of each patient should be individualized, initial laboratory evaluation should be limited to screening laboratory tests to provide reassurance of the lack of significant medical illnesses (see Fig. 121-1). Further tests should be directed primarily toward excluding treatable diseases that may be suggested by the symptoms or physical findings that are present in specific patients.

**MANAGEMENT**

Management of CFS is based on relief of the core and most disruptive symptoms in the individual patient (Fig. 121-1). The diagnostic criterion of 3-6 mo duration of illness should not delay evaluation and symptom management, as these may be initiated as soon as the child or adolescent presents with a CFS-like picture. Problems with sleep can be addressed by encouraging patients to adopt good sleep habits using standard sleep hygiene techniques. It may be beneficial to refer the patient to a specialist for identification and treatment of sleep disorders and disturbances. Once pain is found not to be related to specific diseases or illnesses, it is best addressed through nonpharmacologic treatment (see Chapter 62).

One of the nonpharmacologic approaches to pain management, cognitive behavioral therapy (CBT), may also assist patients in coping with CFS. Through explanation and changes in perception of the origins of the illness, CBT may help patients and their families develop coping skills and provide emotional support. Improved methods of coping may allow some improved function while living with the illness. Comorbid psychiatric disorders require appropriate intervention.

While the overall goal is to help CFS patients tolerate activity, children with CFS should avoid physical or mental efforts that result in aggravated CFS symptoms. Return to school should be initiated gradually but systematically to resume normal attendance. Home tutoring may be an interim alternative. Parents can work with teachers and administrators to redefine expectations of activity and performance for children with CFS. Because of the crucial importance of learning socialization skills during childhood and adolescence, even brief periods of attendance during lunch or favorite after-school activities should be encouraged. Complete bed rest and physical inactivity perpetuates immobility and leads to deconditioning. Activities benefit children with certain chronic illnesses in ways other than overcoming deconditioning; however, rapid remobilization usually exacerbates symptoms and should be avoided.

Continued empathy and support by the treating physician are important in maintaining a physician-patient relationship conducive to managing this illness. Careful attention must be directed to the family dynamics to identify and resolve family problems or psychopathology that may be contributing to a child’s perceptions of his or her
symptoms. Periodic medical reevaluation is warranted for early detection of other identifiable causes of chronic fatigue and other symptoms, especially with interval development of new symptoms. No data suggest relief of symptoms or cure of CFS by dietary or vitamin supplements.

PROGNOSIS

The clinical course of CFS is highly variable and patients should be informed that their symptoms will likely wax and wane. Children and adolescents with CFS appear to have a more optimistic outcome than adults, typically with an undulating course of gradual but substantial symptomatic improvement, or full recovery, 1-4 yr after diagnosis. Overall, a good functional outcome has been reported in up to 80% of cases. Poor prognostic factors include a gradual onset, increasing school absenteeism, lower socioeconomic status, chronic maternal health problems, and untreated comorbid individual or family psychiatric disorders. Favorable prognostic factors include patient control of their individual rehabilitation program with continued support from health professionals and family members and improvement in orthostatic factors.

Bibliography is available at Expert Consult.
Bibliography

Recurrent infections or fevers in children are among the most frequent clinical dilemmas for primary care physicians. A major reason for the apparent high rate of recurrent infections in children is repeated exposure to common and usually benign infectious agents in childcare and other group settings.

Primary care physicians must have a high index of suspicion if defects of the immune system are to be diagnosed early enough that appropriate treatment can be instituted before irreversible damage develops. Diagnosis is difficult because, until recently, primary immunodeficiency diseases have not been screened for at any time during life anywhere in the world, and most affected do not have abnormal physical features. Screening for severe combined immunodeficiency (SCID; T-cell lymphopenia) is part of the newborn screening programs in 21 states of the United States now; the hope is that it will eventually be performed nationwide. There is also a beginning effort to do this in Europe. Extensive use of antibiotics may mask the classic presentation of many primary immunodeficiency diseases. Evaluation of immune function should be initiated in those rare infants or children who do have clinical manifestations of a specific immune disorder and in all who have a positive family history of early infant death or a known immunodeficiency disorder, unusual, chronic, or recurrent infections such as (1) 1 or more systemic bacterial infections (sepsis, meningitis); (2) 2 or more serious respiratory or documented bacterial infections (cellulitis, abscesses, draining otitis media, pneumonia, lymphadenitis) within 1 yr; (3) serious infections occurring at unusual sites (liver, brain abscess); (4) infections with unusual pathogens (Pneumocystis jiroveci, Aspergillus, Serratia marcescens, Nocardia, Burkholderia cepacia); and (5) infections with common childhood pathogens but of unusual severity (Table 122-1). Additional clues to immunodeficiency include failure to thrive with or without chronic diarrhea, persistent infections after receiving live vaccines, and chronic oral or cutaneous moniliasis. Tables 122-2 and 122-3 note certain clinical features that are suggestive of immunodeficiency syndromes.

Children with defects in antibody production, phagocytic cells, or complement proteins have recurrent infections with encapsulated bacteria and may grow and develop normally despite their recurring infections, unless they develop bronchiectasis from repeated lower respiratory tract bacterial infections or persistent entero viral infections of the central nervous system. Patients with only repeated benign viral infections (with the exception of persistent enterovirus infections) are not as likely to have an immunodeficiency. By contrast, patients with deficiencies in T-cell function usually develop opportunistic infections or serious illnesses from common viral agents early in life, and they fail to thrive (Table 122-4).

The initial evaluation of immunocompetence includes a thorough history, physical examination, and family history (Table 122-5). Most immunologic defects can be excluded at minimal cost with the proper choice of screening tests, which should be broadly informative, reliable, and cost-effective (Table 122-6 and Fig. 122-1). A complete blood count (CBC), manual differential count, and erythrocyte sedimentation rate are among the most cost-effective screening tests. If the erythrocyte sedimentation rate is normal, chronic bacterial or fungal infection is unlikely. If an infant's neutrophil count is persistently elevated in the absence of any signs of infection, a leukocyte adhesion deficiency should be suspected. If the absolute neutrophil count is normal, congenital and acquired neutropenias and leukocyte adhesion defects are excluded. If the absolute lymphocyte count is normal, the patient is not likely to have a severe T-cell defect, because T cells normally constitute 70% of circulating lymphocytes and their absence results in striking lymphopenia. Normal lymphocyte counts are higher in infancy and early childhood than later in life (Fig. 122-2). Knowledge of normal values for absolute lymphocyte counts at various ages in infancy and childhood is crucial in the detection of T-cell defects.

At 9 mo of age, an age when infants affected with severe T-cell immunodeficiency are likely to present, the lower limit of normal is 4,500 lymphocytes/mm³. Absence of Howell-Jolly bodies or pitted erythrocytes by microscopic examination of erythrocytes rules against congenital asplenia. Normal platelet size or count excludes Wiskott-Aldrich syndrome. If newborn screening for T-cell lymphopenia were to be performed on all infants, SCID could be detected at birth, and lifesaving immunologic reconstitution could then be provided to all affected infants shortly after birth and before they become infected.

Patients found to have abnormalities on any screening tests should be characterized as fully as possible before any type of immunologic treatment is begun, unless there is a life-threatening illness (Table 122-7). Some "abnormalities" may prove to be laboratory artifacts and, conversely, an apparently straightforward diagnosis may prove to be a much more complex disorder. For patients with recurrent or unusual bacterial infections, evaluation of T-cell and phagocytic cell functions is indicated even if results of initial screening tests including the CBC and manual differential, immunoglobulin levels, and CH₅₀ values are normal.

Because of the lack of screening, the true incidence and prevalence of primary immunodeficiency diseases are unknown, although the incidence has been estimated to be 1:10,000 births (Table 122-8). If true, this is higher than some disorders that are part of the newborn metabolic screening program (phenylketonuria is 1:16,000) (see Chapter 85.1). Approximately 80% of the mutated genes causing the more than 220 known primary immunodeficiency diseases have been identified. This is information crucial for genetic counseling and that could eventually be used in neonatal screening. Newborn or early childhood screening would be extremely valuable so that timely initiation of appropriate therapy can be initiated before infections develop; it is likely that many affected patients die before a diagnosis is determined.

**B CELLS**

Antibody production by B cells is easily evaluated by measuring serum immunoglobulin levels and determining antibody titers to protein and polysaccharide antigens.

A simple screening test for B-cell defects is the measurement of serum immunoglobulin (Ig) A. If the IgA level is normal, selective IgA
### Table 122-1  Predisposition to Specific Infections in Humans

<table>
<thead>
<tr>
<th>PATHOGEN</th>
<th>PRESENTATION</th>
<th>AFFECTED GENE/ CHROMOSOMAL REGION</th>
<th>FUNCTIONAL DEFECT</th>
<th>NOTES</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BACTERIA</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Streptococcus pneumoniae</td>
<td>Invasive disease</td>
<td>IRAK-4, MyD88</td>
<td>Impaired production of inflammatory cytokines</td>
<td>Also susceptible to other pyogenic bacteria such as Staphylococcus aureus</td>
</tr>
<tr>
<td>Neisseria</td>
<td>Invasive disease</td>
<td>MAC components (C5, C6, C7, C8A, C8B, C8G, C9)</td>
<td>Properdin deficiency</td>
<td></td>
</tr>
<tr>
<td>Mycobacteria</td>
<td>Invasive disease, poor prognosis</td>
<td>MSMD</td>
<td>Impaired IFN-γ response to IL-12, IL-23</td>
<td>Also susceptible to Salmonella typhi infections</td>
</tr>
<tr>
<td>Mycobacterium leprae</td>
<td>Leprosy</td>
<td>PARK2, LTA</td>
<td>Impaired cellular response to IFN-γ</td>
<td>Possible E3-ubiquitin ligase dysfunction</td>
</tr>
<tr>
<td><strong>VIRUSES</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Herpes simplex (type 1)</td>
<td>Herpes simplex encephalitis</td>
<td>UNC93B1, TLR3, STAT1</td>
<td>Impaired production of type 1 IFNs</td>
<td>STAT1 and NEMO deficiency also predispose to HSV infections, amongst other infections</td>
</tr>
<tr>
<td>Epstein-Barr virus</td>
<td>XLP</td>
<td>SH2DIA, XIAP/BIRC4</td>
<td>SAP deficiency</td>
<td>Fulminant infectious mononucleosis, malignant and nonmalignant lymphoproliferative disorders, dysgammaglobulinemia, autoimmunity</td>
</tr>
<tr>
<td>Human papillomaviruses</td>
<td>Epidermodysplasia verruciformis</td>
<td>WHIM</td>
<td>EVER1/TMC6, EVER2/TMC8, CXCR4</td>
<td>Altered neutrophil mobilization, T-cell lymphopenia, recurrent bacterial respiratory infections chronic cutaneous/genital papillomavirus disease</td>
</tr>
<tr>
<td><strong>PARASITES</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasmodium falciparum</td>
<td>Malaria fever episodes</td>
<td>10p15</td>
<td>Unknown</td>
<td>Linkage studies</td>
</tr>
<tr>
<td>Schistosoma mansoni</td>
<td>Severe malaria, Severe malaria</td>
<td>GNAS, IFNR1</td>
<td>Unknown</td>
<td>SNP association studies</td>
</tr>
<tr>
<td>Leishmania donovani</td>
<td>Intensity of infection</td>
<td>5q311-q33, 6q22-q23, IFNR1</td>
<td>Unknown</td>
<td>SNP association studies</td>
</tr>
<tr>
<td></td>
<td>Hepatic fibrosis</td>
<td>22q12, 2q35 (NRAMP1)</td>
<td>Unknown</td>
<td></td>
</tr>
<tr>
<td><strong>YEAST</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Candida</td>
<td>APECED, chronic candidiasis</td>
<td>Aire, STAT1, CARD9</td>
<td>Unknown</td>
<td>APS-1 chronic candidiasis, chronic hyperthyroidism, Addison disease</td>
</tr>
<tr>
<td>Deep dermatophytosis</td>
<td>Tissue invasion</td>
<td>CARD9</td>
<td>Unknown</td>
<td>Autosomal recessive</td>
</tr>
</tbody>
</table>

APECED, autoimmune, polyendocrinopathy, candidiasis, ectodermal dys trophy; HSV, herpes simplex virus; IFN, interferon; IL, interleukin; MAC, membrane attack complex; MSMD, mendelian susceptibility to mycobacterial disease; NEMO, nuclear factor kappa B essential modulator; SAP, SLAM-associated protein; SNP, single-nucleotide polymorphism; TLR, Toll-like receptor; WHIM, warts, hypogammaglobulinemia, infections, and myelokathexis syndrome; XIAP, X-linked inhibitor of apoptosis; XLP, X-linked lymphoproliferative disease.


Deficiency, which is the most common B-cell defect, is excluded, as are most of the permanent types of hypogammaglobulinemia, as IgA is usually very low or absent in those conditions. If IgA is low, IgG and IgM should also be measured. Patients who are receiving corticosteroids or who have protein-losing states (nephrosis, protein-losing enteropathy) often have low serum IgG concentrations but produce antibodies normally. Thus, if immunoglobulins are low, it is crucial before starting intravenous immunoglobulin therapy that antibody titers to specific antigens are measured to determine whether the immunoglobulin levels are low because of inadequate antibody synthesis or due to protein loss. Antibody titers are not interpretable after the patient has received a blood transfusion, fresh-frozen plasma or intravenous immunoglobulin, which contains antibodies from a minimum of 10,000 normal donors.

One useful test for B-cell function is to determine the presence and titer of isohemagglutinins, or natural antibodies to type A and B red blood cell polysaccharide antigens. This test measures predominantly IgM antibodies. Isohemagglutinins may be absent normally in the 1st 2 yr of life and are always absent if the patient is blood type AB.

Because most infants and children are immunized with diphtheria-tetanus-pertussis, conjugated *Haemophilus influenzae* type b, and pneumococcal conjugate vaccine, it is often informative to test for specific antibodies to diphtheria, tetanus, *H. influenzae* polyribose phosphate, and pneumococcal antigens. If the titers are low, measurement of antibodies to diphtheria or tetanus toxoids before and 2 wk after a pediatric diphtheria-tetanus-pertussis or diphtheria-tetanus booster is helpful in assessing the capacity to form IgG antibodies to protein antigens. To evaluate a patient’s ability to respond to
### Table 122-2, Characteristic Clinical Patterns in Some Primary Immunodeficiencies

<table>
<thead>
<tr>
<th>FEATURES</th>
<th>DIAGNOSIS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>IN NEWBORNS AND YOUNG INFANTS (0-6 MO)</strong></td>
<td></td>
</tr>
<tr>
<td>Hypocalcemia, unusual facies and ears, heart disease</td>
<td>DiGeorge anomaly</td>
</tr>
<tr>
<td>Delayed umbilical cord detachment, leukocytosis, recurrent infections</td>
<td>Leukocyte adhesion defect</td>
</tr>
<tr>
<td>Persistent thrush, failure to thrive, pneumonia, diarrhea, bloody stools, draining ears, atopic eczema</td>
<td>Severe combined immunodeficiency</td>
</tr>
<tr>
<td>Pneumocystis jiroveci pneumonia, neutropenia, recurring infections</td>
<td>X-linked hyper-IgM syndrome</td>
</tr>
<tr>
<td><strong>IN INFANTS AND YOUNG CHILDREN (6 MO-5 YR)</strong></td>
<td></td>
</tr>
<tr>
<td>Severe progressive infectious mononucleosis</td>
<td>X-linked lymphoproliferative syndrome</td>
</tr>
<tr>
<td>Recurrent staphylococcal abscesses, staphylococcal pneumonia with pneumatocele formation, coarse facial features, pruritic dermatitis</td>
<td>Hyper-IgE syndrome</td>
</tr>
<tr>
<td>Persistent thrush, nail dystrophy, endocrinopathies</td>
<td>Chronic mucocutaneous candidiasis</td>
</tr>
<tr>
<td>Short stature, fine hair, severe varicella</td>
<td>Cartilageilage hypoplasia with short-limbed dwarfism</td>
</tr>
<tr>
<td>Oculocutaneous albinism, recurrent infection</td>
<td>Chédiak-Higashi syndrome</td>
</tr>
<tr>
<td>Abscesses, suppurative lymphadenopathy, antral outlet obstruction, pneumonia, osteomyelitis</td>
<td>Chronic granulomatous disease</td>
</tr>
<tr>
<td><strong>IN OLDER CHILDREN (OLDER THAN 5 YR) AND ADULTS</strong></td>
<td></td>
</tr>
<tr>
<td>Progressive dermatomyositis with chronic enterovirus encephalitis</td>
<td>X-linked agammaglobulinemia</td>
</tr>
<tr>
<td>Sinopulmonary infections, neurologic deterioration, telangiectasia</td>
<td>Ataxia-telangiectasia</td>
</tr>
<tr>
<td>Recurrent neisserial meningitis</td>
<td>C6, C7, or C8 deficiency</td>
</tr>
<tr>
<td>Sinopulmonary infections, splenomegaly, autoimmunity, malabsorption</td>
<td>Common variable immunodeficiency</td>
</tr>
</tbody>
</table>


---

### Table 122-3, Common Clinical Features of Immunodeficiency

| Usually present |          |
| Persistent upper respiratory infections |
| Severe bacterial infections |
| Persistent infections with incomplete or no response to therapy |
| Paucity of lymph nodes and tonsils |

| Often present |          |
| Persistent sinusitis or mastoiditis (Streptococcus pneumoniae, Haemophilus, Pneumocystis jiroveci, Staphylococcus aureus, Pseudomonas spp.) |
| Recurrent bronchitis or pneumonia |
| Failure to thrive or growth retardation for infants or children; weight loss for adults |
| Intermittent fever |
| Infection with unusual organisms |
| Skin lesions: rash, seborrhea, pyoderma, necrotic abscesses, alopecia, eczema, telangiectasia |
| Recurrent thrush |
| Diarrhea and malabsorption |
| Hearing loss caused by chronic otitis |
| Chronic conjunctivitis |
| Arthralgia or arthritis |
| Bronchiectasis |
| Evidence of autoimmune, especially autoimmune thrombocytopenia or hemolytic anemia |
| Hematologic abnormalities: aplastic anemia, hemolytic anemia, neutropenia, thrombocytopenia |
| History of prior surgery, biopsy |

| Occasionally present |          |
| Lymphadenopathy |
| Hepatosplenomegaly |
| Severe viral disease (e.g., EBV, CMV, adenovirus, varicella, herpes simplex) |
| Chronic encephalitis |
| Recurrent meningitis |
| Deep infections: cellulitis, osteomyelitis, organ abscesses |
| Chronic gastrointestinal disease, infections, lymphoid hyperplasia, sprue-like syndrome, atypical inflammatory bowel disease |
| Autoimmune disease such as autoimmune thrombocytopenia, hemolytic anemia, rheumatologic disease, alopecia, thyroiditis, pernicious anemia |
| Pyoderma gangrenosum |
| Adverse reaction to vaccines |
| Delayed umbilical cord detachment |
| Chronic stomatitis or peritonitis |

EBV, Epstein-Barr virus; CMV, cytomegalovirus.

Polysaccharide antigens, anti-pneumococcal antibodies can be measured before and 3 wk after immunization with 23 valent unconjugated pneumococcal polysaccharide vaccine in patients 2-3 yr old or older. Antibodies detected in these tests are of the IgG isotype. These antibody studies can be performed in several different laboratories, but it is important to choose a reliable laboratory and to use the same laboratory for preimmunization and postimmunization titer. In children older than 2 yr of age with low anti-pneumococcal antibody titers after a pneumococcal polysaccharide vaccine immunization, it is useful to boost with conjugate pneumococcal vaccine twice, 1 mo apart, before giving a polysaccharide pneumococcal vaccine 1 mo later and then measuring antibody titers 3 wk later. Patients with significant or permanent B-cell defects do not produce either IgM or IgG antibodies normally. If results of these tests prove to be normal and the immunoglobulins remain low, studies should be performed to evaluate the possible loss of immunoglobulins through the urinary or gastrointestinal tracts (nephrotic syndrome, protein-losing enteropathies, intestinal telangiectasia). Very high serum concentrations of 1 or more immunoglobulin classes suggest HIV infection, chronic granulomatous disease, chronic inflammation, or autoimmune lymphoproliferative syndrome.

IgG subclass measurements are seldom helpful in assessing immune function in children with recurrent infections. It is difficult to know the biologic significance of the various mild to moderate deficiencies of IgG subclasses, particularly when completely asymptomatic individuals have been described as totally lacking IgG2, IgG3, IgG4, and/or IgA1 owing to immunoglobulin heavy-chain gene deletions. Many healthy children have been described as having low levels of IgG, but normal responses to polysaccharide antigens when immunized. When children with low IgG2 subclass levels and histories of
### Table 122-4: Characteristic Features of Primary Immunodeficiency

<table>
<thead>
<tr>
<th>CHARACTERISTIC</th>
<th>PREDOMINANT T-CELL DEFECT</th>
<th>PREDOMINANT B-CELL DEFECT</th>
<th>GRANULOCYTE DEFECT</th>
<th>COMPLEMENT DEFECT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age at the onset of infection</strong></td>
<td>Early onset, usually 2-6 mo of age</td>
<td>Onset after maternal antibodies diminish, usually after 5-7 mo of age, later childhood</td>
<td>Early onset</td>
<td>Onset at any age</td>
</tr>
<tr>
<td><strong>Specific pathogens involved</strong></td>
<td>Bacteria: common Gram-positive and Gram-negative bacteria and mycobacteria</td>
<td>Bacteria: pneumococci, streptococci, staphylococci, Haemophilus, Campylobacter, Mycoplasma</td>
<td>Bacteria: staphylococci, Pseudomonas, Serratia, Klebsiella, Salmonella</td>
<td>Bacteria: pneumococci, Neisseria</td>
</tr>
<tr>
<td><strong>Viruses</strong></td>
<td>CMV, EBV, adenovirus, parainfluenza 3, varicella, enterovirus</td>
<td>Enterovirus*</td>
<td>Fungi and parasites: Candida, Nocardia, Aspergillus</td>
<td></td>
</tr>
<tr>
<td><strong>Fungi</strong></td>
<td>Candida and Pneumocystis jiroveci</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Affected organs</strong></td>
<td>Extensive mucocutaneous candidiasis, lungs, failure to thrive, protracted diarrhea</td>
<td>Recurrent sinopulmonary infections, chronic gastrointestinal symptoms, malabsorption, arthritis, enteroviral meningoencephalitis*</td>
<td>Skin: abscesses, impetigo, cellulitis Lymph nodes: suppurative adenitis Oral cavity: gingivitis, mouth ulcers Internal organs: abscesses, osteomyelitis</td>
<td>Infections: meningitis, arthritis, septicemia, recurrent sinopulmonary infections</td>
</tr>
<tr>
<td><strong>Special features</strong></td>
<td>Graft-vs-host disease caused by maternal engraftment or nonirradiated blood transfusion Postvaccination disseminated BCG or varicella Hypocalcemic tetany in infancy†</td>
<td>Autoimmunity Lymphoreticular malignancy: lymphoma, thymoma Postvaccination paralytic polio</td>
<td>Prolonged attachment of umbilical cord, poor wound healing</td>
<td>Autoimmune disorders: SLE, vasculitis, dermatomyositis, scleroderma, glomerulonephritis, angioedema</td>
</tr>
</tbody>
</table>

*X-linked (Bruton) agammaglobulinemia.

†DiGeorge anomaly.

BCG, Bacille Calmette-Guérin; CMV, cytomegalovirus; EBV, Epstein-Barr virus; SLE, systemic lupus erythematosus.


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**Figure 122-1** A diagnostic testing algorithm for primary immunodeficiency diseases. DTH, delayed-type hypersensitivity. (From Lindegren ML, Kobrynki L, Rasmussen SA: Applying public health strategies to primary immunodeficiency diseases: a potential approach to genetic disorders, MMWR Recomm Rep 53[RR-1]:1–29, 2004.)
**Table 122-5  Special Physical Features Associated with Immunodeficiency Disorders**

<table>
<thead>
<tr>
<th>CLINICAL FEATURES</th>
<th>DISORDERS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DERMATOLOGIC</strong></td>
<td></td>
</tr>
<tr>
<td>Eczema</td>
<td>Wiskott-Aldrich syndrome, IPEX, hyper-IgE syndromes, hypereosinophilia syndromes, IgA deficiency</td>
</tr>
<tr>
<td>Sparse and/or hypopigmented hair</td>
<td>Cartilage hair hypoplasia, Chédiak-Higashi syndrome, Griscelli syndrome</td>
</tr>
<tr>
<td>Ocular telangiectasia</td>
<td>Ataxia-telangiectasia</td>
</tr>
<tr>
<td>Oculocutaneous albinism</td>
<td>Chédiak-Higashi syndrome</td>
</tr>
<tr>
<td>Severe dermatitis</td>
<td>Ommen syndrome, SCID, graft-vs-host disease, Cornel-Netherton syndrome</td>
</tr>
<tr>
<td>Erythroderma</td>
<td>Chronic granulomatous disease</td>
</tr>
<tr>
<td>Recurrent abscesses with pulmonary pneumatoceles</td>
<td>Chronic granulomatous disease, hyper-IgE syndrome, leukocyte adhesion defect</td>
</tr>
<tr>
<td>Recurrent organ granulomas or abscesses, lung, liver and rectum especially</td>
<td>Ataxia telangiectasia, SCID, CVID, RAG deficiency</td>
</tr>
<tr>
<td>Recurrent abscesses or cellulitis</td>
<td>Chronic granulomatous disease, severe combined immunodeficiency, congenital neutropenia</td>
</tr>
<tr>
<td>Cutaneous granulomas</td>
<td>Neutrophil defects</td>
</tr>
<tr>
<td>Oral ulcers</td>
<td>T-cell immune defects, combined defects (SCIDs); mucocutaneous candidiasis; hyper-IgE syndromes; IL-12, -17, -23 deficiencies; CARD9 deficiency; STAT1 deficiency</td>
</tr>
<tr>
<td>Periodontitis, gingivitis, stomatitis</td>
<td>B-cell defects, mucocutaneous candidiasis</td>
</tr>
<tr>
<td>Oral or nail candidiasis</td>
<td>B-cell defects, mucocutaneous candidiasi</td>
</tr>
<tr>
<td><strong>EXTREMITIES</strong></td>
<td></td>
</tr>
<tr>
<td>Clubbing of the nails</td>
<td>Chronic lung disease due to antibody defects</td>
</tr>
<tr>
<td>Arthritis</td>
<td>Antibody defects, Wiskott-Aldrich syndrome, hyper-IgM syndrome</td>
</tr>
<tr>
<td><strong>ENDOCRINOLOGIC</strong></td>
<td></td>
</tr>
<tr>
<td>Hypoparathyroidism</td>
<td>DiGeorge syndrome, mucocutaneous candidiasis</td>
</tr>
<tr>
<td>Endocrinopathies (autoimmune)</td>
<td>Mucocutaneous candidiasis</td>
</tr>
<tr>
<td>Diabetes, hypothyroid</td>
<td>IPEX and IPEX-like syndromes</td>
</tr>
<tr>
<td>Growth hormone deficiency</td>
<td>X-linked agammaglobulinemia</td>
</tr>
<tr>
<td>Gonadal dysgenesis</td>
<td>Mucocutaneous candidiasis</td>
</tr>
<tr>
<td><strong>HEMATOLOGIC</strong></td>
<td></td>
</tr>
<tr>
<td>Hemolytic anemia</td>
<td>B- and T-cell immune defects, ALPS</td>
</tr>
<tr>
<td>Thrombocytopenia, small platelets</td>
<td>Wiskott-Aldrich syndrome</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>Hyper-IgM syndrome, Wiskott-Aldrich variant, chronic granulomatous disease</td>
</tr>
<tr>
<td>Immune thrombocytopenia</td>
<td>B-cell immune defects, ALPS</td>
</tr>
<tr>
<td><strong>SKELETAL</strong></td>
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</tr>
<tr>
<td>Short-limb dwarfism</td>
<td>Short-limb dwarfism with T- and/or B-cell immune defects</td>
</tr>
<tr>
<td>Bony dysplasia</td>
<td>ADA deficiency, cartilage hair hypoplasia</td>
</tr>
</tbody>
</table>

ADA, Adenosine deaminase deficiency; AID, activation-induced cytidine deaminase; ALPS, autoimmune lymphoproliferative syndrome; CVID, common variable immunodeficiency; GVDH, graft-vs-host disease; Ig, immunoglobulin; IPEX, X-linked immune dysfunction enteropathy polyendocrinopathy; SCID, severe combined immunodeficiency.


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**Table 122-6  Initial Screening Immunologic Testing of the Child with Recurrent Infections**

<table>
<thead>
<tr>
<th>COMPLETE BLOOD COUNT, MANUAL DIFFERENTIAL, AND ERYTHROCYTE SEDIMENTATION RATE</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Absolute lymphocyte count (normal result [Chapter 727] rules against T-cell defect)</td>
<td></td>
</tr>
<tr>
<td>Absolute neutrophil count (normal result [Chapter 727] rules against congenital or acquired neutropenia and [usually] both forms of leukocyte adhesion deficiency, in which elevated counts are present even between infections)</td>
<td></td>
</tr>
<tr>
<td>Platelet count (normal result excludes Wiskott-Aldrich syndrome)</td>
<td></td>
</tr>
<tr>
<td>Howell-Jolly bodies (absence rules against asplenia)</td>
<td></td>
</tr>
<tr>
<td>Erythrocyte sedimentation rate (normal result indicates chronic bacterial or fungal infection unlikely)</td>
<td></td>
</tr>
</tbody>
</table>

**SCREENING TESTS FOR B-CELL DEFECTS**

- Immunoglobulin (Ig) A measurement; if abnormal, IgG and IgM measurement
- Isohemagglutinins
- Antibody titers to blood group substances, tetanus, diphtheria, Haemophilus influenzae, and pneumococcus

**SCREENING TESTS FOR T-CELL DEFECTS**

- Absolute lymphocyte count (normal result indicates T-cell defect unlikely)
- Flow cytometry to examine for the presence of naive T cells (CD3+CD45RA+ cells)

**SCREENING TESTS FOR PHAGOCYTIC CELL DEFECTS**

- Absolute neutrophil count
- Respiratory burst assay

**SCREENING TEST FOR COMPLEMENT DEFICIENCY**

$C{H}_4$
frequent infections were studied in depth, they were found to have broader immunologic dysfunction, including poor responses to protein antigens, suggesting that they may have been in the process of developing into common variable immunodeficiency (CVID). Only when profound antibody deficiencies are detected despite normal levels of immunoglobulins are IgG subclass measurements occasionally helpful. Children who completely lack IgG2 are usually unable to make antibodies to polysaccharide antigens, although this may also be found among individuals with normal IgG2. Thus, specific antibody measurements are far more cost-effective than IgG subclass determinations.

Patients found to be agammaglobulinemic should have their blood B cells enumerated by flow cytometry using dye-conjugated monoclonal antibodies to B-cell–specific CD antigens (usually CD19 or CD20). Normally, approximately 8-10% of circulating lymphocytes are B cells. B cells are absent in X-linked agammaglobulinemia (XLA) and in several very rare autosomal recessive conditions, but they are present in CVID, IgA deficiency, and hyper-IgM syndromes. This distinction is important, because children with hypogammaglobulinemia from XLA and CVID can have different clinical problems, and the 2 conditions clearly have different inheritance patterns. Patients with XLA have a heightened susceptibility to persistent enteroviral infections, whereas those with CVID have more problems with autoimmune diseases and lymphoid hyperplasia. Molecular testing for XLA and other B-cell defects (see Chapter 124.1) is indicated in cases without a family history to aid genetic counseling.

### T CELLS

T cells and T-cell subpopulations can be enumerated by flow cytometry using dye-conjugated monoclonal antibodies recognizing CD antigens present on T cells (i.e., CD2, CD3, CD4, and CD8). This is a particularly important test to perform on any infant who is lymphopenic, because CD3+ T cells usually constitute 70% of peripheral lymphocytes. Regardless of molecular type, infants with SCID are unable to produce T cells so are lymphopenic at birth. The flow cytometry for infants suspected of having SCID should also include monoclonal antibodies to naïve (CD45RA) and memory (CD45RO) T cells. In normal infants, more than 95% of the T cells are CD45RA+ (naïve) T cells. If the infant is a SCID, there could be transplacentally transferred maternal T cells detected by flow cytometry, but they would be dominantly CD45RO+ T cells. SCID is a pediatric emergency that can be

---

**Figure 122-2** Absolute lymphocyte counts in normal individual during maturation. (Data graphed from Altman PL: Blood and other body fluids. Prepared under the auspices of the Committee on Biological Handbooks. Washington, DC, 1961, Federation of American Societies for Experimental Biology.)

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**Table 122-7** Laboratory Tests in Immunodeficiency

<table>
<thead>
<tr>
<th>SCREENING TESTS</th>
<th>ADVANCED TESTS</th>
<th>RESEARCH/SPECIAL TESTS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>B-CELL DEFICIENCY</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IgG, IgM, IgA, and IgE levels</td>
<td>B-cell enumeration (CD19 or CD20)</td>
<td>Advanced B-cell phenotyping</td>
</tr>
<tr>
<td>Isohemagglutinin titers</td>
<td>Ab responses to boosters or to new vaccines</td>
<td>Biopsies (e.g., lymph nodes)</td>
</tr>
<tr>
<td>Ab response to vaccine antigens (e.g., tetanus, diphtheria, pneumococci, Haemophilus influenzae)</td>
<td></td>
<td>Ab responses to special antigens (e.g., bacteriophage φX174), mutation analysis</td>
</tr>
</tbody>
</table>

| **T-CELL DEFICIENCY** | | |
| Lymphocyte count | T-cell subset enumeration (CD3, CD4, CD8) | Advanced flow cytometry |
| Chest x-ray examination for thymic size* | Proliferative responses to mitogens, antigens, allogeneic cells | Enzyme assays (e.g., ADA, PNP) |
| Delayed skin tests (e.g., Candida, tetanus toxoid) | HLA typing | Thymic imaging |
| | Chromosome analysis | Mutation analysis |
| | | T-cell activation studies |
| | | Apoptosis studies |
| | | Biopsies |

| **PHAGOCYTIC DEFICIENCY** | | |
| WBC count, morphology | Adhesion molecule assays (e.g., CD11b/CD18, selectin ligand) | Mutation analysis |
| Respiratory burst assay | Mutation analysis | Enzyme assays (e.g., MPO, G6PD, NADPH oxidase) |

| **COMPLEMENT DEFICIENCY** | | |
| CH50 activity | AH50, activity | |
| C3 level | Component assays | |
| C4 level | Activation assays (e.g., C3a, C4a, C4d, C5a) | |

*In infants only.

Ab, antibody; ADA, adenosine deaminase; C, complement; CH, hemolytic complement; G6PD, glucose-6-phosphate dehydrogenase; HLA, human leukocyte antigen; Ig, immunoglobulin; MPO, myeloperoxidase; NADPH, nicotinamide adenine dinucleotide phosphate, PNP, purine nucleoside phosphorylase; WBC, white blood cell; φX, phage antigen.

<table>
<thead>
<tr>
<th>GROUPS AND DISEASES</th>
<th>INHERITANCE</th>
<th>GROUPS AND DISEASES</th>
<th>INHERITANCE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A. PREDOMINANTLY ANTIBODY DEFICIENCIES</strong></td>
<td>XL</td>
<td><strong>F. COMPLEMENT DEFICIENCIES</strong></td>
<td>AR</td>
</tr>
<tr>
<td>XL agammaglobulinemia</td>
<td>XL</td>
<td>C1q deficiency</td>
<td>AR</td>
</tr>
<tr>
<td>AR agammaglobulinemia</td>
<td>AR</td>
<td>C1r deficiency</td>
<td>AR</td>
</tr>
<tr>
<td>Hyper-IgM syndromes</td>
<td>AR</td>
<td>C4 deficiency</td>
<td>AR</td>
</tr>
<tr>
<td>a. CD40L defect</td>
<td>XL and AR</td>
<td>C2 deficiency</td>
<td>AR</td>
</tr>
<tr>
<td>b. AID defect</td>
<td>AR</td>
<td>C3 deficiency</td>
<td>AR</td>
</tr>
<tr>
<td>c. CD40 defect</td>
<td>AR</td>
<td>C5 deficiency</td>
<td>AR</td>
</tr>
<tr>
<td>d. UNG defect</td>
<td>AR</td>
<td>C6 deficiency</td>
<td>AR</td>
</tr>
<tr>
<td>e. Other hyper-IgM defects</td>
<td>AR</td>
<td>C7 deficiency</td>
<td>AR</td>
</tr>
<tr>
<td>Ig heavy-chain gene deletions</td>
<td>AR</td>
<td>C8α deficiency</td>
<td>AR</td>
</tr>
<tr>
<td>X. Chain deficiency mutations</td>
<td>AR</td>
<td>C8β deficiency</td>
<td>AR</td>
</tr>
<tr>
<td>Selective IgA deficiency</td>
<td>AR</td>
<td>C9 deficiency</td>
<td>AR</td>
</tr>
<tr>
<td>Common variable immunodeficiency</td>
<td>AR</td>
<td>C1 inhibitor</td>
<td>AR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Factor I deficiency</td>
<td>AR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Factor H deficiency</td>
<td>AR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Factor D deficiency</td>
<td>AR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Properdin deficiency</td>
<td>XL</td>
</tr>
<tr>
<td><strong>B. SEVERE COMBINED IMMUNODEFICIENCIES</strong></td>
<td>XL</td>
<td><strong>G. IMMUNODEFICIENCY ASSOCIATED WITH OR SECONDARY TO OTHER DISEASES</strong></td>
<td>AR</td>
</tr>
<tr>
<td><strong>T-B-NK- SCID</strong></td>
<td>X-linked (γc deficiency)</td>
<td><strong>Chromosomal Instability or Defective Repair</strong></td>
<td>AR</td>
</tr>
<tr>
<td>a. X-linked (γc deficiency)</td>
<td>XL</td>
<td>Bloom syndrome</td>
<td>AR</td>
</tr>
<tr>
<td>b. Autosomal recessive (Jak3 deficiency)</td>
<td>AR</td>
<td>Fanconi anemia</td>
<td>AR</td>
</tr>
<tr>
<td><strong>T-B-NK+ SCID</strong></td>
<td>AR</td>
<td>ICF syndrome</td>
<td>AR</td>
</tr>
<tr>
<td>a. IL-7Rα deficiency</td>
<td>AR</td>
<td>Nijmegen breakage syndrome</td>
<td>AR</td>
</tr>
<tr>
<td>b. CD38, CD3e, or CD3ζ deficiencies</td>
<td>AR</td>
<td>Seckel syndrome</td>
<td>AR</td>
</tr>
<tr>
<td>c. CD45 deficiency</td>
<td>AR</td>
<td>Xeroderma pigmentosum</td>
<td>AR</td>
</tr>
<tr>
<td><strong>T-B-NK+ SCID</strong></td>
<td>AR</td>
<td><strong>Hyper-IgE Syndromes</strong></td>
<td>AR</td>
</tr>
<tr>
<td>a. RAG-1/2 deficiency</td>
<td>AR</td>
<td>Dyskeratosis congenita</td>
<td>AR</td>
</tr>
<tr>
<td>b. Artemis defect</td>
<td>AR</td>
<td>Netherton syndrome</td>
<td>AR</td>
</tr>
<tr>
<td><strong>Omenn Syndrome</strong></td>
<td>AR</td>
<td>Acrodermatitis enteropathica</td>
<td>AR</td>
</tr>
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<td>a. RAG-1/2 deficiency</td>
<td>AR</td>
<td>Anhidrotic ectodermal dysplasia</td>
<td>AR</td>
</tr>
<tr>
<td>b. IL-7Rα deficiency</td>
<td>AR</td>
<td>Papillon-Lefèvre syndrome</td>
<td>AR</td>
</tr>
<tr>
<td>c. γc deficiency</td>
<td>XL</td>
<td>Immunodeficiency with absent thumbs</td>
<td>AR</td>
</tr>
<tr>
<td><strong>Combined Immunodeficiencies</strong></td>
<td>AR</td>
<td><strong>Schimke Immunossseous Dysplasia</strong></td>
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<tr>
<td>a. Purine nucleoside phosphorylase deficiency</td>
<td>AR</td>
<td>Turner syndrome</td>
<td>AR</td>
</tr>
<tr>
<td>b. CD8 deficiency (ZAP-70 defect)</td>
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<td>Chromosome 18 rings and deletions</td>
<td>AR</td>
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<tr>
<td>c. MHC class II deficiency</td>
<td>AR</td>
<td>Skeletal Abnormalities</td>
<td>AR</td>
</tr>
<tr>
<td>d. MHC class I deficiency caused by TAP-1/2</td>
<td>AR</td>
<td><strong>Short-limbed skeletal dysplasia</strong></td>
<td>AR</td>
</tr>
<tr>
<td>mutations</td>
<td>AR</td>
<td>Cartilage-hair hypoplasia</td>
<td>AR</td>
</tr>
<tr>
<td>Reticular dysgenesis</td>
<td>AR</td>
<td><strong>Immunodeficiency with Generalized Growth Retardation</strong></td>
<td>AR</td>
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<tr>
<td><strong>C. OTHER CELLULAR IMMUNODEFICIENCIES</strong></td>
<td>AR</td>
<td>Schimke immunossseous dysplasia</td>
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<td>Wiskott-Aldrich syndrome</td>
<td>XL</td>
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<tr>
<td>Ataxia-telangiectasia</td>
<td>AR</td>
<td><strong>Dow syndrome</strong></td>
<td>AR</td>
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<tr>
<td>DiGeorge anomaly</td>
<td>?</td>
<td>Turner syndrome</td>
<td>AR</td>
</tr>
<tr>
<td><strong>D. DEFECTS OF PHAGOCYTIC FUNCTION</strong></td>
<td>AR</td>
<td>Chromosome 18 rings and deletions</td>
<td>AR</td>
</tr>
<tr>
<td><strong>Chronic Granulomatous Disease</strong></td>
<td>AR</td>
<td><strong>Skeletal Abnormalities</strong></td>
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</tr>
<tr>
<td>a. XL</td>
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<td><strong>Progeria (Hutchinson-Gilford syndrome)</strong></td>
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<td>b. AR</td>
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<td><strong>Immunodeficiency with Dermatologic Defects</strong></td>
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<td>1. p22 phox deficiency</td>
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<td>Partial albinism</td>
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<td>2. p47 phox deficiency</td>
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<td>Dyserkeratosis congenita</td>
<td>AR</td>
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<td>3. p67 phox deficiency</td>
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<td>Leukocyte adhesion defect 2</td>
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<td>Neutrophil G6PD deficiency</td>
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<td>Papillon-Lefèvre syndrome</td>
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<td>Myeloperoxidase deficiency</td>
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<td><strong>Hereditary Metabolic Defects</strong></td>
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<tr>
<td>Secondary granule deficiency</td>
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<td>Transcobalamin 2 deficiency</td>
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<tr>
<td>Shwachman syndrome</td>
<td>AR</td>
<td>Methylmalonic acidemia</td>
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<td>Severe congenital neutropenia (Kostmann)</td>
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<td>Type 1 hereditary orotic aciduria</td>
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<tr>
<td>Cyclic neutropenia (elastase defect)</td>
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<td>Biotin-dependent carboxylase deficiency</td>
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<td>Leukocyte mycobacterial defects</td>
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<td>Mannosidosis</td>
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<tr>
<td>IFN-γR1 deficiency</td>
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<td>Glycosgen storage disease type 1b</td>
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<tr>
<td>IFN-γR1 or R2 deficiency</td>
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<td>Chédiak-Higashi syndrome</td>
<td>AR</td>
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<tr>
<td>IL-12Rβ1 deficiency</td>
<td>AR</td>
<td><strong>Hypercatabolism of Immunoglobulin</strong></td>
<td>AR</td>
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<tr>
<td>IL-12p40 deficiency</td>
<td>AR</td>
<td>Familial hypercatabolism</td>
<td>AR</td>
</tr>
<tr>
<td>STAT1 deficiency</td>
<td>AR</td>
<td>Intestinal lymphangiectasia</td>
<td>AR</td>
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<td><strong>E. IMMUNODEFICIENCIES ASSOCIATED WITH LYMPHOPROLIFERATIVE DISORDERS</strong></td>
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<td><strong>H. OTHER IMMUNODEFICIENCIES</strong></td>
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<tr>
<td>Fas deficiency</td>
<td>AD</td>
<td>Hyper-IgE syndromes</td>
<td>AD and AR</td>
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<tr>
<td>Fas ligand deficiency</td>
<td>AD</td>
<td><strong>Chronic mucocutaneous candidiasis</strong></td>
<td>AR</td>
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<tr>
<td>FLICE or caspase 8 deficiency</td>
<td>AD</td>
<td><strong>Chronic mucocutaneous candidiasis with polyendocrinopathy (APECED)</strong></td>
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<td>Unknown (caspase 3 deficiency)</td>
<td>AD</td>
<td><strong>Hereditary or congenital hyposplenia or asplenia</strong></td>
<td>AR</td>
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<tr>
<td><strong>TO OTHER DISEASES</strong></td>
<td>AD</td>
<td><strong>Immunodeficiency with absent thumbs</strong></td>
<td>AR</td>
</tr>
<tr>
<td><strong>Hyper-IgM syndromes</strong></td>
<td>AD</td>
<td><strong>Ivemark syndrome</strong></td>
<td>AR</td>
</tr>
<tr>
<td><strong>B1a deficiency</strong></td>
<td>AD</td>
<td><strong>Lymphoproliferative Disorders</strong></td>
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<td><strong>B1b deficiency</strong></td>
<td>AD</td>
<td><strong>IPEX syndromes</strong></td>
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</tr>
<tr>
<td><strong>B1c deficiency</strong></td>
<td>AD</td>
<td><strong>Ectodermal dysplasia</strong></td>
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<tr>
<td><strong>B1d deficiency</strong></td>
<td>AD</td>
<td><strong>Skeletally abnormal hypogammaglobulinemia</strong></td>
<td>AR</td>
</tr>
</tbody>
</table>

AD, autosomal dominant; ADA, adenosine deaminase; AID, activation-induced cytokine deaminase; APECED, autoimmune polyendocrinopathy candidiasis, ectodermal dysplasia, AR, autosomal recessive; caspase, cysteinyl aspartate specific protease; FLICE, Fas-associated protein with death domain–like IL-1–converting enzyme; G6PD, glucose 6-phosphate dehydrogenase; IFN, interferon; Ig, immunoglobulin; IL, interleukin; iPEX, immune dysregulation polyendocrinopathy, enteropathy, X-linked; IUIS, International Union of Immunological Societies; MHC, major histocompatibility complex; NEMO, nuclear factor b essential modulator; SCID, severe combined immunodeficiency; TAP, transporter associated with antigen presentation; UNG, uracil-N-glycosylase; XL, X-linked.

successfully treated by nonablative stem cell transplantation in more
than 92% of cases if diagnosed before serious, untreatable infections
develop. Normally, there are roughly twice as many CD4\(^+\) (helper) T
cells as there are CD8\(^+\) (cytotoxic) T cells. Because there are examples
of severe immunodeficiency in which phenotypically normal T cells
are present, tests of T-cell function are far more informative and cost-
effective than enumeration of T-cell subpopulations by flow cytometry.
T cells are normally stimulated through their T-cell receptors by
antigen present in the groove of major histocompatibility complex
molecules. The T-cell receptor can also be stimulated directly with
mitogens such as phytohemagglutinin, concanavalin A, or pokeweed
mitogen. After 3-5 days of incubation with the mitogen, the prolifera-
tion of T cells is measured by the incorporation of radiolabeled thymi-
dine into DNA. Other stimulants that can be used to assess T-cell
function in the same type of assay include antigens (Candida, tetanus
toxoid) and allogeneic cells (see Table 122-6).

**NATURAL KILLER CELLS**

Natural killer (NK) cells can be enumerated by flow cytometry using
monoclonal antibodies to NK-specific CD antigens, CD16 and CD56.
NK function is assessed by a radiolabeled chromium-release assay,
using the cell line K562, which is readily killed by NK cells.

**PHAGOCYTIC CELLS**

Killing defects of phagocytic cells, which should be suspected if a
patient has recurrent staphylococcal abscesses or gram-negative infec-
tions, can be evaluated by screening tests measuring the neutrophil
respiratory burst after phorbol ester stimulation. The most reliable and
useful test of this type is a flow cytometric assessment of the respiratory
burst using rhodamine dye. Leukocyte adhesion deficiencies can be
easily diagnosed by flow cytometric assays of blood lymphocytes or
neutrophils, using monoclonal antibodies to CD18 or CD11 (LAD1)
or to CD15 (LAD2).

Phagocytic cell defects can be further defined according to their
molecular cause. Mutations in the genes encoding 5 different compo-
nents of the NADPH pathway have been discovered in various patients
with chronic granulomatous disease. It is important to identify the
specific molecular type of chronic granulomatous disease to provide
appropriate genetic counseling, as 1 type is X linked and the other 4
types are autosomal recessive. Early diagnosis of leukocyte adhesion
deficiency is of crucial importance because stem cell transplantation
can be lifesaving.

**COMPLEMENT**

The most effective screening test for complement defects is a CH\textsubscript{50}
assay, which is a bioassay that measures the intactness of the entire
complement pathway and yields abnormal results if complement
has been consumed from the specimen for any reason. Genetic defi-
ciciencies in the complement system are usually characterized by
extremely low CH\textsubscript{50} values. The most common cause of an abnormal
CH\textsubscript{50} result, however, is a delay in or improper transport of the speci-
men to the laboratory. Specific immunoassays for C3 and C4 are
commercially available, but further identification of other comple-
ment component deficiencies is usually possible only in research
laboratories. Nevertheless, it is extremely important to identify which
component is missing, because there are different disease suscepti-
bilities depending on whether there are deficiencies of early or late
components (see Chapter 134). Identifying the mode of inheritance
is also important for genetic counseling. Properdin deficiency is X
linked, but all of the other complement deficiencies are autosomal.
Measurement of C4 can be helpful in assessing suspected hereditary
angioedema.

*Bibliography is available at Expert Consult.*
Bibliography
Defense against infectious agents is secured through a combination of anatomic physical barriers including the skin, mucous membranes, mucous blanket, and ciliated epithelial cells, as well as the various components of the immune system. The immune system of vertebrates integrates 2 fundamental response mechanisms. Innate (natural) immunity responds to infection regardless of previous exposure to the agent and includes polymorphonuclear leukocytes, dendritic and mononuclear phagocytic cells, natural killer (NK) cells, various receptors that recognize common pathogen antigens (Toll-like receptors) and the complement system. Acquired (adaptive) immunity is a highly specific response that includes T and B lymphocytes. The immune system also helps protect against malignancy and autoimmunity.

LYMPHOPOIESIS IN THE FETUS
Origin of the Lymphoid System
The human immune system arises in the embryo from gut-associated tissue. Pluripotential hematopoietic stem cells first appear in the yolk sac at 2.5-3 wk of gestational age, migrate to the fetal liver at 5 wk of gestation, and later reside in the bone marrow, where they remain throughout life (Fig. 123-1). Lymphoid stem cells develop from such precursor cells and differentiate into T, B, or NK cells, depending on the organs or tissues to which the stem cells traffic. Development of the primary lymphoid organs—thymus and bone marrow—begins during the middle of the 1st trimester of gestation and proceeds rapidly. Development of the secondary lymphoid organs—spleen, lymph nodes, tonsils, Peyer patches, and lamina propria—soon follows. These organs serve as sites of differentiation of T, B, and NK lymphocytes from stem cells throughout life. Both the initial organogenesis and the continued cell differentiation occur as a consequence of the interaction of a vast array of lymphocytic and microenvironmental cell surface molecules and proteins secreted by the involved cells. The complexity and number of lymphoid cell surface molecules led to the development of an international nomenclature for clusters of differentiation (CD) (Table 123-1).

T and B lymphocytes are the only components of the immune system that have antigen-specific recognition capabilities and are responsible for adaptive immunity. NK cells are lymphocytes that are also derived from hematopoietic stem cells and are thought to have a role in host defense against viral infections, tumor surveillance, and immune regulation, but they do not have antigen receptors. Nonantibody proteins synthesized and secreted by T, B, and NK cells, and by the cells with which they interact, act as intercellular mediators and are referred to as cytokines or interleukins (ILs) (Table 123-2). Cytokines have the ability to act in an autocrine, paracrine, or endocrine manner.
to promote and facilitate differentiation and proliferation of the cells of the immune system.

T-Cell Development and Differentiation

The primitive thymic rudiment is formed from the ectoderm of the 3rd branchial cleft and endoderm of the 3rd branchial pouch at 4 wk gestation. Beginning at 7-8 wk, the right and left rudiments move caudally and fuse in the midline. Bloodborne T-cell precursors from the fetal liver then begin to colonize the perithymic mesenchyme at 8 wk gestation, and at 8-8.5 wk gestation are found intrathymically. The earliest cells to enter the thymus are found in the subcapsular region and do not express CD3, CD4, CD8, or either type of T-cell receptor. These lymphoid cell precursors are triggered to proliferate and become thymocytes through interactions with the thymic stroma. These cells express CD44 and c-kit (CD117) and slightly later the CD7, CD8, and CD62L (vascular CAM-1) moieties on specialized regions of lymphoid organ blood vessels called lymphocyte surface adhesion molecule, to permit homing. The homing of lymphocytes to peripheral lymphoid organs is directed by the interaction of α4β1 and α4β7 with carbohydrate moieties on specialized regions of lymphoid organ blood vessels called selectins. As immature cortical thymocytes begin to express TCRs, the processes of positive and negative selection take place. Positive selection occurs through the interaction of immature thymocytes, which express low levels of TCR, with major histocompatibility complex (MHC) antigens present on cortical thymic epithelial cells. As a result, thymocytes with TCR capable of interacting with foreign antigens presented on self human leukocyte antigen (HLA) molecules are activated and develop to maturity. Most (>98%) of the cells die by failing to be positively selected or as a consequence of negative selection, but some are selected to mature into CD4 or CD8 single positive cells. Mature thymocytes that survive the selection process either express CD4 and are restricted to interacting with self class II HLA antigens, or express CD8 and are restricted to interacting with self class I HLA antigens when foreign antigens are presented by these MHC molecules. Negative selection occurs next in the medulla and is mediated by interaction of the surviving thymocytes, which have much higher levels of TCR expression, with host peptides presented by HLA class I or II antigens present on bone marrow-derived thymic macrophages, dendritic cells, and possibly B cells. This interaction mediates apoptosis (programmed cell death) of such autoreactive thymocytes. The thymic medulla contains only mature single-positive T cells that eventually leave the thymus and enter the bloodstream. T-cell functions are acquired concomitantly with the development of single-positive thymocytes, but they are not fully developed until the cells emigrate from the thymus. T cells begin to emigrate from the thymus to the spleen, lymph nodes, and appendix at 11-12 wk of embryonic life, and to the tonsils by 14-15 wk. They leave the thymus via the bloodstream and are distributed throughout the body, with the heaviest concentrations in the paracortical areas of lymph nodes, the periarteriolar areas of the spleen, and the thoracic duct lymph. Recent thymic emigrants coexpress the CD45RA isoform of the human leukocyte antigen (HLA) molecules are activated and develop to maturity. Most (>98%) of the cells die by failing to be positively selected or as a consequence of negative selection, but some are selected to mature into CD4 or CD8 single positive cells. Mature thymocytes that survive the selection process either express CD4 and are restricted to interacting with self class II HLA antigens, or express CD8 and are restricted to interacting with self class I HLA antigens when foreign antigens are presented by these MHC molecules. Negative selection occurs next in the medulla and is mediated by interaction of the surviving thymocytes, which have much higher levels of TCR expression, with host peptides presented by HLA class I or II antigens present on bone marrow-derived thymic macrophages, dendritic cells, and possibly B cells. This interaction mediates apoptosis (programmed cell death) of such autoreactive thymocytes. The thymic medulla contains only mature single-positive T cells that eventually leave the thymus and enter the bloodstream. T-cell functions are acquired concomitantly with the development of single-positive thymocytes, but they are not fully developed until the cells emigrate from the thymus. T cells begin to emigrate from the thymus to the spleen, lymph nodes, and appendix at 11-12 wk of embryonic life, and to the tonsils by 14-15 wk. They leave the thymus via the bloodstream and are distributed throughout the body, with the heaviest concentrations in the paracortical areas of lymph nodes, the periarteriolar areas of the spleen, and the thoracic duct lymph. Recent thymic emigrants coexpress the CD45RA isoforms and CD62L (l-selectin). Rearrangement of the TCR locus during intrathymic T-cell development results in the excision of DNA and the excised elements form circular episomes as a by-product. These TCR recombination excision circles can be detected in T cells that are recent thymic emigrants, whereas T cells that develop extrathymically do not contain these episomes. Inability to detect TCR recombination excision circles by real-time polymerase chain reaction of DNA from the dried blood spots collected from infants shortly after birth is the test used for newborn screening for SCID. The homing of lymphocytes to peripheral lymphoid organs is directed by the interaction of a lymphocyte surface adhesion molecule, l-selectin, with carbohydrate moieties on specialized regions of lymphoid organ blood vessels called high endothelial venules. By 12 wk gestation, T cells can proliferate in response to plant lectins, such as phytohemagglutinin and concanavalin A, and to allogeneic cells; antigen-binding T cells have been found by 20 wk gestation. Hassall's corpuscles (bodies), which are swirls of terminally differentiated medullary epithelial cells, are first seen in the thymic medulla at 16-18 wk of embryonic life.
**Table 123-1: CD Classification of Some Lymphocyte Surface Molecules**

<table>
<thead>
<tr>
<th>CD NUMBER</th>
<th>OTHER NAMES</th>
<th>TISSUE/LINEAGE</th>
<th>FUNCTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD1</td>
<td>T6</td>
<td>Cortical thymocytes; Langerhans cells</td>
<td>Lipid antigen presentation to TCRγδ cells</td>
</tr>
<tr>
<td>CD2</td>
<td>SRBC receptor</td>
<td>T and NK cells</td>
<td>Binds LFA-3 (CD58); alternative pathway of T-cell activation</td>
</tr>
<tr>
<td>CD3</td>
<td>T3, Leu 4</td>
<td>T cells</td>
<td>TCR-associated; transduces signals from TCR</td>
</tr>
<tr>
<td>CD4</td>
<td>T4, Leu3a</td>
<td>Helper T-cell subset</td>
<td>Receptor for HLA class II antigens; associated with p56 lck tyrosine kinase</td>
</tr>
<tr>
<td>CD7</td>
<td>3A1, Leu 9</td>
<td>T and NK cells and their precursors</td>
<td>Comitogenic for T lymphocytes</td>
</tr>
<tr>
<td>CD8</td>
<td>T8, Leu2a</td>
<td>Cytotoxic T-cell subset; also on 30% of NK cells</td>
<td>Receptor for HLA class I antigens; associated with p56 lck tyrosine kinase</td>
</tr>
<tr>
<td>CD10</td>
<td>cALLA</td>
<td>B-cell progenitors</td>
<td>Peptide cleavage</td>
</tr>
<tr>
<td>CD11a</td>
<td>LFA-1a V chain</td>
<td>T, B, and NK cells</td>
<td>With CD18, ligand for ICAMs 1, 2, and 3</td>
</tr>
<tr>
<td>CD11b, c</td>
<td>MAC-1, CR3; CR4</td>
<td>NK cells</td>
<td>With CD18, receptors for C3bi</td>
</tr>
<tr>
<td>CD16</td>
<td>FcRIII</td>
<td>NK cells</td>
<td>FcR for IgG</td>
</tr>
<tr>
<td>CD19</td>
<td>B4</td>
<td>B cells</td>
<td>Regulates B-cell activation</td>
</tr>
<tr>
<td>CD20</td>
<td>B1</td>
<td>B cells</td>
<td>Mediates B-cell activation</td>
</tr>
<tr>
<td>CD21</td>
<td>B2</td>
<td>B cells</td>
<td>C3d, also the receptor for EBV; CR2</td>
</tr>
<tr>
<td>CD25</td>
<td>IL-2Rα</td>
<td>T, B, and NK cells</td>
<td>Mediates signaling by IL-2</td>
</tr>
<tr>
<td>CD34</td>
<td>My10</td>
<td>Stem cells</td>
<td>Binds to l-selectin</td>
</tr>
<tr>
<td>CD38</td>
<td>T10</td>
<td>T, B, and NK cells and monocytes</td>
<td>Associates with hyaluronic acid</td>
</tr>
<tr>
<td>CD40</td>
<td>CD40</td>
<td>B cells and monocytes</td>
<td>Initiates isotype switching in B cells when ligated</td>
</tr>
<tr>
<td>CD44</td>
<td>CD44</td>
<td>Bone marrow stromal and many other cells.</td>
<td>Matrix adhesion molecule</td>
</tr>
<tr>
<td>CD45</td>
<td>Leukocyte common antigen, T200</td>
<td>All leukocytes</td>
<td>Tyrosine phosphatase that regulates lymphocyte activation; CD45R0 isoform on memory T cells, CD45RA isoform on naive T cells</td>
</tr>
<tr>
<td>CD56</td>
<td>NCAM; NKH-1</td>
<td>NK cells</td>
<td>Mediates NK homotypic adhesion</td>
</tr>
<tr>
<td>CD62L</td>
<td>l-selectin</td>
<td>Marker for recent thymic emigrants. Also found on other leukocytes.</td>
<td>Cell adhesion molecule</td>
</tr>
<tr>
<td>CD69</td>
<td>CD69</td>
<td>T cells and NK cells</td>
<td>Early activation marker</td>
</tr>
<tr>
<td>CD73</td>
<td>Ecto-5′-nucleotidase</td>
<td>T and B cells</td>
<td>Associates with AMP</td>
</tr>
<tr>
<td>CD80</td>
<td>B7.1</td>
<td>B cells</td>
<td>Costimulatory with CD28 on T cells to upregulate high affinity IL-2 receptor</td>
</tr>
<tr>
<td>CD86</td>
<td>B7.2</td>
<td>B cells</td>
<td>Costimulatory with CD28 on T cells to upregulate high affinity IL-2 receptor</td>
</tr>
<tr>
<td>CD117</td>
<td>c-kit</td>
<td>Pro-B cells, double-negative thymocytes</td>
<td>Receptor for stem cell factor</td>
</tr>
<tr>
<td>CD127</td>
<td>IL-7Rα</td>
<td>T cells</td>
<td>Mediates IL-7 signaling</td>
</tr>
<tr>
<td>CD132</td>
<td>Common γ chain (γc)</td>
<td>T, B, and NK cells</td>
<td>Mediates signaling by IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21</td>
</tr>
<tr>
<td>CD154</td>
<td>CD40 ligand, gp39</td>
<td>Activated CD4+ T cells</td>
<td>Ligates CD40 on B cells and initiates isotype switching</td>
</tr>
<tr>
<td>CD278</td>
<td>ICOS</td>
<td>T cells</td>
<td>Interacts with B7-H2</td>
</tr>
</tbody>
</table>

AMP, Adenosine monophosphate; CD, cluster of differentiation; EBV, Epstein-Barr virus; HLA, human leukocyte antigen; ICAM, intracellular adhesion molecule; ICOS, inducible costimulator; Ig, immunoglobulin; IL, interleukin; LFA, lymphocyte function-associated antigen; MAC, membrane attack complex; NCAM, neural cell adhesion molecule; NK, natural killer; SRBC, sheep red blood cell; TCR, T-cell receptor.

**B-Cell Development and Differentiation**

In parallel with T-cell differentiation, B-cell development begins in the fetal liver before 7 wk of gestation. Fetal liver CD34 stem cells are seeded to the bone marrow of the clavicles by 8 wk of embryonic life and to that of the long bones by 10 wk (see Fig. 123-1). As B cells differentiate from primitive stem cells, they proceed through stages that are marked by the sequential rearrangement of immunoglobulin gene segments to generate a diverse repertoire of antigen receptors. The early pro-B cell is the first descendent of the pluripotential stem cell committed to B-lineage development and in this stage, the heavy chain locus rearranges first. In the early pro-B cell, D-J rearrangements are made on both chromosomes. In the late pro-B cell, the V segment rearranges to a D-J gene segment, but it is a matter of chance whether the juxtaposed J sequence and the 𝜇 constant region sequence downstream can be read in the correct reading frame. There is a roughly 2 in 3 chance that an out-of-frame sequence will occur,
**Table 123-2** Functional Classification of Cytokines

<table>
<thead>
<tr>
<th>1. Cytokines involved in natural immune responses</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Type I interferons (IFN-α and IFN-β): inhibit viral replication, inhibit cell proliferation, activate NK cells, and upregulate class I MHC molecule expression</td>
</tr>
<tr>
<td>• TNF-α: mediates host response to Gram-negative bacteria and other infectious agents</td>
</tr>
<tr>
<td>• IL-1α and IL-1β: mediate host inflammatory response to infectious agents</td>
</tr>
<tr>
<td>• IL-1RA: a natural antagonist of IL-1, blocks signals delivered by IL-1</td>
</tr>
<tr>
<td>• IL-6: mediates and regulates inflammatory responses</td>
</tr>
<tr>
<td>• Chemokines (IL-8, monocyte chemotactic protein-1 or MCP-1, RANTES, and others): mediate leukocyte chemotaxis and activation</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2. Lymphocyte regulatory cytokines</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Immunostimulatory or growth-promoting</td>
</tr>
<tr>
<td>• IL-1: costimulates activation of T cells</td>
</tr>
<tr>
<td>• IL-2: growth factor for T, B, NK cells; activates NK and T effector cells</td>
</tr>
<tr>
<td>• IL-4: T- and B-cell growth factor; stimulates IgE production; upregulates classes I and II MHC molecules and FcRII expression on macrophages; expansion of Th2 subset</td>
</tr>
<tr>
<td>• IL-5: B-cell growth and activation</td>
</tr>
<tr>
<td>• IL-6: growth factor for B cells</td>
</tr>
<tr>
<td>• IL-7: stromal cell factor; growth factor for precursor B and T cells, T-cell homeostatic factor</td>
</tr>
<tr>
<td>• IL-10: growth and differentiation factor for B cells</td>
</tr>
<tr>
<td>• IL-12: expansion of Th1 subset; activates effector cells</td>
</tr>
<tr>
<td>• IL-13: growth and differentiating factor for B cells; stimulates IgE production; upregulates Classes I and II MHC molecules and FcRII expression on macrophages</td>
</tr>
<tr>
<td>• TNF-β: stimulates effector cell function</td>
</tr>
<tr>
<td>• IL-15: regulates NK-cell development and memory cell homeostasis</td>
</tr>
<tr>
<td>• IL-17: promotes inflammation by acting on local tissue cells to cause them to produce chemokines, such as IL-8, that recruit neutrophils and other innate effector cells</td>
</tr>
<tr>
<td>• IL-18: induces IFN-γ, GM-CSF, TNF-α in immunocompetent cells</td>
</tr>
<tr>
<td>• IL-21: together with IL-4 regulates IgG and IgE class-switching and Ig synthesis</td>
</tr>
<tr>
<td>• IL-23: autocrine growth factor for Th17 cells</td>
</tr>
<tr>
<td>• IL-27: produced by antigen presenting cells and regulates both T and B cell activity</td>
</tr>
<tr>
<td>• IFN-γ: activates macrophages, NK cells; upregulates classes I and II MHC molecules expression; inhibits IL-4– or IL-13–induced IgE production</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>b. Immunosuppressive</th>
</tr>
</thead>
<tbody>
<tr>
<td>• IL-1α: regulates IL-1 activities</td>
</tr>
<tr>
<td>• TGF-β: antagonizes lymphocyte responses</td>
</tr>
<tr>
<td>• IL-10: inhibits activities of Th1 cells</td>
</tr>
<tr>
<td>• IFN-α/β: inhibits production of IFN-γ</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>3. Hematopoiesis regulating cytokines</th>
</tr>
</thead>
<tbody>
<tr>
<td>• GM-CSF, G-CSF, M-CSF: colony-stimulating factors</td>
</tr>
<tr>
<td>• Erythropoietin (EPO): differentiation of erythroid precursors</td>
</tr>
<tr>
<td>• IL-3, SCF, c-kit receptor: regulate stem cell development</td>
</tr>
<tr>
<td>• IL-4: mast cell development</td>
</tr>
<tr>
<td>• IL-5: eosinophil differentiation and proliferation</td>
</tr>
<tr>
<td>• IL-6: differentiation of B cells</td>
</tr>
<tr>
<td>• IL-7: differentiation of B and T cells</td>
</tr>
<tr>
<td>• IL-8: promotes cell survival in response to hematopoietic cytokines</td>
</tr>
<tr>
<td>• IL-9: mast-cell growth factor</td>
</tr>
<tr>
<td>• IL-10: suppresses lymphocyte functions and downregulates production of proinflammatory cytokines; antiatherogenic</td>
</tr>
<tr>
<td>• IL-11: elevates platelet count in patients given chemotherapy</td>
</tr>
<tr>
<td>• IL-12: expands and activates resting NK cells</td>
</tr>
<tr>
<td>• IL-15: expands and activates resting NK cells</td>
</tr>
<tr>
<td>• IL-21: limits viability of NK cells</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>4. Proinflammatory cytokines</th>
</tr>
</thead>
<tbody>
<tr>
<td>• IL-1, TNF-α, IL-6: participate in the acute-phase response and synergize to mediate inflammation, shock, and death</td>
</tr>
<tr>
<td>• IL-12: stimulates IFN-γ (production by T and NK cells)</td>
</tr>
<tr>
<td>• IL-17: acts on monocytes to induce secretion of proinflammatory mediators such as IL-8, TNF, and GM-CSF</td>
</tr>
<tr>
<td>• IL-18: induces IFN-γ, GM-CSF, TNF-α; upregulates chemokine receptors</td>
</tr>
<tr>
<td>• IL-23: drives the development of autoreactive IL-17–producing T cells and promotes chronic inflammation</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>5. Antinflammatory cytokines</th>
</tr>
</thead>
<tbody>
<tr>
<td>• IL-4: reduces endotoxin-induced TNF and IL-1 production</td>
</tr>
<tr>
<td>• IL-6: inhibits TNF production</td>
</tr>
<tr>
<td>• IL-10: suppresses lymphocyte functions and downregulates production of proinflammatory cytokines; antiatherogenic</td>
</tr>
<tr>
<td>• IL-11: cytotoxic effect on bowel mucosa, skin and joint inflammation</td>
</tr>
<tr>
<td>• IL-13: downregulates functions of macrophages, suppresses production of proinflammatory cytokines</td>
</tr>
<tr>
<td>• TNFSF: soluble TNF receptor; by binding TNF, blocks interaction of TNF with the target cell</td>
</tr>
</tbody>
</table>

*This is not an exhaustive list.

G-CSF, Granulocyte colony-stimulating factor; GM-CSF, granulocyte macrophage colony-stimulating factor; IFN, interferon; Ig, immunoglobulin; IL, interleukin; IL-1R, interleukin-1 receptor; M-CSF, macrophage colony-stimulating factor; MHC, major histocompatibility complex; MCP-1, monocyte chemotactic protein; NK, natural killer; RANTES, regulated on activation normal t cell expressed and secreted; SCF, stem cell factor; TGF, transforming growth factor; Th1, Th2, Th17, T-helper types 1, 2, and 17; TNF, tumor necrosis factor.

and only those cells that have productive rearrangements will survive, so a majority of cells are lost. The next stage is the pre-B cell, during which immunoglobulin (Ig) light chain genes are rearranged. The pre-B cell is distinguished by the expression of cytoplasmic Ig heavy chains but no IgM, because immunoglobulin light chains are not yet produced. The pre-B cells must rearrange the same light chain gene on both chromosomes for a productive rearrangement, so when this does not happen the cells are lost. Fewer cells are lost between the pre-B and immature B-cell stages than in the pro-B to pre-B transition. Next is the immature B-cell stage, during which the light-chain genes have already been rearranged and IgM but not IgD is expressed. The last stage of antigen-independent B-cell development is the mature or virgin B cell, which co-expresses both IgM and IgD. Pre-B cells can be found in fetal liver at 7 wk gestation, slgM+ and slgG+ B cells at between 7 and 11 wk, and slgD+ and slgA+ B cells by 12-13 wk. By 14 wk of embryonic life, the percentage of circulating lymphocytes bearing slgM and slgD is the same as in cord blood and slightly higher than in the blood of adults.

Antigen-dependent stages of B-cell development are those that develop after the mature or virgin B cell is stimulated by antigen through its antigen receptor (sIg); the outcome is the differentiation of the cell and its progeny into slg+ memory (CD27) B cells (for that particular antigen) and plasma cells, which synthesize and secrete antibody, which is antigen-specific immunoglobulin. Deficiency of activation-induced cytidine deaminase (AICDA) or of uracil DNA glycosylase (UNG), as seen in 2 forms of autosomal recessive hyper IgM, can result in a failure of isotype switching so that only IgM antibodies are formed.

There are 5 immunoglobulin isotypes, which are defined by unique heavy-chains: IgM, IgG, IgA, IgD, and IgE. IgG and IgM, the only complement-fixing isotypes, are the most important immunoglobulins in the blood and other internal body fluids for protection against infectious agents. IgM is confined primarily to the intravascular compartment because of its large size, whereas IgG is present in all internal body fluids. IgA is the major protective immunoglobulin of external body fluids. IgA, which co-expresses both sIgM and sIgD, is the same as in cord blood and slightly higher than in the blood of adults.

Antigen-dependent stages of B-cell development are those that develop after the mature or virgin B cell is stimulated by antigen through its antigen receptor (sIg); the outcome is the differentiation of the cell and its progeny into slg+ memory (CD27) B cells (for that particular antigen) and plasma cells, which synthesize and secrete antibody, which is antigen-specific immunoglobulin. Deficiency of activation-induced cytidine deaminase (AICDA) or of uracil DNA glycosylase (UNG), as seen in 2 forms of autosomal recessive hyper IgM, can result in a failure of isotype switching so that only IgM antibodies are formed.

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Natural Killer–Cell Development

NK cell activity is found in human fetal liver cells at 8-11 wk of gestation. NK lymphocytes are also derived from bone marrow precursors. Thymic processing is not necessary for NK-cell development, although NK cells have been found in the thymus. After release from bone marrow, NK cells enter the circulation or migrate to the spleen, with very few NK cells in lymph nodes. In normal individuals, NK cells represent 8-10% of lymphocytes, but the percentages are sometimes slightly lower in cord blood.

Unlike T and B cells, NK cells do not rearrange antigen receptor genes during their development but are defined by their functional capacity to mediate non–antigen-specific cytotoxicity. NK cells have killer inhibitory receptors that recognize certain MHC antigens and inhibit the killing of normal allogeneic cells in 4 specific patterns of reactivity. The genetic loci controlling these receptors are different from MHC alloantigenic loci, and have been mapped to chromosome 19. Virtually all NK cells express CD56, and more than 90% bear CD16 (FcRIII) on the cell surface. Other CD antigens found on NK cells include CD57 (50-60%), CD7 and CD2 (70-90%), and CD8 (30-40%) (see Table 123-1). Although NK cells share surface antigens with T and myeloid cells, the lineage relationship of NK cells to the latter is still unclear. Some humans with autosomal recessive SCID who have profound deficiencies in T and B cells, have abundant NK cells, whereas those with X-linked and Jak3-deficient SCID have no T or NK cells.

Immune Cell Interactions

Immune cell interaction is of crucial importance to all phases of the adaptive immune response. Unlike the B-cell antigen receptor (Ig), which can recognize native antigen, the TCR can recognize only processed antigenic peptides presented to it by MHC molecules such as HLA-A, -B, and -C antigens (class I) and HLA-DR, -DP, and -DQ antigens (class II). The MHC molecules have a groove in their protein structure where peptides fit. Class I MHC molecules are found on most nucleated cells in the body. Class II MHC molecules are found on antigen-presenting cells (APCs), which include macrophages, dendritic cells, and B cells. The peptides found in the groove of class I HLA molecules come from proteins normally made in the cell that are degraded and inserted into the groove. The peptides include viral peptides if the cell is infected with a virus. The peptides present in the groove of class II molecules come from exogenous native antigens such as vaccine and bacterial proteins. These proteins are taken up by APCs, degraded, and expressed on the cell surface in the groove of class II HLA molecules. The TCR then interacts with the peptide-bearing HLA molecule and, through its functional and physical link to the CD3 complex of signal-transducing molecules, sends a signal to the T cell to produce cytokines that ultimately result in T-cell activation and proliferation.

Two of the main functions of T cells are to signal B cells to make antibody by producing cytokines and membrane molecules that can serve as ligands for non–antigen-receptor B-cell surface molecules and to kill virally infected cells or tumor cells. For a T cell to perform either of these functions, it must first bind to an APC or to a target cell (the immunologic synapse). For high-affinity binding of T cells to APCs or target cells, several molecules on T cells, in addition to TCRs, bind to molecules on APCs or target cells. The CD4 molecule binds directly to MHC class II molecules on APCs. CD8 on cytotoxic T cells binds the MHC class I molecule on the target cell. Both CD4 and CD8 molecules are directly involved in the regulation of T-cell activation and are physically linked intracellularly to the p56-lck protein tyrosine kinase. The cytoplasmic tail of CD45, the common leukocyte antigen, is a tyrosine phosphatase capable of regulating T-cell signal-transduction events by virtue of the fact that p56-lck is a substrate for CD45 phosphatase activity. Depending on which isofrom of CD45 is present on
the T cell (CD45RO on memory T cells, CD45RA on naive T cells), mechanisms by which CD45 could upregulate or downregulate T-cell triggering have been proposed. Indeed, one form of human SCID is caused by a deficiency of CD45. Lymphocyte function-associated antigen 1 (LFA-1) on the T cell binds a protein called ICAM-1 (intracellular adhesion molecule 1), designated CD54, on APCs. CD2 on T cells binds LFA-3 (CD58) on the APCs. With the adhesion of T cells to APCs (the immunologic synapse), T-helper (Th) cells are stimulated to make interleukins and upregulate cell surface molecules, such as the CD40 ligand (CD154), that provide help for B cells, and cytotoxic T cells are stimulated to kill their targets.

In the primary antibody response, native antigen is carried to a lymph node draining the site, taken up by specialized cells called follicular dendritic cells (FDCs), and expressed on their surfaces. Virgin B cells bearing slg specific for that antigen then bind to the antigen on the surfaces of the FDCs. If the affinity of the B-cell slg antibody for the antigen present on the FDCs is sufficient, and if other signals are provided by activated Th cells, the B cell develops into an antibody-producing plasma cell. If the affinity is not high enough or if T-cell signals are not received, the B cell dies through apoptosis. The signals from activated Th cells include several cytokines (IL-4, IL-5, IL-6, IL-10, IL-13, and IL-21) that they secrete (see Table 123-2) and a surface T-cell molecule, the CD40 ligand or CD154, which, on contact of the activated CD4 positive T cell with the B cell, binds to CD40 on the B-cell surface. CD40 is a type I integral membrane glycoprotein expressed on B cells, monocytes, some carcinomas, and a few other types of cells. It belongs to the tumor necrosis factor/nerve growth factor receptor family. Crosslinking of CD40 on B cells by CD154 on T cells in the presence of certain cytokines causes the B cells to undergo proliferation and to initiate immunoglobulin synthesis. In the primary immune response, only IgM antibody is usually made, and most of it is of relatively low affinity. Some B cells become memory B cells during the primary immune response. These cells switch their immunoglobulin genes so that IgG, IgA, and/or IgE antibodies of higher affinity are formed on a secondary exposure to the same antigen. The secondary antibody response occurs when these memory B cells again encounter that antigen. Plasma cells form, just as in the primary response; however, many more cells are rapidly generated, and IgG, IgA, and IgE antibodies are made. In addition, genetic changes in immunoglobulin genes (somatic hypermutation) lead to increased affinity of those antibodies. A lack of somatic hypermutation is seen in deficiency of activation-induced cytidine deaminase (AID) or uracil-N-glycosylase (UNG). The exact pattern of isotype response to antigen in normal individuals varies, depending on the type of antigen and the cytokines present in the microenvironment.

For NK-mediated lysis, binding to the target is of crucial importance. This is best exemplified by persons with leukocyte adhesion deficiency type I (LAD-1) who have mutations in the gene encoding CD18, or the β chain of 3 different adhesion molecules (LFA-1, CR3, and p150,95), and who lack NK function. Thus, binding of NK cells to their targets is facilitated by LFA-1-ICAM interactions. CD56 or NCAM (neural cell adhesion molecule) also mediates homotypic adhesion of NK cells. FcγRIII, or the low-affinity IgG receptor, has a higher affinity for IgG when it is present on NK cells than when it is on neutrophils. FcγRIII also permits NK cells to mediate antibody-dependent cellular cytotoxicity, where antibody is bound through its Fc region to the FcγRIII. The antibody-combining portion of the IgG attaches to the target cell, and the NK cell, attached to the target by the Fc portion of the antibody, kills the target cell.

**POSTNATAL LYMPHOPOIESIS**

**T Cells and T-Cell Subsets**

Although the percentage of CD3 T cells in cord blood is somewhat less than in the peripheral blood of children and adults, T cells are actually present in higher number because of a higher absolute lymphocyte count in normal infants. An additional distinction is that the ratio of CD4 to CD8 T cells is usually higher (3.5-4:1) in cord blood than in blood of children and adults (1.5-2:1). Virtually all T cells in cord blood bear the CD45RA (naïve) isof orm, and a dominance of CD45RA over CD45RO T cells persists during the 1st 2-3 yr of life, after which the number of cells bearing these 2 isof orms gradually equalize. Th cells can be further subdivided according to the cytokines they produce when activated. **Th1 cells** produce IL-2 and IFN-γ, which promote cytotoxic T-cell or delayed hypersensitivity types of responses, whereas **Th2 cells** produce IL-4, IL-5, IL-6, IL-13, and IL-21 (see Table 123-2), which promote B-cell responses and allergic sensitization, and **Th17 cells** produce IL-17. Development of Th cells into Th17 cells occurs when IL-6 and transforming growth factor β are present but IL-4 and IL-12 are absent. Th17 cells produce IL-21, which acts in an autocrine manner to activate STAT3, a transcription factor required for their further development as Th17 cells. Th17 cells express the receptor for the cytokine IL-23, stimulation that is required for development of Th17 effector activity. Th17 promotes inflammation by acting on local tissue cells to cause them to produce chemokines, such as IL-8, that recruit neutrophils and other innate effector cells. It is thought that the absence of these cells in the autosomal dominant form of the hyper-IgE syndrome (see Chapter 126) accounts for those patients' infection susceptibility to *Candida*. There are important additional subsets of T cells that have regulatory functions. These include CD25 high + T cells (Treg cells), also characterized by the presence of FOXP3 (absent in IPEX syndrome [see Chapter 126]) and considered to be important in the prevention of autoimmune diseases, and T cells that have phenotypic characteristics of NK cells (NKT cells). Cord blood T cells have the capacity to respond normally to T-cell mitogens (phytohemagglutinin, concanavalin A, and pokeweed mitogen) and are capable of mounting a normal mixed leukocyte response. Normal newborn infants also have the capacity to develop antigen-specific T-cell responses at birth, as evidenced by vigorous tuberculin reactivity a few wk after bacillus Calmette-Guérin vaccination on day 1 of life. Because patients in the 1st few mo of life may have unrecognized severe T-cell defects, most hospitals now routinely irradiate all blood products given young infants. T-cell defects can readily be detected even at birth by calculating the absolute lymphocyte count because T cells normally constitute 70% of circulating lymphocytes and their absence results in striking lymphopenia (see Fig. 122-2). T-cell lymphopenia also serves as the basis for the currently used newborn screening test for SCID.

**B Cells and Immunoglobulins**

Newborn infants have increased susceptibility to infections with Gram-negative organisms because IgM antibodies, which are heat-stable opsonins, do not cross the placenta. The level of the heat-labile opsonin, C3b, is also lower in newborn serum than in adults. These factors probably account for impaired phagocytosis of some organisms by newborn polymorphonuclear cells. Maternally transmitted IgG antibodies serve quite adequately as heat-stable opsonins for most Gram-positive bacteria, and IgG antibodies to viruses afford adequate protection against those agents. Because there is a relative deficiency of the IgG1 subclass, antibodies to capsular polysaccharide antigens may be deficient. Because premature infants have received less maternal IgG by the time of birth than full-term infants, their serum opsonic activity is low for all types of organisms.

B lymphocytes are present in cord blood in slightly higher percentages but considerably higher numbers than in the blood of children and adults, reflecting the higher absolute lymphocyte counts in all normal infants. Cord blood B cells do not synthesize the range of immunoglobulin isotypes made by B cells from children and adults when stimulated with anti-CD40 plus IL-4 or IL-10, producing primarily IgM and at a much reduced quantity. Neonates begin to synthesize antibodies of the IgM class at an increased rate very soon after birth in response to the immense antigenic stimulation of their new environment. Premature infants appear to be as capable of doing this as do full-term infants. At about 6 days after birth, the serum concentration of IgM rises sharply. This rise continues until adult levels are achieved by ~1 yr of age. Cord serum from noninfected normal newborns does not contain detectable IgA. Serum IgA is normally first detected at around the 13th day of postnatal life; the level gradually increases during early childhood until adult levels are achieved by 6-7 yr of age. Cord serum contains an IgG
concentration comparable to or greater than that of maternal serum. Maternal IgG gradually disappears during the 1st 6-8 mo of life, while the rate of infant IgG synthesis increases (IgG1 and IgG3 faster than IgG2 and IgG4, during the 1st yr) until adult concentrations of total IgG are reached and maintained by 7-8 yr of age. IgG1 and IgG3, reach adult levels first, followed by IgG3, at 10 yr and IgG4, at 12 yr of age. The serum IgG level in infants usually reaches a low point at ~3-4 mo of postnatal life. The rate of development of IgG generally follows that of IgA. After adult concentrations of each of the 3 major immunoglobulins are reached, these levels remain remarkably constant for a normal individual. The capacity to produce specific antibodies to protein antigens is intact at the time of birth. Normal infants cannot usually produce antibodies to polysaccharide antigens until after 2 yr of age unless the polysaccharide is conjugated to a protein carrier, as is the case for the conjugate *Haemophilus influenzae* type b and *Streptococcus pneumoniae* vaccines.

**Natural Killer Cells**
The percentage of NK cells in cord blood is usually lower than in the blood of children and adults, but the absolute number of NK cells is approximately the same, owing to the higher lymphocyte count. The capacity of cord blood NK cells to mediate target lysis in either NK-cell assays or antibody-dependent cellular cytotoxicity assays is roughly two-thirds that of adults.

**Lymphoid Organ Development**
Lymphoid tissue is proportionally small but rather well developed at birth and matures rapidly in the postnatal period. The thymus is largest relative to body size during fetal life and at birth is ordinarily two-thirds of its mature weight, which it attains during the 1st yr of life. It reaches its peak mass, however, just before puberty, and then gradually involutes thereafter. By 1 yr of age, all lymphoid structures are mature histologically. Absolute lymphocyte counts in the peripheral blood also reach a peak during the 1st yr of life (see Fig. 122-2). Peripheral lymphoid tissue increases rapidly in mass during infancy and early childhood. It reaches adult size by approximately 6 yr of age, exceeds those dimensions during the prepubertal years, and then undergoes involution coincident with puberty. The spleen, however, gradually accretes its mass during maturation and does not reach full weight until adulthood. The mean number of Peyer patches at birth is one-half the adult number, and gradually increases until the adult mean number is exceeded during adolescent years.

**INHERITANCE OF ABNORMALITIES IN T-, B-, AND NATURAL KILLER-CELL DEVELOPMENT**
More than 220 immunodeficiency syndromes have been described (see Table 122-8). Specific molecular defects have been identified in approximately 80% of these diseases. Most are recessive traits, several of which are caused by mutations in genes on the X chromosome and others by mutations on autosomal chromosomes. The molecular bases of 7 X-linked immunodeficiency disorders affecting T, B, and/or NK cells are known (see Chapters 124-126): X-linked immunodeficiency with hyper-IgM, X-linked lymphoproliferative syndrome, XIAD, X-linked agammaglobulinemia, X-linked SCID, the Wiskott-Aldrich syndrome, and nuclear factor kappa B essential modulator (NEMO). A few of the autosomal defects for which the molecular basis is known include (1) combined immunodeficiencies caused by abnormalities of purine salvage pathway enzymes, either adenosine deaminase (encoded by a gene on chromosome 20q13-ter) or purine nucleoside phosphorylase (encoded by a gene on chromosome 14q13.1); (2) combined immunodeficiencies caused by mutations in the gene encoding ZAP-70 (localized to chromosome 2q12), a non-src family protein tyrosine kinase important in T-cell signaling; (3) SCID caused by mutations in the gene on chromosome 19p13.1 encoding Janus kinase 3 (Jak3), the primary signal transducer from the common cytokine receptor γ chain (γc); (4) mutations in genes on chromosome 11 that encode components of the TCR, that is, CD3 γ, δ, and ε; (5) SCID caused by mutations in recombination activating genes (RAG1 and RAG2); and (6) SCID caused by mutations in the gene on chromosome 5p13 that encodes the α chain of the IL-7 receptor. These are only a few of the conditions for which the mutated genes have been discovered and the number is steadily growing.

**PRENATAL DIAGNOSIS AND CARRIER DETECTION**
Intrauterine diagnosis of adenosine deaminase and purine nucleoside phosphorylase deficiencies can be established by enzyme analyses on amnion cells (fresh or cultured) obtained before 20 wk gestation. Diagnosis of X-linked or autosomal defects causing SCID, other severe T-cell deficiencies, MHC class I and/or II antigen deficiencies, chronic granulomatous disease, or Wiskott-Aldrich syndrome can be established by direct mutation analysis of cells obtained by chorionic villus sampling or by amniocentesis if the mutation is known in the family or, if not known, by appropriate tests of phenotype or function on small samples of blood obtained by fetoscopy at 18-22 wk of gestation. The same diagnostic procedures can be performed on cord blood, but the only immunodeficiency disorder being routinely screened for is SCID and only 21 states are currently doing this (see Chapter 122). Carriers of any of these conditions can be identified by direct mutation analysis if the family's mutation is known.

*Bibliography is available at Expert Consult.*
**Bibliography**


Of all of the primary immunodeficiency diseases, those affecting antibody production are most frequent. Selective absence of serum and secretory immunoglobulin (Ig)A is the most common defect, with rates ranging from 1 in 333 to 1 in 18,000 persons among different races and ethnicities. By contrast, agammaglobulinemia is estimated to occur with a frequency of only 1 in 10,000 to 1 in 50,000 persons. Patients with antibody deficiency are usually recognized because they have recurrent infections with encapsulated bacteria, predominantly in the upper and lower respiratory tracts; some individuals with selective IgA deficiency or infants with transient hypogammaglobulinemia may have few or no infections. The defective gene products for many primary antibody deficiency disorders have been identified (Table 124-1) and localized (Fig. 124-1). Sometimes the defect is not in the B cell itself but in T cells, which are required for complete B-cell function; some disorders are caused by unknown factors or are secondary to an underlying disease or its treatment (Table 124-2).

X-LINKED AGAMMAGLOBULINEMIA
Patients with X-linked agammaglobulinemia (XLA), or Bruton agammaglobulinemia, have a profound defect in B-lymphocyte development resulting in severe hypogammaglobulinemia, an absence of circulating B cells, small to absent tonsils, and no palpable lymph nodes.

Genetics and Pathogenesis
The abnormal gene in XLA maps to q22 on the long arm of the X chromosome and encodes the B-cell protein tyrosine kinase Btk (Bruton tyrosine kinase). Btk is a member of the Tec family of cytoplasmic protein tyrosine kinases and is expressed at high levels in all B-lineage cells, including pre-B cells. It appears to be necessary for
primary genetic basis of primary antibody deficiency disorders. of phosphatidylinositol-3 kinase. α leucine-rich repeat-containing 8 (LRRC8); and (7) the p85 subunit of phosphatidylinositol-3 kinase.

B lymphocytes is not normal. T-cell subsets are normal, and T-cell function is intact. The thymus is affected male fetuses is possible if the mutation is known in the family. Carriers are detected by mutation analysis, and prenatal diagnosis of XLA only when rapid production of such cells is needed. Some pre-B cells are found in the bone marrow; the percentage of peripheral blood B cells is low in XLA.

Expression of Btk in cells of myeloid lineage is of interest because Btk participates in myeloid maturation and that neutropenia is observed in XLA. It is conceivable that Btk is only one of the signaling molecules; (4) B-cell linker adaptor protein (BLNK); (5) the surrogate light chain, λ5/14.1; (6) leucine-rich repeat-containing 8 (LRRC8); and (7) the p85 subunit of phosphatidylinositol-3 kinase.

The expression of Btk in cells of myeloid lineage is of interest because boys with XLA often have neutropenia at the height of an acute infection. Growth hormone deficiency has also been observed. These observations suggest a primary role for antibody, particularly secretory IgA, in host defense against enteroviruses. Viral infections are usually handled normally with the exception of hepatitis viruses and enteroviruses. Thereafter, they acquire infections with extracellular pyogenic organisms, such as Haemophilus influenzae, Strep-tococcus pneumoniae and Mycoplasma are also particularly problematic. Chronic fungal infections are seen; Pneumocystis jiroveci pneumonia rarely occurs. Viral infections are usually handled normally with the exceptions of hepatitis viruses and enteroviruses. There were several examples of paralysis when live polio vaccine was administered to these patients, and chronic, eventually fatal, central nervous system infections with various echoviruses and coxsackieviruses have occurred in a significant number of them. Echovirus-associated myositis has also been observed. These observations suggest a primary role for antibody, particularly secretory IgA, in host defense against enteroviruses. Growth hormone deficiency has also been reported in association with XLA. Neutropenia, responsive to G-CSF, may be present in patients with XLA.

Clinical Manifestations

Most boys afflicted with XLA remain well during the 1st 6-9 mo of life by virtue of maternally transmitted IgG antibodies. Thereafter, they acquire infections with extracellular pyogenic organisms, such as Streptococcus pneumoniae and Haemophilus influenzae, unless they are given prophylactic antibiotics or immunoglobulin therapy. Infections include sinusitis, otitis media, pneumonia, or, less often, sepsis or meningitis. Infections with Mycoplasma are also particularly problematic. Chronic fungal infections are seen; Pneumocystis jiroveci pneumonia rarely occurs. Viral infections are usually handled normally with the exceptions of hepatitis viruses and enteroviruses. There were several examples of paralysis when live polio vaccine was administered to these patients, and chronic, eventually fatal, central nervous system infections with various echoviruses and coxsackieviruses have occurred in a significant number of them. Echovirus-associated myositis has also been observed. These observations suggest a primary role for antibody, particularly secretory IgA, in host defense against enteroviruses. Growth hormone deficiency has also been reported in association with XLA. Neutropenia, responsive to G-CSF, may be present in patients with XLA.

Diagnosis

The diagnosis of XLA should be suspected if lymphoid hypoplasia is found on physical examination (minimal or no tonsillar tissue and no

| Table 124-1 Genetic Basis of Primary Antibody Deficiency Disorders |
|------------------------|-------------------|-----------------|-----------------------------|
| CHROMOSOME AND REGION  | GENE PRODUCT      | DISORDER        | FUNCTIONAL DEFICIENCIES     |
| 1q32                   | CD21              | CVID            | Low IgG, low binding of EBV-gp350 |
| 2p11                   | κ Chain           | κ Chain deficiency | Absence of immunoglobulins bearing κ chains |
| 2q33                   | ICOS              | ICOS-deficient CVID | Low or absent concentrations of all immunoglobulins |
| 5q13.1                 | PI3K              | B-cell-negative agammaglobulinemia | Low or absent concentrations of all immunoglobulins |
| 6p21.3                 | Unknown           | Selective IgA deficiency; CVID | Low or absent IgA; low concentrations of all immunoglobulins and of switched memory B cells in CVID |
| 11p15.5                | CD81              | CVID caused by a lack of CD19 | Low IgG concentration and poor response to antigens |
| 11q12                  | CD20              | CVID            | Low IgG concentration and poor response to polysaccharide antigens |
| 12p13                  | AID*              | Autosomal recessive HIGM type 2 | Failure to produce IgG, IgA, and IgE antibodies |
| 12p13                  | CD27              | EBV Lymphoproliferation | Memory B-cell deficiency |
| 12q23-q24.1            | UNG               | Autosomal recessive HIGM type 5 | Failure to produce IgG, IgA, and IgE antibodies |
| 14q32.3                | Immunoglobulin heavy chains* | B-cell-negative agammaglobulinemia; in others, selective isotype deficiencies | Absence of antibody production, lack of B cells, in μ heavy-chain mutations; in others, subclasses missing but B cells present |
| 16p11.2                | CD19              | CD19 deficient CVID | Low or absent concentrations of all immunoglobulins |
| 17p11.2                | TACI*             | TACI-deficient CVID | Low or absent concentrations of all immunoglobulins |
| 20                     | CD40*             | Autosomal recessive HIGM type 3 | Failure to produce IgG, IgA, and IgE antibodies |
| 22q13.1-q13.31         | BAFF-R            | BAFF-R-deficient CVID | Low or absent concentrations of all immunoglobulins |
| Xq22                   | Btk*              | XLA or Bruton agammaglobulinemia | Absence of antibody production, lack of B cells |
| Xq25                   | SLAM-associated protein (SH2D1A)* | XLP | Lack of anti-EBNA and long-lived T-cell immunity; low immunoglobulins |
| Xq26                   | CD154 (CD40 ligand)* | X-linked HIGM type 1 | Failure to produce IgG, IgA, and IgE antibodies |
| Xq28                   | NEMO              | Anhidrotic ectodermal dysplasia with immunodeficiency | Hyper-IgM or -IgG subclass and antipolsaccharide antibody deficiencies |

*The gene has been cloned and sequenced.

AID, Activation-induced cytidine deaminase; BAFF-R, B-cell–activating factor of the tumor necrosis factor family receptor; Btk, Bruton tyrosine kinase; CVID, common variable immunodeficiency; EBNA, Epstein-Barr virus nuclear antigen; EBV, Epstein-Barr virus; HIGM, hyper-IgM syndrome; ICOS, inducible costimulatory; NEMO, nuclear factor κB essential modulator; PI3K, phosphatidylinositol 3 kinase; TACI, transmembrane activator, calcium modulator, and cyclophilin ligand interactor; UNG, uracil DNA glycosylase; XLA, X-linked agammaglobulinemia; XLP, X-linked lymphoproliferative disease.
Common variable immunodeficiency (CVID) is a syndrome characterized by hypogammaglobulinemia with phenotypically normal B cells. It has also been called acquired hypogammaglobulinemia because of a generally later age of onset of infections. CVID patients may appear similar clinically to those with XLA in the types of infections experienced and bacterial etiologic agents involved, except that echovirus meningoencephalitis is rare in patients with CVID (see Table 124-3). In contrast to XLA, the sex distribution in CVID is almost equal, the age at onset is later (although it may be present in infancy), and infections may be less severe.

Genetics and Pathogenesis

Most patients have no identified molecular diagnosis. CVID is a category of primary immunodeficiency disorders that likely consists of several different genetic defects with autosomal recessive or dominant inheritance. Genes known to produce the CVID phenotype when mutated include ICOS (inducible costimulator) deficiency, SH2D1A (responsible for X-linked lymphoproliferative disease [XLP]), CD19, CD20, CD21, CD81, BAFF-R (B-cell–activating factor of the tumor necrosis factor family receptors), TACI (transmembrane activator, calcium modulator, and cyclophilin ligand interactor), and 2 genes that encode DNA methyl transferase (DNMT3B and ZBTB24). These mutations in aggregate account for less than 10% of all cases of CVID.

Because CVID occurs in 1st-degree relatives of patients with selective IgA deficiency, and some patients with IgA deficiency later become panhypogammaglobulinemic, a large subtype of CVID may have a common genetic basis with IgA deficiency. The high incidence of abnormal immunoglobulin concentrations, autoantibodies, autoimmune disease, and malignancy in both CVID and IgA deficiency and in other members of those patients’ families also suggests a shared hereditary influence. This concept is supported by the discovery of a high incidence of C4-A gene deletions and C2 rare gene alleles in the class III major histocompatibility complex (MHC) region in individuals with either IgA deficiency or CVID, suggesting that a common susceptibility gene is on chromosome 6. Only a few human leukocyte antigen (HLA) haplotypes are shared by individuals affected with IgA deficiency and CVID, with at least 1 of 2 particular haplotypes being present in 77% of those affected. In 1 large family with 13 members, 2 had IgA deficiency and 3 had CVID. All of the immunodeficient patients in the family had at least 1 copy of an MHC haplotype that is abnormal in chromosome 6p21 in the proximal part of the MHC was observed in a susceptibility locus now designated as ICADI. More sensitive genetic analysis in 101 multiple-case and 110 single-case families further localized the defect to the HLADQ/DR locus. Environmental factors, particularly drugs such as phenytoin, d-penicillamine, gold, and sulfasalazine are suspected to be triggers for disease expression in individuals with the permissive genetic background.

Most cases of CVID are sporadic or follow an autosomal dominant pattern of inheritance. Patients who lack ICOS, a surface protein on palpable lymph nodes, and serum concentrations of IgG, IgA, IgM, and IgE are far below the 95% confidence limits for appropriate age- and race-matched controls usually with total immunoglobulins <100 mg/dL. Levels of natural antibodies to type A and B red blood cell polysaccharide antigens (isohemagglutinins) and antibodies to antigens given during routine immunizations are abnormally low in this disorder, whereas they are normal in transient hypogammaglobulinemia of infancy. Flow cytometry is an important test to demonstrate the absence of circulating B cells, which will distinguish this disorder from common variable immunodeficiency, the hyper-IgM syndrome and transient hypogammaglobulinemia of infancy.

**COMMON VARIABLE IMMUNODEFICIENCY**

Common variable immunodeficiency (CVID) is a syndrome characterized by hypogammaglobulinemia with phenotypically normal B cells. It has also been called acquired hypogammaglobulinemia because of a generally later age of onset of infections. CVID patients may appear similar clinically to those with XLA in the types of infections experienced and bacterial etiologic agents involved, except that echovirus meningoencephalitis is rare in patients with CVID (see Table 124-3). In contrast to XLA, the sex distribution in CVID is almost equal, the age at onset is later (although it may be present in infancy), and infections may be less severe.

**Genetics and Pathogenesis**

Most patients have no identified molecular diagnosis. CVID is a category of primary immunodeficiency disorders that likely consists of several different genetic defects with autosomal recessive or dominant inheritance. Genes known to produce the CVID phenotype when mutated include ICOS (inducible costimulator) deficiency, SH2D1A (responsible for X-linked lymphoproliferative disease [XLP]), CD19, CD20, CD21, CD81, BAFF-R (B-cell–activating factor of the tumor necrosis factor family receptors), TACI (transmembrane activator, calcium modulator, and cyclophilin ligand interactor), and 2 genes that encode DNA methyl transferase (DNMT3B and ZBTB24). These mutations in aggregate account for less than 10% of all cases of CVID.

Because CVID occurs in 1st-degree relatives of patients with selective IgA deficiency, and some patients with IgA deficiency later become panhypogammaglobulinemic, a large subtype of CVID may have a common genetic basis with IgA deficiency. The high incidence of abnormal immunoglobulin concentrations, autoantibodies, autoimmune disease, and malignancy in both CVID and IgA deficiency and in other members of those patients’ families also suggests a shared hereditary influence. This concept is supported by the discovery of a high incidence of C4-A gene deletions and C2 rare gene alleles in the class III major histocompatibility complex (MHC) region in individuals with either IgA deficiency or CVID, suggesting that a common susceptibility gene is on chromosome 6. Only a few human leukocyte antigen (HLA) haplotypes are shared by individuals affected with IgA deficiency and CVID, with at least 1 of 2 particular haplotypes being present in 77% of those affected. In 1 large family with 13 members, 2 had IgA deficiency and 3 had CVID. All of the immunodeficient patients in the family had at least 1 copy of an MHC haplotype that is abnormal in chromosome 6p21 in the proximal part of the MHC was observed in a susceptibility locus now designated as ICADI. More sensitive genetic analysis in 101 multiple-case and 110 single-case families further localized the defect to the HLADQ/DR locus. Environmental factors, particularly drugs such as phenytoin, d-penicillamine, gold, and sulfasalazine are suspected to be triggers for disease expression in individuals with the permissive genetic background.

Most cases of CVID are sporadic or follow an autosomal dominant pattern of inheritance. Patients who lack ICOS, a surface protein on
activated T cells, have an autosomal recessive pattern of inheritance. Nine such patients from 6 families in the Black Forest of Germany have been found to have identical homozygous large genomic deletions of ICOS, suggesting a founder effect. Those who have XLP have an X-linked pattern of inheritance and those with autosomally inherited TACI defects may have heterozygous or homozygous mutations.

Despite normal numbers of circulating immunoglobulin-bearing B lymphocytes and the presence of lymphoid cortical follicles, blood B lymphocytes from CVID patients do not differentiate normally into immunoglobulin-producing cells when stimulated with pokeweed mitogen in vitro, even when cocultured with normal T cells. They also have a deficiency of switched memory B cells. B cells from some CVID and some IgA-deficient patients can be stimulated both to switch isotype and to synthesize and secrete some immunoglobulin when stimulated with anti-CD40 and interleukin (IL)–4 or IL–10. T cells and T-cell subsets are usually present in normal percentages, although T-cell function is depressed in some patients.

**Clinical Manifestations**

The serum immunoglobulin and antibody deficiencies in CVID may be as profound as in XLA. Patients with CVID often have autoantibody formation and normal-sized or enlarged tonsils and lymph nodes; ≈25% of patients have splenomegaly. CVID has also been associated with a sprue-like enteropathy with or without nodular follicular lymphoid hyperplasia of the intestine, thymoma, alopecia areata, hemolytic anemia, gastric atrophy, achlorhydria, thrombocytopenia, and pernicious anemia. Lymphoid interstitial pneumonia, intestinal lung disease, pseudolymphoma, B-cell lymphomas, amyloidosis, and noncaseating sarcoid-like granulomas of the lungs, spleen, skin, and liver also occur. There is a 438-fold increase in lymphomas among affected women in the 5th and 6th decades of life. CVID has been reported to resolve transiently or permanently in patients who acquire HIV infection.

Recurrent or chronic infections include pneumonia, sinusitis, otitis media, and diarrhea (bacterial, giardiasis). Repeated pulmonary infections may produce bronchiectasis. Sepsis and meningitis with encapsulated bacteria occur more frequently than in the general population. There is often a delay in the diagnosis of more than 5 yr between the first infections and a definitive diagnosis.

**SELECTIVE IgA DEFICIENCY**

An isolated absence or near absence (<10 mg/dL) of serum and secretory IgA is the most common well-defined immunodeficiency disorder, with a disease frequency as high as 0.33% in some populations. This condition can also be and often is associated with ill health.

The basic defect resulting in IgA deficiency is unknown. Phenotypically normal blood B cells are present. IgA deficiency occasionally remits spontaneously or after discontinuation of phenytoin therapy. The occurrence of IgA deficiency in both males and females and in members of successive generations within families suggests autosomal dominant inheritance with variable expressivity. This defect also occurs commonly in pedigrees containing individuals with CVID. Indeed, IgA deficiency may evolve into CVID, and the finding of rare alleles and deletions of MHC class III genes in both conditions suggests that the susceptibility gene common to these 2 conditions may reside in the MHC region on chromosome 6. IgA deficiency is noted in patients treated with the same drugs associated with producing CVID (phenytoin, D–penicillamine, gold, and sulfasalazine), suggesting that environmental factors may trigger this disease in a genetically susceptible person.

**Clinical Manifestations**

Infections occur predominantly in the respiratory, gastrointestinal, and urogenital tracts. Bacterial agents responsible are the same as in other antibody deficiency syndromes. Intestinal giardiasis is common. Children with IgA deficiency vaccinated intranasally with killed poliovirus produced local IgM and IgG antibodies. Serum concentrations of other immunoglobulins are usually normal in patients with selective IgA deficiency, although IgG2 (and other) subclass deficiency has been reported, and IgM (usually elevated) may be monomorphic.

Patients with IgA deficiency often have IgG antibodies against cow’s milk and ruminant serum proteins. These antiruminant antibodies may cause false-positive results in immunoassays for IgA that use goat (but not rabbit) antiserum. IgA deficiency is associated with a celiac-like syndrome, which may or may not respond to a gluten-free diet. The incidence of autoantibodies, autoimmune diseases, and malignancy is increased. Serum antibodies to IgA are reported in as many as 44% of patients with selective IgA deficiency. If these antibodies are of the IgE isotype, they can cause severe or fatal anaphylactic reactions after intravenous administration of blood products containing IgA. Only 5-times washed (in 200-mL volumes) normal donor erythrocytes (frozen blood would have this done routinely), or blood products from other IgA-deficient individuals, should be administered to patients with IgA deficiency. Many intravenous immunoglobulin (IVIG) preparations contain sufficient IgA to cause anaphylactic reactions. Administration of IVIG, which is >99% IgG, is not indicated because most IgA-deficient patients make IgG antibodies normally.

**IgG SUBCLASS DEFICIENCIES**

Some patients have deficiencies of 1 or more of the 4 subclasses of IgG despite normal or elevated total IgG serum concentration. Some
patients with absent or very low concentrations of IgG2 also have IgA deficiency. Other patients with IgG subclass deficiency have gone on to develop CVID, suggesting that the presence of IgG subclass deficiency may be a marker for more generalized immune dysfunction. The biologic significance of the numerous moderate deficiencies of IgG subclasses that have been reported is difficult to assess, particularly because commercial laboratory measurement of IgG subclasses is problematic. IgG subclass measurement is not cost-effective in evaluating immune function in the child with recurrent infection. The more relevant issue is a patient's capacity to make specific antibodies to protein and polysaccharide antigens, because profound deficiencies of antipolysaccharide antibodies have been noted even in the presence of normal concentrations of IgG. IVIG should not be administered to patients with IgG subclass deficiency unless they are shown to have a deficiency of antibodies to a broad array of antigens.

### IMMUNOGLOBULIN HEAVY- AND LIGHT-CHAIN DELETIONS

Some completely asymptomatic individuals have been documented to have a total absence of IgG, IgG2, IgG3, and/or IgA, as a result of gene deletions. These abnormalities were discovered fortuitously in 16 individuals, 15 of whom had no history of undue susceptibility to infection, and all of whom produced antibodies of all other isotypes in normal quantities. These patients illustrate the importance of assessing specific antibody formation before deciding to initiate IVIG therapy in IgG subclass-deficient patients.

### HYPER-IgM SYNDROME

The hyper-IgM syndrome is genetically heterogeneous and characterized by normal or elevated serum IgM levels associated with low or absent IgG, IgA, and IgE serum levels, indicating a defect in the class-switch recombination (CSR) process. Causative mutations have been identified in 2 genes on the X chromosome, the CD40 ligand (hyper-IgM syndrome type 1 [HIGM1]) and NEMO (nuclear factor κB essential modulator, XHM-ED) genes; and 3 genes on autosomal chromosomes, the activation-induced cytokine deaminase (AID) gene (hyper-IgM type 2 [HIGM2]) on chromosome 12, the uracil DNA glycosylase gene (UNG, hyper-IgM type 5 [HIGM5]), on chromosome 20. Distinctive clinical features permit presumptive recognition of the type of mutation in these patients, thereby aiding proper choice of therapy. All such patients should undergo molecular analysis to ascertain the affected gene for purposes of genetic counseling, carrier detection, and decisions regarding definitive therapy.

### X-Linked Hyper-IgM Caused By Mutations in the CD40 Ligand: Hyper-IgM Type 1

HIGM1 is caused by mutations in the gene that encodes the CD40 ligand (CD154, CD40L), which is expressed on activated T-helper cells. Boys with this syndrome have very low serum concentrations of IgG and IgA, with a usually normal or sometimes elevated concentration of polyclonal IgM, may or may not have small tonsils, usually have no palpable lymph nodes, and often have profound neutropenia.

### Genetics and Pathogenesis

B cells from boys with the CD40 ligand defect are capable of synthesizing not only IgM but also IgA and IgG when cocultured with normal activated T-helper cells, indicating that the B cells are actually normal in this condition and that the defect is in the T cells. The abnormal gene is localized to Xq26, and the gene product, CD154 (CD40L), is the ligand for CD40, which is present on B cells and monocytes. CD154 is upregulated on activated T cells. Mutations in CD154 result in an inability to signal B cells to undergo isotype switching, and thus the B cells produce only IgM. The failure of T cells to interact with B cells through this receptor–ligand pair also causes a failure of upregulation of the B cell and monocyte surface molecules CD80 and CD86 that interact with CD28/CTLA4 on T cells, resulting in failure of “crosstalk” between immune system cells. The failure of interaction of the molecules of those pathways results in a propensity for tolerogenic T-cell signaling and defective recognition of tumor cells.

#### Table 124-3 The Main Phenotypes of Primary Antibody Deficiencies

<table>
<thead>
<tr>
<th>PHENOTYPE</th>
<th>MAIN CLINICAL FEATURES</th>
<th>MAIN B-CELL BIOLOGIC FEATURES</th>
<th>KNOWN AFFECTED PROTEINS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pan-agammaglobulinemia (absence of IgM, IgG, and IgA)</td>
<td>Bacterial infections (in the respiratory tract) and enterovirus infections</td>
<td>Absence of CD19* B cells</td>
<td>A5, BLNK, Btk, C4, Igα, Igβ, and PI3K</td>
</tr>
<tr>
<td>Variable pan-hypogammaglobulinemia (CVID)</td>
<td></td>
<td>Decreased frequency of CD27* memory B cells: defective plasma cells in tissues</td>
<td>CD19, CD20, CD21, CD27, CD81, DNMT3B, ZBTB24, ICOS, SAP, TACI, and BAFF-R</td>
</tr>
<tr>
<td>CSR deficiencies (absence or decrease in levels of IgG and IgA)</td>
<td></td>
<td>Normal frequency of CD27* memory B cells</td>
<td>CD40 and CD40L</td>
</tr>
<tr>
<td>Selective IgA deficiency</td>
<td></td>
<td></td>
<td>AID and UNG</td>
</tr>
<tr>
<td>Selective IgM deficiency</td>
<td></td>
<td>No IgM antibody production (absence of allohemagglutinins and polysaccharide-specific antibodies)</td>
<td>ND</td>
</tr>
<tr>
<td>Selective IgG2 and/or IgG4 deficiency</td>
<td></td>
<td>Defective polysaccharide-specific antibody production</td>
<td>ND</td>
</tr>
<tr>
<td>Selective polysaccharide antibody deficiency</td>
<td></td>
<td>Normal IgG (including IgG2 and IgG4) levels</td>
<td>NF-κB pathway proteins (CARD11, HIOL1 and NEMO), Btk, and CD20</td>
</tr>
</tbody>
</table>

**AID, Activation-induced cytidine deaminase; BAFF-R, B-cell-activating factor of the tumor necrosis factor family receptor; BLNK, B-cell linker; Btk, Bruton tyrosine kinase; C4, constant region γ; CD40L, CD40 ligand; CSR, class-switch recombination; CVID, common variable immunodeficiency; ICOS, inducible costimulator; ND, not determined; NEMO, nuclear factor kappa B essential modulator; NF-κB, nuclear factor kappa B; PI3K, phosphatidylinositol 3-kinase; TACI, transmembrane activator, calcium modulator, and cyclophilin ligand interactor; UNG, uracil DNA glycosylase.**

distinct point mutations or deletions in the gene encoding CD154 have been identified in 87 unrelated families, giving rise to frame shifts, premature stop codons, and single amino acid substitutions, most of which are clustered in the domain with homology to tumor necrosis factor (TNF), located in the carboxyterminal region.

**Clinical Manifestations**

Similar to patients with XLA, boys with the CD40 ligand defect become symptomatic during the 1st or 2nd yr of life with recurrent pyogenic infections, including otitis media, sinusitis, pneumonia, and tonsillitis. They have marked susceptibility to *P. jiroveci* pneumonia, and are frequently profoundly neutropenic. Lymph node histology shows only abortive germinal center formation with severe depletion and phenotypic abnormalities of follicular dendritic cells. These patients have normal numbers of circulating B lymphocytes, but a decreased frequency of CD27+ memory B cells. Circulating T cells are also present in normal number and in vitro responses to mitogens are normal, but there is decreased antigen-specific T-cell function. In a study of patients with the CD40 ligand defect, 23.3% had died at a mean age of death of 11.7 yr. In addition to opportunistic infections such as *P. jiroveci* pneumonia, there is an increased incidence of extensive verruca vulgaris lesions, *Cryptosporidium* enteritis, subsequent liver disease, and an increased risk of malignancy. Because of the poor prognosis, the treatment of choice is an HLA-identical hematopoietic stem cell transplant at an early age. Alternative treatment for this condition is monthly infusion of IVIG. In patients with severe neutropenia, the use of granulocyte colony-stimulating factor has been beneficial.

**X-Linked Hyper-IgM Caused By Mutations in the Gene Encoding Nuclear Factor κB Essential Modulator; XHM-ED**

This syndrome in males is characterized most often clinically as anhydrotic ectodermal dysplasia with associated immunodeficiency (EDA-ID). The condition results from missense mutations in the IKKBG gene at position 28q on the X chromosome that encodes NEMO, a regulatory protein required for the activation of the transcription factor NF-κB. Germ line loss-of-function mutations cause the X-linked dominant condition incontinentia pigmenti in females and are lethal in male fetuses. Mutations in the coding region of IKKBG are associated with EDA-ID. The immunodeficiency is variable, with most patients showing impaired antibody responses to polysaccharide antigens. Some patients with EDA-ID have hyper-IgM. Pharmacologic inhibitors of NF-κB activation have been shown to downregulate CD154 messenger RNA and protein levels, suggesting the mechanism of hyper-IgM in this condition. The hyper-IgM patients with this defect should be easily recognizable because of the presence of ectodermal dysplasia, although there are some patients with this condition who do not have ectodermal dysplasia.

**Autosomal Recessive Hyper-IgM Caused By Mutations in the Gene for Activation-Induced Cytidine Deaminase: Hyper-IgM Type 2**

An autosomal recessive form of hyper-IgM syndrome is caused by mutations in the gene for AID.

**Genetics and Pathogenesis**

Patients with autosomal recessive hyper-IgM usually have normal numbers of circulating B lymphocytes, but, in contrast to patients with the CD40 ligand defect, B cells from these patients are not able to switch from IgM-secreting to IgG-, IgA-, or IgE-secreting cells, even when cocultured with normal T cells or with monoclonal antibodies to CD40 and a variety of cytokines. When their B cells are cultured in vitro, they spontaneously secrete large amounts of IgM, but this is not further augmented by the addition of cytokines. Thus, in these patients, there is truly an intrinsic B-cell abnormality. The defect in many such patients has been identified as due to mutations in a gene on chromosome 12p13 that encodes AID. AID is a single-stranded DNA deaminase required for somatic hypermutation (SHM) and class-switch recombination (CSR) of immunoglobulin genes. Histologic examination of the enlarged lymph nodes reveals the presence of giant germinal centers (5-10 times larger than normal) filled with highly proliferating B cells. Proliferating B cells coexpress IgM, IgD, and CD38, a phenotype previously described for a small B-cell subset corresponding to germinal center founder cells. These cells are thought to correspond to a transitional stage between follicular mantle and germinal center B cells, at the onset of somatic mutation of the Ig variable region gene and antigen-driven selection. Deficiency of AID results in impaired terminal differentiation of B cells, a failure of CSR, and lack of immunoglobulin gene SHM. They have a normal frequency of CD27+ memory B cells.

**Clinical Manifestations**

Concentrations of serum IgG, IgA, and IgE are very low in AID deficiency. In contrast to the CD40 ligand defect, however, the serum IgM concentration in patients with AID deficiency is usually markedly elevated and polyclonal. Patients with this form of hyper-IgM have lymphoid hyperplasia, are generally older at age at onset, do not have susceptibility to *P. jiroveci* pneumonia, often do have isohemagglutinins, and are much less likely to have neutropenia unless it occurs on an autoimmune basis. They have a tendency, however, to develop autoimmune and inflammatory disorders including diabetes mellitus, polyarthritis, autoimmune hepatitis, hemolytic anemia, immune thrombocytopenia, Crohn disease, and chronic uveitis. With early diagnosis and monthly infusions of IVIG, as well as good management of infections with antibiotics, patients with AID mutations generally have a more benign course than do boys with the CD40 ligand defect.

**Autosomal Recessive Hyper-IgM Caused By Mutations in the Gene for Uracil DNA Glycosylase; Hyper-IgM Type 5**

**Genetics and Pathogenesis**

AID deaminates cytosine into uracil in targeted DNA, which is followed by uracil removal by UNG. Severely impaired CSR was found in 3 hyper-IgM patients reported to have UNG deficiency. Their clinical characteristics were similar to those with AID deficiency, with increased susceptibility to bacterial infections and lymphoid hyperplasia. The patients had a markedly elevated serum IgM and profoundly decreased serum IgG and IgA concentrations. Their B cells had an intrinsic defect in CSR when stimulated with anti-CD40 and IL-4 and constitutively produced high quantities of IgM. They had only a partial defect in SHM, however, and they have a normal frequency of CD27+ memory B cells.

**Autosomal Recessive Hyper-IgM Caused By Mutations in CD40: Hyper-IgM Type 3**

Five patients with autosomal recessive hyper-IgM from 4 unrelated families failed to express CD40 on their B-cell surfaces and were found to have mutations in the CD40 gene. Clinical manifestations included recurrent sinopulmonary infections, *P. jiroveci* pneumonia and *Cryptosporidium parvum* infections. The patients had very low levels of IgG and IgA and normal or high levels of IgM. More recently, 2 patients were identified with such mutations who did express the CD40 protein on their B cells and monocytes, so mutation analysis was required to make the diagnosis.

**Genetics and Pathogenesis**

CD40 is a type 1 integral membrane glycoprotein encoded by a gene on chromosome 20 and belonging to the TNF and nerve growth factor receptor superfamily. It is expressed on B cells, macrophages, dendritic cells, and a few other types of cells. Mutations in the CD40 gene cause an autosomal recessive form of hyper-IgM syndrome that is clinically indistinguishable from HIGM1, resulting from the X-linked CD40 ligand (CD154) defect. In contrast to the CD40 ligand defect, however, the B cells in the autosomal recessive condition are intrinsically abnormal and cannot isotype switch. The T cells are normal except to the extent that they cannot cause upregulation of CD80 and CD86 on B cells and macrophages to interact with CD28/CTLA4 on T cells.
Hyper-IgM Type 4

The defective gene in a 4th autosomal recessive form of hyper-IgM syndrome has not yet been identified, but appears to be in a gene downstream of AID. These patients all have defective CSR with preserved SHM.

X-LINKED LYMPHOPROLIFERATIVE DISEASE

XLP disease, also referred to as Duncan disease after the original kindred in which it was described, is an X-linked recessive trait characterized by an inadequate immune response to infection with Epstein-Barr virus (EBV).

Genetics and Pathogenesis

The defective gene in XLP was localized to Xq25, cloned, and the gene product was initially named SAP (for SLAM-associated protein), but is now known officially as SH2D1A. SLAM (signaling lymphocyte activation molecule) is an adhesion molecule that is upregulated on both T and B cells with infection and other stimulation. SH2D1A is highly expressed in thymocytes and peripheral blood T and NK cells, with a prevalent expression on T-helper type 1 cells. Its presence on B lymphocytes is unclear. Thus, although antibody deficiency is frequently present, this is really a T- and natural killer (NK)-cell defect. SH2D1A competes with SHP-2 for binding to SLAM and, as such, is a regulatory molecule. In XLP patients, the absence of SH2D1A can lead to an uncontrolled cytotoxic T-cell immune response to EBV. The SH2D1A protein associates permissively with 2B4 on NK cells; thus, selective impairment of 2B4-mediated NK-cell activation also contributes to the immunopathology of XLP. All XLP type 2 is less common and is caused by a mutation in XIAP (X-linked inhibitor of apoptosis protein); disease manifestations are similar to XLP. X-linked immunodeficiency with magnesium defect (XMEN syndrome) is due to a loss of function mutation of the magnesium transporter protein and manifests with chronic EBV infection, EBV lymphoproliferative disorders, and CD4 lymphopenia.

Clinical Manifestations

Affected males are usually healthy until they acquire EBV infection. The mean age of presentation is <5 yr. There are 3 major clinical phenotypes: (1) fulminant, often fatal, infectious mononucleosis (50% of cases); (2) lymphomas, predominantly involving B-lineage cells (25%); and (3) acquired hypogammaglobulinemia (25%). There is a marked impairment in production of antibodies to the EBV nuclear antigen, whereas titers of antibodies to the viral capsid antigen have ranged from absent to markedly elevated. XLP has an unfavorable prognosis; 70% of affected boys die by age 10 yr. Only 2 XLP patients are known to have survived beyond 40 yr of age. Unless there is a family history of XLP, diagnosis prior to the onset of complications is difficult because affected individuals are asymptomatic initially. Using mutation analysis, it is possible to identify affected males within identified kindreds before they develop primary EBV infection. Approximately half of the few patients with XLP given HLA-identical related or unrelated stem cell transplants are surviving without signs of the disease.

Two pedigrees have been reported in which boys in one arm of each pedigree were diagnosed with CVID, whereas those in the other arms had fulminant infectious mononucleosis. The family members with CVID never gave a history of infectious mononucleosis. All affected members of each pedigree had the same distinct SH2D1A mutation, however, despite the different clinical phenotypes. Because the SH2D1A mutation was the same but the phenotype varied in these families, XLP should be considered in all males with a diagnosis of CVID, particularly if there is more than one male family member with this phenotype.

CD27 Deficiency

CD27 deficiency, an autosomal recessive condition, was found to be associated with EBV lymphoproliferation, EBV lymphoma and hypogammaglobulinemia. CD27 is commonly used as marker of memory B cells for the classification of B-cell deficiencies including common variable immune deficiency. It is a member of the TNF receptor family and interacts with CD70 to influence T-, B-, and NK-cell functions. Disturbance of this axis impairs immunity and memory generation against viruses including EBV, influenza, and others.

Bibliography is available at Expert Consult.

124.1 Treatment of B-Cell Defects

Rebecca H. Buckley

Except for the CD40 ligand defect and XLP, for which stem cell transplantation is recommended, judicious use of antibiotics to treat documented infections and regular administration of IVIG are the only effective treatments for primary B-cell disorders. The most common forms of replacement therapy are either intravenous or subcutaneous immunoglobulin (IVIG or SCIG). Broad antibody deficiency should be carefully documented before such therapy is initiated. The rationale for the use of IVIG or SCIG is to provide missing antibodies, not to raise the serum IgG or IgG subclass level. The development of safe and effective immunoglobulin preparations is a major advance in the treatment of patients with severe antibody deficiencies, although it is expensive and there have been national shortages. Almost all commercial preparations are isolated from normal plasma by the Cohn alcohol fractionation method or a modification of it. Cohn fraction II is then further treated to remove aggregated IgG. Additional stabilizing agents such as sugars, glycine, and albumin are added to prevent reaggregation and protect the IgG molecule during lyophilization. The ethanol used in preparation of immunoglobulin inactivates HIV; an organic solvent/detergent step inactivates hepatitis B and C viruses. Some preparations are also nanofiltered to remove infectious agents. Most commercial lots are produced from plasma pooled from 10,000 to 60,000 donors and therefore contain a broad spectrum of antibodies. Each pool must contain adequate levels of antibody to antigens in various vaccines, such as tetanus and measles. However, there is no standardization based on titers of antibodies to more clinically relevant organisms, such as S. pneumoniae and H. influenzae type b.

The IVIG and SCIG preparations available in the United States have similar efficacy and safety. Rare transmission of hepatitis C virus has occurred in the past, but the potential transmission of hepatitis C virus has been resolved by additional treatment with an organic solvent/detergent mixture. There has been no documented transmission of HIV by any of these preparations. IVIG or SCIG at a dose of 400 mg/kg per month achieves trough IgG levels close to the normal range. Higher doses are indicated in patients with chronic or severe respiratory infections. Systemic reactions may occur, but rarely are these true anaphylactic reactions. Anaphylactic reactions caused by a patient's IgE antibodies to IgA in the IVIG or SCIG preparation may occur in patients with CVID or IgA deficiency. Newly diagnosed patients with CVID should be screened through the American Red Cross for anti-IgA antibodies. If anti-IgA antibodies are detected, IVIG therapy should consist of the one available immunoglobulin preparation containing almost no IgA (Gammagard S/D, Baxter).

Bibliography is available at Expert Consult.
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In general, patients with defects in T-cell function have infections or other clinical problems that are more severe than in patients with antibody deficiency disorders (see Table 122-4). The defective gene products for some primary T-cell diseases are identified (Table 125-1). These individuals rarely survive beyond infancy or childhood. Transplantation of thymic tissue, or of major histocompatibility complex–compatible sibling or haploidalidentical (half-matched) parental hematopoietic stem cells, is the treatment of choice for patients with primary T-cell defects (see Chapter 135).

**THYMIC HYPOPLASIA (DIGEORGE SYNDROME)**

Thymic hypoplasia results from dysmorphogenesis of the 3rd and 4th pharyngeal pouches during early embryogenesis, leading to hypoplasia or aplasia of the thymus and parathyroid glands. Other structures forming at the same age are also frequently affected, resulting in anomalies of the great vessels (right-sided aortic arch), esophageal atresia, bifid uvula, congenital heart disease (conotruncal, atrial, and ventricular septal defects), a short philtrum of the upper lip, hypertelorism, an antimongoloid slant to the eyes, mandibular hypoplasia, and low-set, often notched ears (see Chapters 81 and 108). The diagnosis is often first suggested by hypocalcemic seizures during the neonatal period.

**Table 125-1 Genetic Basis of Primary Cellular Immunodeficiency Diseases**

<table>
<thead>
<tr>
<th>CHROMOSOME AND REGION</th>
<th>GENE PRODUCT</th>
<th>DISORDER</th>
<th>FUNCTIONAL DEFICIENCIES</th>
</tr>
</thead>
<tbody>
<tr>
<td>1p35-p34.3</td>
<td>Lck</td>
<td>↓↓ CD4 CD8</td>
<td>Lack of T-cell responses to mitogens or to anti-CD3</td>
</tr>
<tr>
<td>2p12</td>
<td>CD8α</td>
<td>↓↓ CD8 deficiency</td>
<td>Lack of cytotoxic T cells</td>
</tr>
<tr>
<td>2q12</td>
<td>ZAP-70</td>
<td>CD8 deficiency</td>
<td>Failure of CD4 T cells to respond to usual signals</td>
</tr>
<tr>
<td>4p13</td>
<td>RhoH</td>
<td>↓ Naive CD4+ cells</td>
<td>Low number of recent thymic emigrants, restricted T-cell repertoire</td>
</tr>
<tr>
<td>5q31-34</td>
<td>ITK</td>
<td>↓ Naive CD4+ cells Absence of NKT cells</td>
<td>Poor T-cell responses to mitogens, antigens, and anti-CD3</td>
</tr>
<tr>
<td>10p13</td>
<td>Unknown</td>
<td>Thymic hypoplasia (DiGeorge syndrome, velocardiofacial syndrome)</td>
<td>Low number of T cells and impaired T-cell function</td>
</tr>
<tr>
<td>11q23</td>
<td>CD3γ and ε</td>
<td>CD3 deficiency</td>
<td>Poor T-cell responses to mitogens; lack of cytotoxic T cells; IgG subclass deficiency</td>
</tr>
<tr>
<td>14q11.2</td>
<td>TRAC</td>
<td>TCR αβ T-cell deficiency</td>
<td>Poor T-cell responses to mitogens</td>
</tr>
<tr>
<td>16p11.2</td>
<td>Coronin-1A</td>
<td>↓↓ CD4 ↓↓ CD8</td>
<td>Poor T-cell response to phytohemagglutinin; impaired antibody responses</td>
</tr>
<tr>
<td>20q13.12</td>
<td>MST1/STK4</td>
<td>↓ Naive T cells</td>
<td>Low number of recent thymic emigrants, restricted T-cell repertoire</td>
</tr>
<tr>
<td>21q22.3</td>
<td>AIRE</td>
<td>APECED, chronic mucocutaneous candidiasis, parathyroid and adrenal autoimmunity</td>
<td>Poor response to Candida antigen; autoimmune responses</td>
</tr>
<tr>
<td>22q11.22</td>
<td>?TBX1</td>
<td>Thymic hypoplasia (DiGeorge syndrome, velocardiofacial syndrome)</td>
<td>Low number of T cells and impaired T-cell function</td>
</tr>
</tbody>
</table>

AIRE, Autoimmune regulator; APECED, autoimmune polyendocrinopathy-candidiasis ectodermal dysplasia; Ig, immunoglobulin; ITK, IL-2–inducible tyrosine kinase deficiency; MST1, macrophage-stimulating factor 1; NKT, natural killer T; RhoH, Ras homology family member H; STK4, serine threonine kinase 4; TCR, T-cell receptor; TRAC, T-cell receptor α chain constant region; ZAP-70, zeta-associated protein 70.

**Genetics and Pathogenesis**

DiGeorge syndrome occurs in both males and females. Microdeletions of specific DNA sequences from chromosome 22q11.2, the DiGeorge chromosomal region, are found in a majority of cases. Several candidate genes have been identified in this region. A T-box transcription family member, TBX1, is implicated as an etiology for most of the major signs of DiGeorge syndrome. There appears to be an excess of 22q11.2 deletions of maternal origin. Polymerase chain reaction–based genotyping using microsatellite DNA markers located within the commonly deleted region permits rapid detection of such microdeletions. Conotruncal heart defects and 22q deletions are observed in DiGeorge syndrome, velocardiofacial syndrome, and conotruncal anomaly face syndrome. The CATCH 22 syndrome (cardiac, abnormal facies, thymic hypoplasia, cleft palate, hypocalcemia) includes the broad clinical spectrum of conditions with 22q11.2 deletions. Other deletions associated with DiGeorge and velocardiofacial syndromes have been identified on chromosome 10p13 (see Chapter 81).

Variable hypoplasia of the thymus and parathyroid glands defines partial DiGeorge syndrome, which is more frequent than total aplasia; aplasia is present in <1% of patients with DiGeorge syndrome and defines complete DiGeorge syndrome. Slightly less than half of patients with complete DiGeorge syndrome are hemizygous at chromosome 22q11. Approximately 15% are born to diabetic mothers. Another 15% of infants have no identified risk factors. Approximately one-third of infants with complete DiGeorge syndrome have CHARGE association (coloboma, heart defect, choanal atresia, growth or developmental retardation, genital hypoplasia, and ear anomalies including deafness). Mutations in the chromodomain helicase DNA binding protein 7 (CHD7) gene on chromosome 8q12.2 are found in approximately 60-65% of individuals with CHARGE syndrome. Concentrations of serum immunoglobulins in DiGeorge syndrome are usually normal, but immunoglobulin (Ig) A may be diminished and IgE elevated. Other laboratory findings vary depending on the degree of thymic dysfunction.
Absolute lymphocyte counts are usually only moderately low for age. The CD3 T-cell counts are variably decreased in number, corresponding to the degree of thymic hypoplasia, resulting in an increased percentage of B cells. Lymphocyte responses to mitogen stimulation are absent, reduced, or normal, depending on the degree of thymic deficiency. Thymic tissue, when found, contains Hassall corpuscles, a normal density of thymocytes, and corticomediulary distinction. Lymphoid follicles are usually present, but lymph node paracortical areas and thymus-dependent regions of the spleen show variable degrees of depletion.

Clinical Manifestations
Children with partial thymic hypoplasia may have little trouble with infections and grow normally. Patients with complete DiGeorge syndrome resemble patients with severe combined immunodeficiency in their susceptibility to infections with low-grade or opportunistic pathogens, including fungi, viruses, and Pneumocystis jiroveci, and to graft-versus-host disease from nonirradiated blood transfusions. Patients with complete DiGeorge syndrome can develop an atypical phenotype in which oligoclonal T-cell populations appear in the blood associated with rash and lymphadenopathy. These atypical patients appear phenotypically to be similar to patients with Omenn syndrome or maternal T lymphocyte engraftment.

It is critical to confirm the diagnosis of complete DiGeorge syndrome in a timely manner because this disease is fatal without treatment. A T-cell count should be obtained on all infants born with primary hypoparathyroidism, CHARGE syndrome, truncus arteriosus, or maternal T lymphocyte engraftment. If a patient has findings consistent with DiGeorge syndrome and without a rash and lymphadenopathy, the patient should be referred to an immunologist for evaluation.

Treatment
The immune deficiency in the complete DiGeorge syndrome is correctable by cultured unrelated thymic tissue transplants. Some have been given nonirradiated unfractonated bone marrow or peripheral blood transplants from an human leukocyte antigen–identical sibling with subsequent improved immune function because of adoptively transferred donor immunity; however, they have no way of renewing T-cell production because they have no thymus.

DEFECTIVE EXPRESSION OF THE T-CELL RECEPTOR–CD3 COMPLEX
The first type of this disorder was found in 2 brothers in a Spanish family. The proband presented with severe infections and died at 31 mo of age with autoimmune hemolytic anemia and viral pneumonia. His lymphocytes had responded poorly to mitogens and to anti-CD3 in vitro, and could not be stimulated to develop cytotoxic T cells. His antibody responses to protein antigens had been normal, indicating normal T-helper cell function. His 12 yr old brother was healthy but had almost no CD3-bearing T cells and had IgG2 deficiency similar to his sibling. The defect in this family was caused by mutations in the gene encoding the CD3γ chain (Fig. 125-1).

The second type of this disorder was diagnosed in a 4 yr old French boy who had recurrent Haemophilus influenzae pneumonia and otitis media in early life but was later healthy. He had a partial defect in expression of T-cell receptor–CD3 complex, and thus the percentage of CD3 cells was about half-normal, but the level of expression was markedly decreased. The defect was caused by 2 independent CD3ε gene mutations, leading to defective CD3ε chain synthesis. There was a splice site mutation on one allele that did not totally abrogate the normal intron 7 splicing, resulting in partial expression of CD3 on the T cells. Thus, this mutation did not result in failure of T-cell development, whereas mutations in the portions of the gene that encode the extracellular component of CD3ε result in a profound deficiency of circulating mature CD3 T cells.

Two additional unrelated patients from Pakistan were discovered to lack T-cell receptor (TCR)-αβ-positive T cells and were found to have mutations in the TCR α-chain constant (TRAC) gene. Clinically they

Figure 125-1 Schematic representation of signaling through the T-cell receptor–CD3 complex. Molecules the mutations of which have been associated with partial defect of T-cell development and impaired T-cell function are indicated in red and highlighted in boldface. AP1, Activator protein 1; DHR, DOCK-homology region; Grb2, growth factor receptor-bound protein 2; IKK, IκB kinase; JNK, c-Jun N-terminal kinase; MAPK, mitogen-activated protein kinase; NFAT, nuclear factor of activated T cells; NFκB, nuclear factor κB; PI3K, phosphoinositide-3 kinase; PIP3, phosphatidylinositol (3,4,5)-triphosphate. (From Notarangelo L: Partial defects of T-cell development associated with poor T-cell function. J Allergy Clin Immunol 131:1297–1305, 2013, Fig. 1, p. 1299.)
had increased susceptibility to infections, autoimmunity and profound T cell dysfunction but normal antibody responses. All of their T cells contained TCR gamma delta receptors.

**T-CELL ACTIVATION DEFECTS**

T-cell activation defects are characterized by the presence of normal or elevated numbers of blood T cells that appear phenotypically normal but fail to proliferate or produce cytokines normally in response to stimulation with mitogens, antigens, or other signals delivered to the TCR, owing to defective signal transduction from the TCR to intracellular metabolic pathways (see Fig. 125-1). These patients have problems similar to those of other T-cell-deficient individuals, and some with severe T-cell activation defects may clinically resemble severe combined immunodeficiency patients. At least 8 new forms of T-cell activation defects have been discovered. The description of only a few of these conditions is included here (see Table 125-1) and DOCK8 deficiency is discussed in Chapter 126.

**CD8 LYMPHOCYTOPENIA CAUSED BY MUTATIONS IN THE GENE ENCODING ZETA-ASSOCIATED PROTEIN 70**

Patients with this T-cell activation defect present during infancy with severe, recurrent, and often fatal infections. The majority of cases are reported among Mennonites. These patients have normal or elevated numbers of blood B cells and low to elevated serum immunoglobulin concentrations. Their blood lymphocytes exhibit normal expression of the T-cell surface antigens CD3 and CD4, but CD8 cells are almost totally absent. These cells fail to respond normally to mitogens or to allogeneic cells in vitro or to generate cytotoxic T lymphocytes. Natural killer (NK) cell activity is normal. The thymus of 1 patient exhibited normal architecture with normal numbers of CD4:CD8 double-positive thymocytes, but an absence of CD8 single-positive thymocytes. This condition is caused by mutations in the gene encoding zeta-associated protein 70 (ZAP-70), a non-src family protein tyrosine kinase important in T-cell signaling that is localized to chromosome 2q12 (see Fig. 125-1). The normal number of CD4:CD8 double-positive T cells results because the thymocytes can use the other member of the same tyrosine kinase family, Syk, to facilitate positive selection. Syk is present at 4-fold higher levels in thymocytes than in peripheral T cells, possibly accounting for the lack of normal responses by the CD4 blood T cells.

Another condition that can result in CD8 deficiency is a mutation in the gene that encodes CD8α. There is a deficiency of cytotoxic T cells in that condition, but the functional immune defect is mild compared to that of ZAP-70 deficiency.

**T-Cell Defects Characterized By Epstein-Barr Virus Lymphoproliferation/Lymphoma**

In addition to the X-linked lymphoproliferative and X-linked inhibitor of apoptosis protein syndromes and CD27 deficiency characterized primarily as antibody deficiencies (see Chapter 124), there are at least 4 additional primarily T-cell defects that predispose to Epstein-Barr virus (EBV) infections or lymphomas. These include Ras homology family member H (RhoH) deficiency, macrophage-stimulating 1 (MST1)/serine threonine kinase 4 (STK4) deficiency, interleukin (IL)-2–inducible tyrosine kinase (ITK) deficiency and Coronin-1A deficiency (see Table 125-1).

**RhoH Deficiency**

Two siblings who had a homozygous nonsense mutation in the RhoH gene had persistent cutaneous human papillomavirus infections and the older sibling had Burkitt lymphoma. RhoH plays an important role in T-cell activation. Following stimulation of the TCR, RhoH becomes tyrosine phosphorylated and mediates recruitment of ZAP-70 and LCK to the TCR/linker of activation in T cells (LAT) signalosome (see Fig. 125-1). Immunologic findings in the 2 patients included a reduced number of naive CD4+ T cells and recent thymic emigrants, restricted T-cell diversity and impaired responsiveness of the cells to anti-CD3.

**MST1/STK4 Deficiency**

Autosomal recessive MST1/STK4 deficiency is associated with recurrent bacterial and viral infections, candidiasis and autoimmunity. The viral infections include warts, molluscum contagiosum, and EBV lymphoproliferative disease. Congenital heart disease and moderate neutropenia have also been reported. Immunologically, there is a severe reduction in naïve T cells, a near absence of recent thymic emigrants, oligoclonal T cells and increased apoptosis of T cells. Thus, MST1/STK4 plays a major role in T-cell development, survival, and migration.

**ITK Deficiency**

Several patients with EBV lymphoproliferative disease have been described who had mutations in the ITK gene. In addition, some also had *P. jiroveci* pneumonia, candidiasis, and BK polyoma infection. The immunologic abnormalities described included marked lymphopenia, a predominance of activated T cells, an absence of NK T cells, and poor T-cell responses to mitogens, antigens and anti-CD3. ITK is a Tec nonreceptor tyrosine kinase expressed in T lymphocytes. The ITK pleckstrin homology domain binds to phosphatidylinositol monophosphates and this binding permits ITK recruitment to the T cell membrane where, upon TCR crosslinking, ITK increases phospholipase Cγ (PLCγ) 1 activation and calcium influx.

**Coronin-1a Deficiency**

Three siblings from a consanguineous family presented with EBV-associated B-cell lymphoproliferation at an early age (12, 7, and 14 mo) and profound naive T-cell lymphopenia. In addition, there was impaired development of a diverse T-cell repertoire and near absent invariant NK T cells. They were discovered to have a missense mutation in the gene encoding Coronin-1A that abrogated protein expression. Coronin-1A is a member of a family of proteins that bind F-actin and the Arp2/3 complex; it has an important role in cytoskeletal organization.

**LCK DEFICIENCY**

A female infant presented at age 15 mo with protracted diarrhea, failure to thrive and recurrent respiratory tract infections. She developed recurring fevers, multiple nodular skin lesions and inflammation of the interphalangeal joints as well as retinal vasculitis and polyserositis. At age 29 mo, she developed a normocytic regenerative anemia and peripheral thrombocytopenia with antiplatelet autoantibodies. She died from venoocclusive disease shortly after a chemoablated bone marrow transplant. Immunologic investigation revealed CD4 T lymphopenia and low levels of CD4 and CD8 expression on the T-cell surfaces. The T cells present had an oligoclonal T-cell repertoire and exhibited a prolonged TCR signaling defect. She was found to have a homozygous missense mutation of the LCK gene.

Very closely related to this defect is a deficiency of uncoordinated 119 (UNC119), which is a chaperone involved in LCK-mediated signaling. Through LCK, UNC119 regulates T-cell proliferation, differentiation into T effector cells and immunologic synapse formation. A heterozygous dominant-negative missense mutation of the UNC119 gene was reported in a 32 yr old female with idiopathic CD4 T lymphopenia who had a history of recurrent respiratory infections, shingles, oral herpes infections and persistent fungal infections of the skin and nails. Both LCK deficiency and UNC119 deficiency should be considered when there is idiopathic CD4 T lymphopenia.

**CHRONIC MUCOCUTANEOUS CANDIDIASIS**

Chronic mucocutaneous candidiasis is a syndrome characterized by impaired immune responsiveness to *Candida*. Some of the known immunodeficiencies that have this complication as a prominent feature include autoimmune polyendocrinopathy syndrome type 1 (APS1, or autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy [APTED], described below), homozygous caspase recruitment domain-containing protein 9 (CARD9) mutations, both types of hyperimmunoglobulin E syndromes (see Chapter 126), an autosomal recessive deficiency in the IL-17 receptor A (IL-17RA) chain, and an...
autosomal dominant deficiency of STAT1 and of the cytokine IL-17F. IL-17RA deficiency is complete, abolishing cellular responses to IL-17A and IL-17F homo- and heterodimers. By contrast, IL-17F deficiency is partial, with mutant IL-17F–containing homo- and heterodimers displaying impaired, but not abolished, activity.

Although the underlying immune disorders are varied, the clinical presentation of chronic mucocutaneous candidiasis is usually similar. Symptoms can begin in the 1st mo of life or as late as the 2nd decade of life. The disorder is characterized by chronic and severe Candida skin and mucous membrane infections. Patients rarely develop systemic Candida disease except as noted below. Topical antifungal therapy can provide limited improvement early in the course of the disease, but systemic courses of azoles are usually necessary. The infection usually responds temporarily to treatment but is not eradicated and recurs. Patients with CARD9 gene mutations have a more severe fungal susceptibility than typical chronic mucocutaneous candidiasis patients. Two described patients with CARD9 gene mutations had fungal sepsis in addition to chronic mucocutaneous candidiasis; deep tissue dermatophyte infections were also present.

**AUTOIMMUNE POLYENDOCRINOPATHY-CANDIDIASIS ECTODERMAL DYSPLASIA**

Patients with this syndrome present with chronic mucocutaneous candidiasis and autoimmune polyendocrinopathy, usually producing hypoparathyroidism and Addison disease. Additional features include hypogonadism, chronic active hepatitis, alopecia, vitiligo, pernicious anemia, enamel hypoplasia, type 1 diabetes, and Sjögren syndrome. APECED, or APS1, is caused by a mutation in the autoimmune regulator (AIRE) gene (see Table 125-1). The gene product, AIRE, is expressed at high levels in purified human thymic medullary stromal cells and is thought to regulate the cell surface expression of tissue-specific proteins such as insulin and thyroglobulin. Expression of these self-proteins allows for the negative selection of autoreactive T cells during their development. Failure of negative selection results in organ-specific autoimmune destruction. The overall significance of AIRE in the establishment and maintenance of T-cell self-tolerance is not well understood.

_Bibliography is available at Expert Consult._
Bibliography


Patients with combined antibody and cellular defects have severe, frequently opportunistic infections that lead to death in infancy or childhood unless they are provided hematopoietic stem cell transplantation early in life. These are thought to be rare defects, although the true incidences are unknown because until recently there had been no newborn screening for any of these defects. It is possible that many affected children died of infection during infancy without being diagnosed. The causative mutated genes for many combined immunodeficiencies have been identified (Table 126-1). Because life-threatening infections may occur early in infancy, the U.S. Secretary of Health and Human Services recommends that routine screening for severe combined immunodeficiency (SCID) be included in state newborn screening testing. Live, vaccine-derived rotaviral infections have already occurred during the 1st few mo of life in SCID infants, so very early knowledge of this diagnosis could prevent such vaccine-acquired infections. In addition, early identification and subsequent bone marrow transplantation before infections develop result in a very high (92%) survival rate.

126.1 Severe Combined Immunodeficiency

Rebecca H. Buckley

The syndromes of SCID are caused by diverse genetic mutations that lead to absence of all adaptive immune function and, in some, a lack of B cells and natural killer (NK) cells. Patients with this group of disorders have the most severe immunodeficiency.

PATHOGENESIS

SCID results from mutations in any 1 of at least 13 known genes that encode components of the immune system crucial for lymphoid cell development (Table 126-2). All patients with SCID have very small thymuses (<1 g) that usually fail to descend from the neck, contain no thymocytes, and lack corticomedullary distinction or Hassall corpuscles. The thymic epithelium appears histologically normal. Both the follicular and paracortical areas of the spleen are depleted of lymphocytes. Lymph nodes, tonsils, adenoids, and Peyer patches are absent or extremely underdeveloped.

CLINICAL MANIFESTATIONS

Affected infants present within the 1st few mo of life with recurrent or persistent diarrhea, pneumonia, otitis media, sepsis, and cutaneous infections. Growth may appear normal initially but extreme wasting usually ensues after diarrhea and infections begin. Persistent infections with opportunistic organisms including Candida albicans, Pneumocystis jiroveci, parainfluenza 3 virus, adenovirus, respiratory syncytial virus, rotavirus vaccine virus, cytomegalovirus, Epstein-Barr virus (EBV), varicella-zoster virus, measles virus, MMR-V (measles, mumps, rubella, varicella) vaccine virus, or bacillus Calmette-Guérin (BCG) lead to death. Affected infants also lack the ability to reject foreign tissue and are therefore at risk for severe or fatal graft-versus-host disease (GVHD) from T lymphocytes in nonirradiated blood products or in allogeneic stem cell transplants or less severe GVHD from maternal immunocompetent T cells that crossed the placenta while the infant was in utero.

Because all molecular types of SCID lack T cells, the profound T-cell lymphopenia can be detected on dried blood spots routinely collected from heel sticks shortly after birth for the purpose of newborn screening by assaying for the presence of T-cell receptor recombination excision circles by real time polymerase chain reaction. T-cell receptor recombination excision circles are absent or extremely low in SCID infants. These infants also have an absence of lymphocyte proliferative responses to mitogens, antigens, and allogeneic cells in vitro. Patients with adenosine deaminase (ADA) deficiency have the lowest absolute lymphocyte counts, usually <500/mm³, but infants with all molecular types of SCID are lymphopenic because they lack T cells (normally accounting for 70% of circulating lymphocytes). Serum immunoglobulin concentrations are low or absent, and no antibodies are formed after immunizations. Analyses of lymphocyte populations and subpopulations demonstrate distinctive phenotypes for the various genetic forms of SCID (see Table 126-2). T cells are extremely low or absent in all types; when detected, in most cases they are transplacentally derived maternal T cells.

TREATMENT

SCID is a true pediatric emergency. Unless immunologic reconstitution is achieved through stem cell transplantation or gene therapy, death usually occurs during the 1st yr of life and almost invariably before 2 yr of age. If diagnosed at birth or within the 1st 3.5 mo of life, >92% of cases can be treated successfully with human leukocyte antigen (HLA)-identical or T-cell-depleted haploidentical (half-matched) parental hematopoietic stem cell transplantation without the need for pretransplant chemoablation or posttransplant GVHD prophylaxis. ADA-deficient SCID and X-linked SCID have been treated...
Table 126-1  Genetic Basis of Combined Immunodeficiency Disorders

<table>
<thead>
<tr>
<th>CHROMOSOME AND REGION</th>
<th>GENE PRODUCT</th>
<th>DISORDER</th>
<th>FUNCTIONAL DEFICIENCIES</th>
</tr>
</thead>
<tbody>
<tr>
<td>1q</td>
<td>RFXS</td>
<td>MHC class II antigen deficiency</td>
<td>Low immunoglobulins, lack of T-cell responses to antigens, CD4 deficiency</td>
</tr>
<tr>
<td>1q31-q32</td>
<td>CD45</td>
<td>T–B+NK+ SCID</td>
<td>Absence of T- and B-cell functions</td>
</tr>
<tr>
<td>3p22.2</td>
<td>Myd88</td>
<td>Toll-receptor innate immune defect</td>
<td>T and B cell functions normal; Failure of activation of nuclear factor κB (NF-κB) and mitogen-activated protein kinase (MAPK) by Toll receptor stimuli</td>
</tr>
<tr>
<td>5p13</td>
<td>IL-7Rxα</td>
<td>T–B+NK+ SCID</td>
<td>Absence of T- and B-cell functions</td>
</tr>
<tr>
<td>6p21.3</td>
<td>TAP1, TAP2</td>
<td>MHC class I antigen deficiency</td>
<td>Marked deficiency of CD8 T cells; combined B- and T-cell defects</td>
</tr>
<tr>
<td>6q22-q23</td>
<td>IFN-γR1, IFN-γR2, IL-12Rβ</td>
<td>Disseminated mycobacterial infections</td>
<td>Failure of macrophages and other cells to produce TNF-α in response to IFN-γ</td>
</tr>
<tr>
<td>9p21-p13</td>
<td>Endonuclease RNase MRP*</td>
<td>Cartilage-hair hypoplasia</td>
<td>Combined B- and T-cell defects of varying severity</td>
</tr>
<tr>
<td>9p24</td>
<td>DOCK8</td>
<td>Autosomal recessive Hyper-IgE syndrome</td>
<td>↓ CD4, CD8 and Th17 T cells ↓ Naive T cells; poor T-cell responses to mitogens; elevated serum IgE levels Decreased switched memory B cells Decreased antibody responses</td>
</tr>
<tr>
<td>10p13</td>
<td>Artemis</td>
<td>T–B–NK+ SCID</td>
<td>Absence of T- and B-cell functions</td>
</tr>
<tr>
<td>11p13</td>
<td>RAG1 or RAG2</td>
<td>T–B–NK+ SCID</td>
<td>Absence of T- and B-cell functions</td>
</tr>
<tr>
<td>11q22.3</td>
<td>ATM, a DNA-dependent kinase</td>
<td>Ataxia-telangiectasia</td>
<td>Selective IgA deficiency; T-cell deficiency</td>
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<tr>
<td>11q23</td>
<td>CD3β or CD3ζ</td>
<td>T–B+NK+ SCID</td>
<td>Absence of T- and B-cell functions</td>
</tr>
<tr>
<td>12q12</td>
<td>IRAK4</td>
<td>Toll-receptor innate immune defect</td>
<td>T- and B-cell functions normal; failure of activation of NF-κB and MAPK by Toll receptor stimuli</td>
</tr>
<tr>
<td>13q</td>
<td>RFXAP</td>
<td>MHC class II antigen deficiency</td>
<td>Low immunoglobulins, lack of T-cell responses to antigens, CD4 deficiency</td>
</tr>
<tr>
<td>14q13.1</td>
<td>Purine nucleosidase</td>
<td>PNP deficiency</td>
<td>Severe T-cell deficiency; may have normal immunoglobulins</td>
</tr>
<tr>
<td>16p13</td>
<td>CIITA</td>
<td>MHC class II antigen deficiency</td>
<td>Low immunoglobulins, lack of T-cell responses to antigens, CD4 deficiency</td>
</tr>
<tr>
<td>17q21.3</td>
<td>STAT3</td>
<td>Autosomal dominant hyper-IgE syndrome</td>
<td>Elevated IgE and IgD, low CD45RO (memory) T cells, no Th17 T cells</td>
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<td>19p13.1</td>
<td>Jak3</td>
<td>T–B–NK– SCID</td>
<td>Absence of T-, B-, and NK-cell functions</td>
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<tr>
<td>20q13.11</td>
<td>ADA</td>
<td>T–B–NK– SCID</td>
<td>Absence of T- and B-cell functions</td>
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<tr>
<td>Xp11.22</td>
<td>WASP</td>
<td>Wiskott-Aldrich syndrome</td>
<td>Thrombocytopenia; poor antibody production to polysaccharides; T-cell deficiency</td>
</tr>
<tr>
<td>Xp11.23</td>
<td>FOXP3</td>
<td>Immune-dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome</td>
<td>Early onset of diarrhea and autoimmune diseases Elevated IgE</td>
</tr>
<tr>
<td>Xq13.1</td>
<td>Common γ chain (γc) for several cytokine receptors (including IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21)</td>
<td>T–B+NK– SCID</td>
<td>Absence of T-, B-, and NK-cell functions</td>
</tr>
</tbody>
</table>

ADA, Adenosine deaminase; CIITA, class II transactivator; DOCK8, dedicator of cytokinesis 8; FOXP3, forkhead-winged helix transcription factor; IFN-γR1, interferon receptor chain 1; Ig, immunoglobulin; IL, interleukin; IL-7Rxα, interleukin 7 receptor α chain; IL-12Rβ, interleukin 12 receptor β chain; IFN, interferon; IRAK4, interleukin-1 receptor-associated kinase 4; Jak3, Janus kinase 3; MHC, major histocompatibility complex; Myd88, myeloid differentiation factor 88; NK, natural killer; PNP, purine nucleoside phosphorylase; RAG1 and RAG2, recombination activating genes 1 and 2; SCID, severe combined immunodeficiency; STAT3, signal transducer and activator of transcription 3; TAP, transporter of antigenic peptide; Th17, T-helper cell type 17; TNF, tumor necrosis factor; WASP, Wiskott-Aldrich syndrome protein.

Successfully with somatic gene therapy; although serious adverse events occurred in the case of X-linked SCID. ADA-deficient SCID can also be treated with repeated injections of polyethylene glycol modified bovine ADA (PEG-ADA), although the immune reconstitution achieved is not nearly as good as with stem cell or gene therapy. PEG-ADA should not be started if nonablative stem cell transplantation is contemplated because it will enable the infant to reject the graft.

X-LINKED SEVERE COMBINED IMMUNODEFICIENCY CAUSED BY MUTATIONS IN THE GENE ENCODING THE COMMON CYTOKINE RECEPTOR γ CHAIN

X-linked SCID (X-SCID) is the most common form of SCID in the United States, accounting for 47% of cases (Fig. 126-1). Clinically, immunologically, and histopathologically, affected individuals appear
similar to those with other forms of SCID except for having uniformly low percentages of T and NK cells and an elevated percentage of B cells (T−, B+, NK−), a characteristic feature shared only with Janus kinase 3 (Jak3)−deficient SCID. The abnormal gene in X-SCID was mapped to Xq13, cloned, and found to encode the common γ chain (γc) for several cytokine receptors, including interleukin (IL)-2, IL-4, IL-7, IL-9, IL-15, and IL-21. The shared γc functions both to increase the affinity of the receptor for the respective cytokine and to enable the receptors to mediate intracellular signaling. Incapacitation of the receptor by mutation ultimately results in impaired signaling downstream of γc (IL-4, -7, -9, -13, -21). Jak3 deficiency AR Abnormal signaling downstream of γc None HSCT

RAG1 and 2 deficiency AR Defective V(D)J recombination None HSCT

Artemis deficiency AR Defective V(D)J recombination, radiation sensitivity DCLERE1C gene defects HSCT

DNA-PK deficiency AR Defective V(D)J recombination None HSCT

DNA ligase IV deficiency AR Defective V(D)J recombination, radiation sensitivity Growth delay, microcephaly, bone marrow abnormalities, lymphoid malignancies HSCT

Cernunnos-XLF AR Defective V(D)J recombination, radiation sensitivity Growth delay, microcephaly, bird-like facies, bone defects HSCT

CD3ε deficiency AR Arrest of thymocytes differentiation at the CD4−CD8− stage γδ T cells absent HSCT

CD3ζ deficiency AR Arrest of thymocytes differentiation at the CD4−CD8− stage Thymus size may be normal HSCT

CD45 deficiency AR None HSCT

Coronin-1A deficiency AR Abnormal T-cell egress from thymus and lymph nodes Normal thymus size. Attention deficit disorder. HSCT

Adenosine Deaminase Deficiency

An absence of the enzyme ADA is observed in approximately 15% of patients, the second most common form of SCID, resulting from various point and deletional mutations in the ADA gene on chromosome 20q13.3. Marked accumulations of adenosine, 2′-deoxyadenosine, and 2′-O-methyladenosine lead directly or indirectly to T-cell apoptosis, which causes the immunodeficiency. ADA-deficient patients usually have a much more profound lymphopenia than do infants with other types of SCID, with mean absolute lymphocyte counts of <500/mm3; the absolute numbers of T, B, and NK cells are very low. NK function is normal. After T-cell function is conferred by hematopoietic stem cell transplantation without pretransplant chemotherapy, there is generally excellent B−cell function despite the fact that the B cells are of host origin. This is because ADA deficiency affects primarily T-cell function. Milder forms of ADA deficiency have led to delayed diagnosis of immunodeficiency, even to adulthood. Other distinguishing features of ADA-deficient SCID include the presence of rib cage abnormalities similar to a rachitic rosary and numerous skeletal abnormalities of chondroosseous dysplasia, which occur predominantly at the costochondral junctions, at the apophyses of the iliac bones, and in the vertebral bodies where a “bone-in-bone” effect is observed.

AUTOSOMAL RECESSIVE SEVERE COMBINED IMMUNODEFICIENCY

This pattern of inheritance is less common in the United States than in other countries. Mutated genes on autosomal chromosomes have been identified in 12 forms of SCID: ADA deficiency; Jak3 deficiency; IL-7 receptor α chain (IL-7Rα) deficiency; recombination-activating gene 1 or 2 (RAG1 or RAG2) deficiency; Artemis deficiency; ligase 4 deficiency; DNA–protein kinase catalytic subunit (DNA–PKcs) deficiency; CD3ε, CD3ζ, CD3γ deficiency; and CD45 deficiency (see Fig. 126-1).

Adenosine Deaminase Deficiency

An absence of the enzyme ADA is observed in approximately 15% of patients, the second most common form of SCID, resulting from various point and deletional mutations in the ADA gene on chromosome 20q13.3. Marked accumulations of adenosine, 2′-deoxyadenosine, and 2′-O-methyladenosine lead directly or indirectly to T-cell apoptosis, which causes the immunodeficiency. ADA-deficient patients usually have a much more profound lymphopenia than do infants with other types of SCID, with mean absolute lymphocyte counts of <500/mm3; the absolute numbers of T, B, and NK cells are very low. NK function is normal. After T-cell function is conferred by hematopoietic stem cell transplantation without pretransplant chemotherapy, there is generally excellent B−cell function despite the fact that the B cells are of host origin. This is because ADA deficiency affects primarily T-cell function. Milder forms of ADA deficiency have led to delayed diagnosis of immunodeficiency, even to adulthood. Other distinguishing features of ADA-deficient SCID include the presence of rib cage abnormalities similar to a rachitic rosary and numerous skeletal abnormalities of chondroosseous dysplasia, which occur predominantly at the costochondral junctions, at the apophyses of the iliac bones, and in the vertebral bodies where a “bone-in-bone” effect is observed.
As with other types of SCID, ADA deficiency can be cured by HLA-identical or haploidentical T-cell–depleted stem cell transplantation without the need for pre- or posttransplant chemotherapy; this remains the treatment of choice. Enzyme replacement therapy should not be initiated if stem cell transplantation is possible because it confers graft-rejection capability. Enzyme replacement provides protective immunity but over time there is a decline of lymphocyte counts and proliferative responses. A number of infants with ADA deficiency have become successfully immune reconstituted by gene therapy in Italy, Great Britain and the United States; in all cases, PEG-ADA was withheld. Spontaneous reversion to normal of a mutation in the ADA gene has also been reported.

Jak3 Deficiency
Patients with this autosomal recessive defect resemble all other types of SCID patients clinically. They have a lymphocyte phenotype similar only to that of patients with X-SCID, with an elevated percentage of B cells and very low or no T and NK cells. Because Jak3 is the only signaling molecule known to be associated with γc, it was a candidate gene for mutations leading to autosomal recessive SCID. Jak3 deficiency accounts for 6% of SCID cases. Even after successful T-cell reconstitution by transplantation of haploidentical stem cells, patients with Jak3-deficient SCID fail to develop NK cells or normal B-cell function owing to the defective function of those host cells that bear abnormal cytokine receptors that share γc.

IL-7Rα Deficiency
Patients with IL-7Rα–deficient SCID have a distinctive lymphocyte phenotype in that, although lacking T cells, they have normal or elevated numbers of both B and NK cells (T−, B+, NK+). This is the third most common form of SCID, accounting for 12% of cases in the United States (see Fig. 126-1). In contrast to patients with γc- and Jak3-deficient SCID, the immunologic defect in these patients is completely correctable by T-cell reconstitution alone, because the host B and NK cells appear to be normal.

RAG1 or RAG2 Deficiencies
Infants with these causes of SCID have a different lymphocyte phenotype from those of patients with SCID caused by γc, Jak3, IL-7Rα, or ADA deficiencies in that they lack both B and T lymphocytes and have primarily NK cells in their circulation (T−, B−, NK+). This suggested a problem with their antigen receptor genes, which led to the discovery of mutations in RAG1 or RAG2. Such mutations result in a functional inability to form antigen receptors through genetic recombination.

Ommen syndrome is an autosomal recessive syndrome characterized by profound susceptibility to infection and by clonal T-cell infiltration of skin, intestines, liver, and spleen, leading to an exfoliative erythroderma, lymphadenopathy, hepatosplenomegaly, and intractable diarrhea. Mutations in the RAG1 and RAG2, as well as rarely in other SCID-causing mutated genes, have been found in patients with this condition. These infants have persistent leukocytosis with marked eosinophilia and lymphocytosis; elevated serum immunoglobulin (Ig) E; low IgG, IgA, and IgM; and low or absent B cells. There is dominance of clonal T-helper (Th)2-like cells, with severely impaired T-cell function as the result of the restricted heterogeneity of the host T-cell repertoire.

Artemis Deficiency
Another cause of SCID is a deficiency of a novel V(DJ) (variable, diversity, joining) recombination/DNA repair factor, named Artemis, that belongs to the metallo-β-lactamase superfamily, which is encoded on chromosome 10p by a gene named DCLRE1C. Deficiency of Artemis results in an inability to repair DNA after double-stranded cuts by the RAG1 or RAG2 gene products in rearranging antigen receptor genes from their germline configuration. Similar to RAG1- and RAG2-deficient SCID, this defect results in failure to develop T and B cells and is, therefore, another form of T−, B−, NK+ SCID, which is called Athabaskan SCID. There is increased radiation sensitivity of both skin fibroblasts and bone marrow cells of those affected with this type of SCID as well as with DNA-PKcs and ligase 4 deficiencies.

CD45 Deficiency
Another molecular defect causing SCID is a mutation in the gene encoding the common leukocyte surface protein CD45. This hematopoietic cell–specific transmembrane protein tyrosine phosphatase functions to regulate src kinases required for T- and B-cell antigen receptor signal transduction. Three examples of this have been reported. One was found to have a large deletion on 1 CD45 allele and a point mutation causing an alteration of the intervening sequence 13 donor splice site on the other allele. The author has evaluated and treated a third case that was caused by uniparental disomy of chromosome 1 with an inactivating mutation in the gene encoding CD45.

CD3δ, CD3ε, and CD3ζ Deficiencies
Other causes of autosomal recessive SCID are deficiencies of components of the T-cell receptor (CD3δ, CD3ε, and CD3ζ chains). Mutations in the portions of these genes that encode the extracellular components of the proteins result in a profound deficiency of circulating mature CD3 T cells. Thus, CD3δ-, CD3ε-, and CD3ζ-deficient T cells are essential for intrathymic development of T cells. Because only T-cell development is affected in these defects, both B and NK cells are normal. Thus, the lymphocyte phenotype resembles that of SCID infants with IL-7Rα chain deficiency (T−B+NK+).

Reticular Dysgenesis
Reticular dysgenesis was first described in identical twin boys who exhibited a total lack of both lymphocytes and granulocytes in their peripheral blood and bone marrow. The thymus glands weigh <1 g, have no Hassall corpuscles, and have few or no thymocytes. Reticular dysgenesis is considered a variant of SCID. The molecular basis of this autosomal recessive disorder is caused by mutations in the gene encoding adenylate kinase 2. The condition is fatal without definitive therapy and the treatment of choice is a fully myeloablative matched sibling bone marrow transplant. However, such transplants have been successful in only 7 of 17 evaluable patients so transplanted.

Figure 126-1 Relative frequencies of the different genetic types among 212 patients with severe combined immunodeficiency seen consecutively over 4 decades. ADA, adenosine deaminase; IL-7Rα, interleukin 7 receptor α chain; Jak3, Janus kinase 3; RAG, recombinase activating gene.
126.2 Combined Immunodeficiency

Rebecca H. Buckley

Combined immunodeficiency (CID) is distinguished from SCID by the presence of low but not absent T-cell function. Similar to SCID, CID is a syndrome of diverse genetic causes (see Table 126-1). Patients with CID have recurrent or chronic pulmonary infections, failure to thrive, oral or cutaneous candidiasis, chronic diarrhea, recurrent skin infections, Gram-negative bacterial sepsis, urinary tract infections, and severe varicella in infancy. Although they usually survive longer than infants with SCID, they fail to thrive and die early in life. Neutropenia and eosinophilia are common. Serum immunoglobulins may be normal or elevated for all classes, but selective IgA deficiency, marked elevation of IgE, and elevated IgD levels occur in some cases. Although antibody-forming capacity is impaired in most patients, it is not absent.

Studies of cellular immune function show lymphopenia, profound deficiencies of T cells, and extremely low but not absent lymphocyte proliferative responses to mitogens, antigens, and allogeneic cells in vitro. Peripheral lymphoid tissues demonstrate paracortical lymphocyte depletion. The thymus is very small, with a paucity of thymocytes and usually no Hassall corpuscles. An autosomal recessive pattern of inheritance is common.

PURINE NUCLEOSIDE PHOSPHORYLASE DEFICIENCY

More than 40 patients with CID have been found to have purine nucleoside phosphorylase deficiency. Point mutations identified in the purine nucleoside phosphorylase gene on chromosome 14q13.1 account for these deficiencies. In contrast to ADA deficiency, no characteristic physical or skeletal abnormalities have been noted, but serum and urinary uric acid are usually markedly deficient. Deaths result from generalized vaccinia, varicella, lymphosarcoma, or GVHD mediated by allogeneic T cells in nonirradiated blood or bone marrow. Two-thirds of patients have neurologic abnormalities, one-third of patients have autoimmune diseases, and some have had allergic diseases. Lymphopenia is striking, primarily because of a marked deficiency of T cells; T-cell function is decreased to various degrees. B cell function may be near normal. The proportion of circulating NK cells is increased. Prenatal diagnosis or diagnosis at birth is possible. Bone marrow transplantation is the only successful form of therapy.

CARTILAGE HAIR HYPOPLASIA

Cartilage hair hypoplasia (CHH) is an unusual form of short-limbed dwarfism with frequent and severe infections. It occurs predominantly among the Amish, but non-Amish patients have been described.

Genetics and Pathogenesis

CHH is an autosomal recessive condition. Numerous mutations that cosegregate with the CHH phenotype have been identified in the untranslated RNase MRP (RMRP) gene, which has been mapped to chromosome 9p21-p13 in Amish and Finnish families (see Table 126-1). The RMRP endonuclease consists of an RNA molecule bound to several proteins and has at least 2 functions: cleavage of RNA in the cytoplasm and translational repression. In vitro. Studies show decreased numbers of T cells and defective T-cell proliferation because of an intrinsic defect related to the G1 phase, resulting in a longer cell cycle for individual cells. NK cells are increased in number and function.

Clinical Manifestations

Clinical features include short, pudgy hands; redundant skin; hyperextensible joints of hands and feet but an inability to extend the elbows completely; and fine, sparse, light hair and eyebrows. Severe and often fatal varicella infections, progressive vaccinia, and vaccine-associated polyomyelitis have been observed. Associated conditions include deficient erythropoiesis, Hirschsprung disease, and an increased risk of malignancies. The bones radiographically show scollopng and sceleritic or cystic changes in the metaphyses and flaring of the costochondral junctions of the ribs. Three patterns of immune dysfunction have emerged: defective antibody-mediated immunity, CID (most common), and SCID. The severity of the immunodeficiency varies; in 1 series, 11 of 77 patients died before age 20 yr, but 2 were still alive at age 76 yr. Stem cell transplantation has resulted in immunologic reconstitution in some CHH patients who had the SCID phenotype.

DEADIFIC EXPRESSION OF MAJOR HISTOCOMPATIBILITY COMPLEX ANTIGENS

The 2 main forms of immunodeficiency and abnormalities of expression of the major histocompatibility complex (MHC) are MHC class I (HLA-A, -B, and -C) antigen deficiency and MHC class II (HLA-DR, -DQ, and -DP) antigen deficiency. The associated defects of both B- and T-cell immunity and of HLA expression emphasize the important biologic role for HLA determinants in effective immune cell cooperation.

Major Histocompatibility Complex Class I Antigen Deficiency

Isolated deficiency of MHC class I (HLA-A, -B, and -C) antigens, the bare lymphocyte syndrome, is rare. The resulting immunodeficiency is much milder than in SCID, contributing to a later age of presentation. Sera from affected children contain normal quantities of MHC class I antigens and β2-microglobulin, but MHC class I antigens are not detected on any cells in the body. There is a deficiency of CD8 but not CD4 T cells. Mutations have been found in 2 genes within the MHC locus on chromosome 6 that encode the peptide transporter proteins TAP1 and TAP2. TAP functions to transport antigenic peptides from the cytoplasm across the Golgi apparatus membrane to join the α chain of MHC class I antigens and β2-microglobulin. All these are then assembled into a MHC class I complex that can then move to the cell surface. If the assembly of the complex cannot be completed because there is no antigenic peptide, the MHC class I complex is destroyed in the cytoplasm.

Major Histocompatibility Complex Class II Antigen Deficiency

Many affected with MHC class II (HLA-DR, -DQ, and -DP) deficiency are of North African descent. Patients present in early infancy with persistent diarrhea that is often associated with cryptosporidiosis and enteroviral infections (e.g., poliovirus, coxsackievirus). They also have an increased frequency of infections with herpesviruses and other viruses, oral candidiasis, bacterial pneumonia, P. jiroveci pneumonia, and septicemia. The immunodeficiency is not as severe as in CID, as evidenced by their failure to develop disseminated infection after BCG vaccination or GVHD from nonirradiated blood transfusions.

Four different molecular defects resulting in impaired expression of MHC class II antigens have been identified (see Table 126-1 and Fig. 124-1). One form is a mutation in the gene on chromosome 1q that encodes a protein called RXF5, a subunit of RFX, which is a multiprotein complex that binds the X box motif of MHC-II promoters. A second form is caused by mutations in a gene on chromosome 13q that encodes a second 36-kD subunit of the RFX complex, called RFX-associated protein (RFXAP). The most common cause of MHC class II defects is a mutation in RFXANK, the gene encoding a 3rd subunit of RFX. In a 4th type, there is a mutation in the gene on chromosome 16p13 that encodes a novel MHC class II transactivator, a non-DNA-binding coactivator that controls the cell-type specificity and inducibility of MHC-II expression. All 4 of these defects cause impairment in the coordinate expression of MHC class II molecules on the surface of B cells and macrophages.

MHC class II-deficient patients have a very low number of CD4 T cells but normal or elevated numbers of CD8 T cells. Lymphopenia is only moderate. The MHC class II antigens HLA-DR, -DQ, and -DP are undetectable on blood B cells and monocytes, even though B cells are present in normal number. Patients are hypogammaglobulinemic owing to impaired antigen-specific responses caused by the absence of these antigen-presenting molecules. In addition, MHC antigen-deficient B cells fail to stimulate allogeneic cells in mixed leukocyte culture. Lymphocyte proliferation studies show normal responses to
mitogens but no response to antigens. The thymus and other lymphoid organs are severely hypoplastic, and the lack of class II molecules results in abnormal thymic selection with circulating CD4 T cells that have altered CDR3 profiles.

**IMMUNODEFICIENCY WITH THROMBOCYTOPENIA AND ECZEMA (WISKOTT-ALDRICH SYNDROME)**

Wiskott-Aldrich syndrome, an X-linked recessive syndrome, is characterized by atopic dermatitis, thrombocytopenic purpura with normal-appearing megakaryocytes but small defective platelets, and undue susceptibility to infection.

**Genetics and Pathogenesis**

The abnormal gene, on the proximal arm of the X chromosome at Xp11.22-11.23 near the centromere, encodes a 501 amino acid proline-rich cytoplasmic protein restricted in its expression to hematopoietic cell lineages. The Wiskott-Aldrich syndrome protein (WASP) binds CDC42H2 and rac, members of the Rho family of guanosine triphosphatases. Wiskott-Aldrich syndrome protein appears to control the assembly of actin filament stress fibers required for microvesicle formation downstream of protein kinase C and tyrosine kinase signaling. Carriers can be detected by demonstration of the deleterious mutation.

**Clinical Manifestations**

Patients often have prolonged bleeding from the circumcision site or bloody diarrhea during infancy. The thrombocytopenia is not initially due to antplatelet antibodies. Atopic dermatitis and recurrent infections usually develop during the 1st yr of life. Streptococcus pneumoniae and other bacteria having polysaccharide capsules cause otitis media, pneumonia, meningitis, and sepsis. Later, infections with agents such as *P. jiroveci* and the herpesviruses become more frequent. Survival beyond the teens is rare; infections, bleeding, and EBV-associated malignancies are major causes of death.

Patients with this defect uniformly have an impaired humoral immune response to polysaccharide antigens, as evidenced by absent or markedly diminished isohemagglutinins, and poor or absent antibody responses after immunization with polysaccharide vaccines. IgG subclass concentrations, surprisingly, are normal. Anamnestic responses to protein antigens are poor or absent. There is an accelerated rate of synthesis as well as hypercatabolism of albumin, IgG, IgA, and IgM, resulting in highly variable concentrations of different immunoglobulins, even within the same patient. The predominant immunoglobulin pattern is a low serum level of IgM, elevated IgA and IgE, and a normal or slightly low IgG concentration. Because of their profound antibody deficiencies, these patients should be given monthly infusions of intravenous immunoglobulin (IVIG) regardless of their serum levels of the different immunoglobulin isotypes. Percentages of T cells are moderately reduced, and lymphocyte responses to mitogens are variably depressed.

**Treatment**

Good supportive care includes appropriate nutrition, routine IVIG, use of killed vaccines, aggressive management of eczema and associated cutaneous infections, platelet transfusion for serious bleeding episodes, splenectomy if a transplant is not going to be done, and high-dose IVIG with systemic steroids for autoimmune complications. Bone marrow or cord blood transplantation is the treatment of choice and is usually curative.

**ATAXIA-TELANGIECTASIA**

Ataxia-telangiectasia is a complex syndrome with immunologic, neurologic, endocrinologic, hepatic, and cutaneous abnormalities.

**Genetics and Pathogenesis**

The mutated gene responsible for this defect, ataxia-telangiectasia mutation (ATM), was mapped to the long arm of chromosome 11 (11q22-23) and has been cloned. The gene product is a DNA-dependent protein kinase localized predominantly to the nucleus and involved in mitotic signal transduction, meiotic recombination, and cell-cycle control. Cells from patients, as well as from heterozygous carriers, have increased sensitivity to ionizing radiation, defective DNA repair, and frequent chromosomal abnormalities.

In vitro tests of lymphocyte function have generally shown moderately depressed proliferative responses to T- and B-cell mitogens. Percentages of CD3 and CD4 T cells are moderately reduced, with normal or increased percentages of CD8 and elevated numbers of Tishop B T cells. The thymus is very hypoplastic, exhibits poor organization, and lacks Hassall corpuscles.

**Th1 responses appeared to be**

**Th2, IL-12R deficiency may be inherited as a complete autosomal recessive (early onset ≈3 yr of age, more episodes, more severe disease, and higher mortality) or partial dominant (onset ≈10 yr of age) disease. Patients with mutations in the IFN-γR2 have also been identified. Related defects were found in other patients who had disseminated mycobacterial infections, who have mutations in either the gene encoding the β chain of the IL-12 receptor (IL-12Rβ2) or in the gene encoding IL-12p40. IL-12 is a powerful inducer of IFN-γ production by T and NK cells, and the mutated receptor chain gene resulted in unresponsiveness of the cells of these patients to IL-12 and inadequate IFN-γ production. The children deficient in IFN-γR1, IFN-γR2, IL-12Rβ1, or IL-12p40 appeared not to be susceptible to infection with many agents other than mycobacteria (occasionally *Salmonella, Listeria, Histoplasma*). Th1 responses appeared to be normal in these patients, and the susceptibility to mycobacterial infections thus apparently results from an intrinsic impairment of the IFN-γ pathway response to these particular intracellular pathogens, showing that IFN-γ is obligatory for efficient macrophage antimycobacterial activity.
GERMLINE STAT-1 MUTATION
Interferons induce the formation of 2 transcriptional activators: gamma-activating factor (GAF) and interferon-stimulated gamma factor 3 (ISGF3). A natural heterozygous dominant germline STAT-1 mutation associated with susceptibility to mycobacterial but not viral disease was found in 2 unrelated patients with unexplained mycobacterial disease. This mutation caused a loss of GAF and ISGF3 activation but was dominant for 1 cellular phenotype and recessive for the other. The mutation impaired the nuclear accumulation of GAF, but not of ISGF3, in cells stimulated by interferons, implying that the antmycobacterial but not the antiviral effects of human interferons are mediated by GAF. Two patients were identified with homozygous STAT-1 mutations; they developed both post–BCG vaccination disseminated disease and lethal viral infections. The mutations in these patients caused a complete lack of STAT-1 and resulted in a lack of formation of both GAF and ISGF3.

IL-1R-ASSOCIATED KINASE 4 DEFICIENCY AND MYELOID DIFFERENTIATION FACTOR 88
Members of IL-1R and the Toll-like receptor superfamily share an intracytoplasmic Toll–IL-1 receptor (TIR) domain, which mediates recruitment of the IL-1R-associated kinase (IRAK) complex via TIR-containing adapter molecules. Three unrelated, otherwise healthy children with recurrent pyogenic infections caused by pneumococci and staphylococci had normal immunocompetence by standard immune studies. They had normal titers of antipneumococcal antibodies. Their blood and fibroblast cells did not activate nuclear factor κB, and mitogen-activated protein kinase and failed to induce downstream cytokines in response to any of the known ligands of TIR-bearing receptors. All were found to have an inherited deficiency of IRAK-4. The TIR-IRAK signaling pathway appears to be crucial for protective immunity against specific bacteria but is redundant against most other microorganisms. There are now more than 50 documented cases of IRAK4 deficiency, and a commonality among cases is susceptibility to pyogenic bacterial infection with pneumococcus and Pseudomonas. The pneumococcal infections have the potential to be invasive (even as a presenting feature) and lead to poor clinical outcomes. Severe viral and fungal infections are atypical. The myeloid differentiatation factor 88 (MYD88) is an effective phenocopy of IRAK4 deficiency. While discovered later than IRAK4 deficiency, myeloid differentiation factor 88 is an upstream adaptor for IRAK4 and links it to Toll-like receptors, which results in a very similar immunologic defect and clinical syndrome.

NATURAL KILLER CELL DEFICIENCY
NK cells are the major lymphocytes of the innate immune system. NK cells recognize virally infected and malignant cells and mediate their elimination. Individuals with absence or functional deficiencies of NK cells are rare, and they typically have susceptibility to the herpesviruses (including varicella–zoster virus, herpes simplex virus, cytomegalovirus, and EBV) as well as papillomaviruses. A number of gene defects are associated with these isolated abnormalities in NK cells. Autosomal recessive CD16 gene mutations were described in 3 separate families and they altered the first immunoglobulin-like domain of this important NK cell activation receptor. Patients with these mutations have NK cells that are functionally impaired and have clinical susceptibility to herpesviruses. Autosomal dominant deficiency of NK cells occurs in individuals with mutations in the GATA2 transcription factor. These patients also have low numbers of monocytes. They have extreme susceptibility to human papilloma virus as well as mycobacteria—the latter presumably from the monocytic defect. Autosomal recessive mutations in the MCM4 gene have been identified in a cohort of consanguineous Irish who had growth failure and susceptibility to herpesviruses. These individuals possessed the immature CD56dim minor subset, but lacked the major mature CD56bright subset of NK cells. The reason why MCM4, which encodes a DNA helicase, would interfere with NK cell development remains unclear. Therapeutically, patients should be maintained on antiviral prophylaxis, and allogeneic stem cell transplantation has been successful in certain cases.

HYPER-IGE SYNDROMES
The hyper-IGE syndromes are relatively rare primary immunodeficiency syndromes characterized by recurrent severe staphylococcal abscesses of the skin, lungs, and other sites and markedly elevated levels of serum IgE (Table 126-3). They occur in 2 forms: autosomal dominant and autosomal recessive.

Autosomal Dominant Hyper-IGE Syndrome
This is the most common form in the United States. More than 200 patients with autosomal dominant hyper-IGE syndrome, also known as the Buckley syndrome, have been reported.

Genetics and Pathogenesis
The autosomal dominant hyper-IGE syndrome is caused by heterozygous mutations in the gene encoding STAT-3. These mutations result in a dominant negative effect on the expression of STAT-3 by the other nonmutated gene. It is not clear exactly how the STAT-3 mutation causes all parts of the syndrome, but it is thought that IL-17 deficiency may account in part for the susceptibility to Candida infection. IL-17 is a cytokine that acts on monocytes to induce secretion of proinflammatory mediators such as IL-8, TNF, and granulocyte-macrophage colony-stimulating factor.

Clinical Manifestations
The characteristic clinical features of the autosomal dominant form of the hyper-IGE syndrome are staphylococcal abscesses, pneumatoceles, osteopenia, and unusual facial features. There is a history from infancy of recurrent staphylococcal abscesses involving the skin, lungs, joints, viscera and other sites. Persistent pneumatoceles develop as a result of recurrent pneumonia. They often have histories of sinusitis and mastoiditis. C. albicans is the second most common pathogen. Allergic respiratory symptoms are usually absent. The pruritic dermatitis that occurs is not typical atopic eczema and does not always persist. The first 2 reported patients were described as having coarse facial features, including a prominent forehead, deep-set wide-eyed eyes, a broad nasal bridge, a wide fleshy nasal tip, mild prognathism, facial asymmetry, and hemihyper trophy. In older children, delay in shedding primary teeth, recurrent fractures, and scoliosis occur.

These patients demonstrate an exceptionally high serum IgE concentration; an elevated serum IgD concentration; usually normal concentrations of IgG, IgA, and IgM; pronounced blood and sputum eosinophilia; abnormally low anamnestic antibody responses; and poor antibody and cell-mediated responses to neoadjuvant. Traditionally, IgE levels >2000 IU/mL confirm the diagnosis. However, IgE levels may fluctuate and even decrease in adults. In neonates and infants with the pruritic purulent dermatosis, IgE levels will be elevated for age and are usually in the 100s. In vitro studies show normal percentages of blood T, B, and NK lymphocytes, except for a decreased percentage of T cells with the memory (CD45RO) phenotype and an absence or deficiency of Th17 T cells. Most patients have normal T-lymphocyte proliferative responses to mitogens but very low or absent responses to antigens or allogeneic cells from family members. Blood, sputum, and histologic sections of lymph nodes, spleen, and lung cysts show striking eosinophilia. Hassall corpuscles and thymic architecture are normal. Phagocytic cell ingestion, metabolism, killing, and total hematocrit complement activity are normal in all patients, and results of chemotaxis studies have been mostly normal.

Autosomal Recessive Hyper-IGE Syndrome
Genetics and Pathogenesis
With the exception of 1 patient who had a mutation in the gene encoding Tyk2, most reported patients with autosomal recessive hyper-IGE syndrome have had mutations in the gene encoding DOCK8, which is on chromosome 9. DOCK8 is a member of the 11-member DOCK protein family. DOCK8 is likely to function as a guanine exchange factor for the Rac-GTPases, Rac1 and Rac2. GTPase triphosphatase activity induces dynamic filamentous actin rearrangements and lamellipodia formation, leading to cell growth, migration, and adhesion. DOCK8 may be important for the formation of...
of the immunologic synapse that leads to T-cell activation, proliferation, and differentiation. Of the 33 patients reported, 25 were from Turkey, 2 each were from Mexico and Iran, and 1 each was from Lebanon, Oman, Italy, and Ireland. Autosomal recessive hyper-IgE syndrome may rarely be due to mutations in phosphoglucomutase 3 (PGM3 deficiency).

Clinical Manifestations
Unlike those with the autosomal dominant form of this syndrome, a large majority of patients with autosomal recessive hyper-IgE have severe atopic dermatitis, asthma, food allergies, and anaphylaxis. They also have recurrent skin viral infections, including severe herpes simplex, herpes zoster, molluscum contagiosum, and papillomavirus skin infections (see Table 126-3). In addition, patients can have abscesses, mucocutaneous candidiasis, upper respiratory infections, and pneumonia. Neurologic problems, including strokes, meningitis, and aneurysms, are prominent. Malignancies are also more common than in the autosomal dominant form. Patients with the autosomal recessive hyper-IgE syndrome do not have pneumatoceles, a history of fractures, unusual facial features, or delayed shedding of the baby teeth, as seen with the autosomal dominant form of the hyper-IgE syndrome (see Table 126-3).

Most patients with autosomal recessive hyper-IgE have elevated serum IgE levels, low serum IgM levels, and variable IgG antibody responses. They also have eosinophilia and lymphopenia, low T-cell numbers and impaired T-cell function. Their immunologic phenotype is that of a CID.

Treatment
The most effective therapy for the autosomal dominant hyper-IgE syndrome is long-term administration of therapeutic doses of a penicillinase-resistant antistaphylococcal antibiotic, adding other agents as required for specific infections. IVIG should be administered to antibody-deficient patients, and appropriate thoracic surgery should be provided for superinfected pneumatoceles or those persisting beyond 6 mo. Bone marrow transplantation has been variably successful in this condition. The prognosis in the autosomal recessive form of the hyper-IgE syndrome is much poorer than in the autosomal dominant form, and most patients die early (see Table 126-3). The treatment of choice for the autosomal recessive form is allogeneic bone marrow transplantation.

126.4 Treatment of Cellular or Combined Immunodeficiency

Rebecca H. Buckley

Good supportive care, including prevention and treatment of infections, is critical while patients await more definitive therapy (see Table 126-4). Having knowledge of the pathogens causing disease with specific immune defects is also useful (see Table 126-4).

Transplantation of MHC-compatible sibling or rigorously T-cell–depleted haploidentical (half-matched) parental hematopoietic stem cells is the treatment of choice for patients with fatal T-cell or combined T- and B-cell defects. The major risk to the recipient from transplants of bone marrow or peripheral blood stem cells is GVHD from donor T cells. Patients with less severe forms of cellular immunodeficiency, including some forms of CID, Wiskott-Aldrich syndrome, cytokine deficiency, and MHC antigen deficiency, reject even HLA-identical marrow grafts unless chemoablative treatment is given before transplantation. Several patients with these conditions have been treated successfully with hematopoietic stem cell transplantation after conditioning.

More than 90% of patients with primary immunodeficiency transplanted with HLA-identical related marrow will survive with immune reconstitution. T-cell–depleted haploidentical-related marrow transplants in patients with primary immunodeficiency have had their greatest success in patients with SCID, who do not require

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<thead>
<tr>
<th>Table 126-3</th>
<th>Hyperimmunoglobulin E Syndromes</th>
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<tr>
<td><strong>Gene</strong></td>
<td>STAT3</td>
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<tr>
<td><strong>INFECTIONS</strong></td>
<td>DOCK8: less often TYK2</td>
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<td></td>
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<tr>
<td>Recurrent bacterial</td>
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</tr>
<tr>
<td>Lymphomas</td>
<td>Yes</td>
</tr>
<tr>
<td>Cutaneous malignancy</td>
<td>No</td>
</tr>
<tr>
<td>Mortality</td>
<td>Adulthood</td>
</tr>
</tbody>
</table>

*Coarse facies includes broad nose, prominent forehead and chin, deep set eyes
HPV, human papillomavirus; HSV, herpes simplex virus; MCV, molluscum virus; UBO, unidentified bright objects of cerebral cortex on T2 MRI; VZV, varicella-zoster virus.
Table 126-4  Infection in the Host Compromised by B- and T-Cell Immunodeficiency Syndromes

<table>
<thead>
<tr>
<th>IMMUNODEFICIENCY SYNDROME</th>
<th>OPPORTUNISTIC ORGANISMS ISOLATED MOST FREQUENTLY</th>
<th>APPROACH TO TREATMENT OF INFECTIONS</th>
<th>PREVENTION OF INFECTIONS</th>
</tr>
</thead>
</table>
| B-cell immunodeficiencies | Encapsulated bacteria (Streptococcus pneumoniae, Staphylococcus aureus, Haemophilus influenzae, and Neisseria meningitidis), Pseudomonas aeruginosa, Campylobacter sp., enteroviruses, rotaviruses, Giardia lamblia, Cryptosporidium sp., Pneumocystis jiroveci, Ureaplasma urealyticum, and Mycoplasma pneumoniae | 1. IVIG 200-800 mg/kg  
2. Vigorous attempt to obtain specimens for culture before antimicrobial therapy  
3. Incision and drainage if abscess present  
4. Antibiotic selection on the basis of sensitivity data | 1. Maintenance IVIG for patients with quantitative and qualitative defects in IgG metabolism (400-800 mg/kg q 3-5 wk)  
2. In chronic recurrent respiratory disease, vigorous attention to postural drainage  
3. In selected cases (recurrent or chronic pulmonary or middle ear), prophylactic administration of ampicillin, penicillin, or trimethoprim-sulfamethoxazole |
| T-cell immunodeficiencies | Encapsulated bacteria (S. pneumoniae, H. influenzae, S. aureus), facultative intracellular bacteria (Mycobacterium tuberculosis, other Mycobacterium sp., and Listeria monocytogenes; Escherichia coli; P. aeruginosa; Enterobacter sp.; Klebsiella sp.; Serratia marcescens; Salmonella sp.; Nocardia sp.; viruses (cytomegalovirus, herpes simplex virus, varicella-zoster virus, Epstein-Barr virus, rotaviruses, adenoviruses, enteroviruses, respiratory syncytial virus, measles virus, vaccinia virus, and parainfluenza viruses); protozoa (Toxoplasma gondii and Cryptosporidium sp.); and fungi (Candida sp., Cryptococcus neoformans, Histoplasma capsulatum, and P. jiroveci) | 1. Vigorous attempt to obtain specimens for culture before antimicrobial therapy  
2. Incision and drainage if abscess present  
3. Antibiotic selection on the basis of sensitivity data  
4. Early antiviral treatment for herpes simplex, cytomegalovirus, and varicella-zoster viral infections  
5. Topical and nonadsorbable antimicrobial agents frequently are useful | 1. Prophylactic administration of trimethoprim-sulfamethoxazole for prevention of P. jiroveci pneumonia  
2. Oral nonadsorbable antimicrobial agents to lower concentration of gut flora  
3. No live virus vaccines or bacillus Calmette-Guérin vaccine  
4. Careful tuberculosis screening |


pretransplant conditioning or GVHD prophylaxis. Of patients with SCID, 92% have survived after T-cell-depleted parental marrow is given soon after birth when the infant is healthy without pretransplant chemotherapy or posttransplant GVHD prophylaxis. Currently, bone marrow transplantation remains the most important and effective therapy for SCID. Early in 2000, there was remarkable success with gene therapy in X-SCID. Unfortunately, leukemic-like clonal T cells or lymphomas developed in 5 of 20 children so treated as a result of insertional mutagenesis, which led to a cessation of those trials. By contrast, in ADA-deficient SCID, there has been outstanding success without insertional oncogenesis. More recently, gene therapy has been successful in the Wiskott–Aldrich syndrome but unfortunately with the problem of insertional mutagenesis.

126.5  Immune Dysregulation with Autoimmunity or Lymphoproliferation

Rebecca H. Buckley

AUTOIMMUNE LYMPHOPROLIFERATIVE SYNDROME

Autoimmune lymphoproliferative syndrome (ALPS), also known as Canale-Smith syndrome, is a disorder of abnormal lymphocyte apoptosis leading to polyclonal populations of T cells (double-negative T cells), which express CD3 and α/β antigen receptors but do not have CD4 or CD8 coreceptors (CD3 + T cell receptor αβ/CD4 − CD8 −). These T cells respond poorly to antigens or mitogens and do not produce growth or survival factors (IL-2). The genetic deficit in most patients is a germline or somatic mutation in the Fas gene, which produces a cell-surface receptor of the TNF receptor superfamily (TNFRSF6), which, when stimulated by its ligand, will produce programmed cell death (Table 126-5). Persistent survival of these lymphocytes leads to immune dysregulation and autoimmunity. ALPS is also caused by other genes in the Fas pathway (FASLG and CASP10). In addition, ALPS-like disorders are associated with other mutations; RAS-associated autoimmune lymphoproliferative disorder (RALD), CASPASE-8 deficiency syndrome (CEDS), Fas-associated protein with death domain deficiency (FADD), and protein kinase C delta deficiency (PRKCD). These disorders have varying degrees of immune deficiency, autoimmunity, and lymphoproliferation.

Clinical Manifestations

ALPS is characterized by autoimmunity, chronic persistent or recurrent lymphadenopathy, splenomegaly, hepatomegaly (in 50%), and hypergammaglobulinemia (IgG, IgA). Many patients present in the 1st yr of life, and most are symptomatic by yr 5. Lymphadenopathy can be striking (Fig. 126-2). Splenomegaly may produce hypersplenism with cytopenias. Autoimmunity also produces anemia (Coombs-positive hemolytic anemia) or thrombocytopenia or a mild neutropenia. The lymphoproliferative process (lymphadenopathy, splenomegaly) may regress over time, but autoimmunity does not and is characterized by frequent exacerbations and recurrences. Other autoimmune features include urticaria, uveitis, glomerulonephritis, hepatitis, vasculitis, glomerulonephritis, vasculitis, panniculitis, arthritis, and central nervous system involvement (seizures, headaches, encephalopathy).

Malignancies are also more common in patients with ALPS and include Hodgkin and non-Hodgkin lymphomas and solid-tissue tumors of thyroid, skin, heart, or lung. ALPS is one cause of Evan syndrome (immune thrombocytopenia and immune hemolytic anemia).

Diagnosis

Laboratory abnormalities depend on the lymphoproliferative organ response (hypersplenism) or the degree of autoimmunity (anemia, thrombocytopenia). There may be lymphocytosis or lymphopenia. Table 126-5 lists the criteria for the diagnosis. Flow cytometry helps identify the lymphocyte type (see Fig. 126-2). Functional genetic analysis for the TNFRSF6 gene often reveals a heterozygous mutation.
**Chapter 126 • Primary Combined Antibody and Cellular Immunodeficiencies**

**Treatment**
Lymphoproliferative manifestations have been managed with corticosteroids and immunosuppressive agents (Cytoxan [cyclophosphamide], methotrexate, azathioprine); once weaned, the manifestation recurs. Hypersplenism may require splenectomy. Malignancies can be treated with the usual protocols used in patients unaffected by ALPS. Stem cell transplantation is another possible option in treating the autoimmune manifestations of ALPS.

**IMMUNE-DYSREGULATION, POLYENDOCRINOPATHY, ENTEROPATHY, X-LINKED SYNDROME**
This immune dysregulation syndrome is characterized by onset within the 1st few wk or mo of life with watery diarrhea (autoimmune enteropathy), an eczematous rash (erythroderma in neonates), insulin-dependent diabetes mellitus, hyperthyroidism or more often hypothyroidism, severe allergies, and other autoimmune disorders (Coombs-positive hemolytic anemia, thrombocytopenia, neutropenia). Psoriasiform or ichthyosiform rashes and alopecia have also been reported.

Immune-dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome is caused by a mutation in the **FOXP3** gene, which encodes a forkhead-winged helix transcription factor (scurfin) involved in the function and development of CD4+CD25+ regulatory T cells. The absence of regulatory cells may predispose to abnormal activation of effector T cells. Dominant gain of function mutations in **STAT1** and other gene mutations (Table 126-6) produces an IPEX-like syndrome.

**Clinical Manifestations**
Watery diarrhea with intestinal villous atrophy leads to failure to thrive in most patients. Cutaneous lesions (usually eczema) and

---

**Table 126-5** Diagnostic Criteria for Autoimmune Lymphoproliferative Syndrome

<table>
<thead>
<tr>
<th>REQUIRED</th>
<th>ACCESSORY</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Chronic nonmalignant lymphoproliferation (&gt;6 mo lymphadenopathy and/or splenomegaly)</td>
<td>Primary</td>
</tr>
<tr>
<td>2. Elevated peripheral blood double-negative T cells</td>
<td>Defective in vitro Fas-mediated apoptosis (in 2 separate assays)</td>
</tr>
<tr>
<td></td>
<td>Somatic or germline mutation in ALPS causative gene (FAS, FASL, CASP10)</td>
</tr>
<tr>
<td></td>
<td>Secondary</td>
</tr>
<tr>
<td></td>
<td>1. Elevated biomarkers (Any of following)</td>
</tr>
<tr>
<td></td>
<td>a. Plasma soluble FASL &gt;200 pg/mL</td>
</tr>
<tr>
<td></td>
<td>b. Plasma IL-10 &gt;20 pg/mL</td>
</tr>
<tr>
<td></td>
<td>c. Plasma or serum vitamin B12 &gt;1500 ng/L</td>
</tr>
<tr>
<td></td>
<td>d. Plasma IL-18 &gt;500 pg/mL</td>
</tr>
<tr>
<td></td>
<td>2. Immunohistochemical findings consistent with ALPS as determined by experienced histopathologist</td>
</tr>
<tr>
<td></td>
<td>3. Autoimmune cytopenias and polyclonal hypergammaglobulinemia</td>
</tr>
<tr>
<td></td>
<td>4. Family history of ALPS or nonmalignant lymphoproliferation</td>
</tr>
</tbody>
</table>

**DIAGNOSIS**
Definitive: Required plus 1 primary accessory criterion
Probable: Required plus 1 secondary accessory criterion
Of note, probable and definitive ALPS should be treated the same in the clinic


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**Figure 126-2** Clinical, radiographic, immunologic, and histologic characteristics of the autoimmune lymphoproliferative syndrome. A, Front view of the National Institutes of Health patient. B, Top middle, a CT scan of the neck is shown demonstrating enlarged preauricular, cervical, and occipital lymph nodes. Arrowheads denote the most prominent lymph nodes. The **lower left quadrant contains CD4-CD8 (double-negative) T cells, which are usually present at <1% of T cells expressing the αβ T-cell receptor.** The bottom panels show CD3, CD4, and CD8 staining on serial sections of a lymph node biopsy specimen from a patient with ALPS and also shows that large numbers of DNCD3+ CD4-CD8 (double-negative) T cells are present in the interfollicular areas of the lymph node. (Adapted from Siegel RM, Fleisher TA: The role of Fas and related death receptors in autoimmune and other disease states, J Allergy Clin Immunol 103:729–738, 1999.)
insulin-dependent diabetes begin in infancy. Lymphadenopathy and splenomegaly are also present. Serious bacterial infections (meningitis, sepsis, pneumonia, osteomyelitis) may be related to neutropenia, malnutrition, or immune dysregulation. Laboratory features reflect the associated autoimmune diseases, dehydration, and malnutrition. In addition, serum IgE levels are elevated with normal levels of IgM, IgG, and IgA. The diagnosis is made clinically and by mutational analysis of the FOXP3 gene.

**Treatment**

Inhibition of T-cell activation by cyclosporine, tacrolimus, or sirolimus with steroids is the treatment of choice, along with the specific care of the endocrinopathy and other manifestations of autoimmunity. Stem cell transplantation is the only possibility for curing IPEX. Overall, the combination of the risks for serious bacterial infection in the untreated condition and the risks of immunosuppression and bone marrow transplantation gives IPEX a poor prognosis. Untreated, most die by 2 yr of age.

*Bibliography is available at Expert Consult.*
THE PHAGOCYTIC INFLAMMATORY RESPONSE
The phagocyte system includes both granulocytes (neutrophils, eosinophils, and basophils) and mononuclear phagocytes (monocytes and tissue macrophages). Neutrophils and mononuclear phagocytes share primary functions, including the defining properties of large particle ingestion and microbial killing. Phagocytes participate primarily in the innate immune response but also help initiate acquired immunity. Mononuclear phagocytes, including tissue macrophages and circulating monocytes, are discussed in Chapter 128.

Neutrophils provide the rapid effector arm of the innate immune system. They circulate in the bloodstream for only about 6 hr (Table 127-1), but upon encountering specific chemotactic signals, they adhere to the vascular endothelium and transmigrate into tissues, where they ingest and kill microbes and release chemotactic signals to recruit more neutrophils and to attract dendritic cells and other initiators of the acquired immune response.

Table 127-1 Neutrophil and Monocyte Kinetics

<table>
<thead>
<tr>
<th></th>
<th>Neutrophil and Monocyte Kinetics</th>
</tr>
</thead>
<tbody>
<tr>
<td>NEUTROPHILS</td>
<td></td>
</tr>
<tr>
<td>Average time in mitosis</td>
<td>7-9 days</td>
</tr>
<tr>
<td>myeloblast to myelocyte</td>
<td></td>
</tr>
<tr>
<td>Average time in postmitosis</td>
<td>3-7 days</td>
</tr>
<tr>
<td>and storage</td>
<td></td>
</tr>
<tr>
<td>(metamyelocyte to neutrophil)</td>
<td></td>
</tr>
<tr>
<td>Average half-life in the circulation</td>
<td>6 hr</td>
</tr>
<tr>
<td>Average total body pool</td>
<td>$6.5 \times 10^8$ cells/kg</td>
</tr>
<tr>
<td>Average circulating pool</td>
<td>$3.2 \times 10^8$ cells/kg</td>
</tr>
<tr>
<td>Average marginating pool</td>
<td>$3.3 \times 10^8$ cells/kg</td>
</tr>
<tr>
<td>Average daily turnover rate</td>
<td>$1.8 \times 10^8$ cells/kg</td>
</tr>
<tr>
<td>MONONUCLEAR PHAGOCYTES</td>
<td></td>
</tr>
<tr>
<td>Average time in mitosis</td>
<td>30-48 hr</td>
</tr>
<tr>
<td>Average half-life in the circulation</td>
<td>36-104 hr</td>
</tr>
<tr>
<td>Average circulating pool (monocytes)</td>
<td>$1.8 \times 10^7$ cells/kg</td>
</tr>
<tr>
<td>Average daily turnover rate</td>
<td>$1.8 \times 10^9$ cells/kg</td>
</tr>
<tr>
<td>Average survival in tissues (macrophages)</td>
<td>Months</td>
</tr>
</tbody>
</table>

mokines, which help direct the cells to sites of inflammation. Chemokine receptors such as CXCR4 and its ligand SDF-1 play a key role in retention of developing myeloid cells within bone marrow.

**NEUTROPHIL MATURATION AND KINETICS**

The process of intramedullary granulocyte maturation involves changes in nuclear configuration and accumulation of specific intracytoplasmic granules. The bone marrow microenvironment supports the normal steady-state renewal of peripheral blood neutrophils through the generation of growth and differentiation factors by stromal cells. Growth factors such as granulocyte colony-stimulating factor and granulocyte-macrophage colony-stimulating factor not only stimulate cell division, but also induce the expression of transcription factors that regulate the biosynthesis of functional components of the neutrophil, such as granule proteins. The transcription factor PU.1 is essential for myeloid progenitor survival or self-renewal of stem cells are shown at the top (light green panel) and stages of hematopoiesis blocked after the depletion of indicated transcription factors for multipotent and committed progenitors are shown in light green boxes throughout. CFU-E, erythroblast colony-forming unit; CFU-E/b/M, erythrocyte, basophil, and megakaryocyte colony-forming unit; CFU-Eo, eosinophil colony-forming unit; CFU-G, granulocyte colony-forming unit; CFU-M, macrophage colony-forming unit; MSC, myeloid stem cells; NK, natural killer; PSC, pluripotent stem cells. (From Nathan DG, Orkin SH, Ginsburg D, et al, editors: Nathan and Oski’s hematology of infancy and childhood, ed 7, Philadelphia, 2009, WB Saunders.)
myb are downregulated, whereas PU.1 and C/EBPε expression rises to initiate terminal differentiation.

Granulocytes survive for only 6-12 hr in the circulation, and therefore daily production of $2 \times 10^4$ granulocytes/µL of blood is required to maintain a level of circulating granulocytes of $5 \times 10^3$/µL (see Table 127-1). The relatively small peripheral blood pool includes the rapidly interchanging circulating and marginating pools; the latter provides entrance into the tissue phase, where neutrophils may survive for hours or days. The circulating pool is fed and buffered by a much larger marrow population of mature neutrophils and myeloid precursors, representing the marrow reserve and proliferating pools, respectively. Proliferation of myeloid cells, encompassing approximately 5 mitotic divisions, takes place only during the 1st 3 stages of neutrophil development, in myeloblasts, promyelocytes, and myelocytes. After the myelocyte stage, the cells terminally differentiate into nondividing, maturing metamyelocytes, bands, and neutrophils.

Neutrophil maturation is associated with nuclear condensation and lobulation and with the sequential production of characteristic granule populations. A myeloblast is a relatively undifferentiated cell with a large oval nucleus, a sizeable nucleolus, and a deficiency of granules. Promyelocytes acquire peroxidase-positive azurophilic (primary) granules, and then myelocytes and metamyelocytes acquire specific (secondary) granules; tertiary granules and secretory vesicles develop in the final stage of neutrophil maturation.

**NEUTROPHIL FUNCTION**

Neutrophil responses are initiated as circulating neutrophils flowing through the postcapillary venules detect low levels of chemokines and other chemotactic substances released from a site of infection. The sequence of events as the neutrophil moves from circulating in the blood to the encounter and destruction of bacteria is carefully orchestrated by a series of biochemical events, defects of which are associated with genetic disorders of neutrophil function (Fig. 127-2). In fact, these disorders of neutrophil function lead to our understanding of the cell biology of phagocyte function. A subset of circulating neutrophils loosely adheres to the endothelium through low-affinity receptors called selectins and rolls along the endothelium forming the marginated pool. Soluble effectors of inflammation trigger subtle changes in surface adhesion molecules on endothelial cells at the site of infection. The rolling of neutrophils allows more intense exposure of neutrophils to activating factors such as tumor necrosis factor or interleukin-1 (Fig. 127-2). Exposure of neutrophils to these same activating factors induces...
 qualitative and quantitative changes in the family of β₂-integrin adhesion receptors (the CD11/CD18 group of surface molecules), leading to tight adhesion between neutrophils and endothelial cells at the site of inflammation and ultimately to transmigration of the neutrophil into the tissue.

Once through the endothelium, the neutrophil senses the gradient of chemokines or other chemoattractants and migrates to sites of infection. Neutrophil migration is a complex process involving rounds of receptor engagement, signal transduction, and remodeling of the actin-microfilaments composing in part the cytoskeleton. Actin polymerization–depolymerization occurs in approximately 8 sec cycles and drives cyclic extension and retraction of the actin-rich lamella at the front of the neutrophil. Receptors at the leading edge of the lamella detect the gradient of attractant and follow microorganisms, ingest and destroy them. When the neutrophil reaches the site of infection, it recognizes pathogens by means of Fc immunoglobulin and complement receptors, Toll-like receptors, fibronectin receptors, and other adhesion molecules.

The neutrophil ingests microbes that are coated by opsonins, serum proteins such as immunoglobulin and complement component C3. The pathogens are engulfed into a closed vacuole, the phagosome (Fig. 127-3) where 2 cellular responses essential for optimal microbicidal activity occur concomitantly: degranulation and activation of nicotinamide-adenine dinucleotide phosphate (NADPH)–dependent oxidase. Fusion of neutrophil granule membranes with the phagosome membrane delivers potent antimicrobial proteins and small peptides into the phagosome.

Assembly and activation of NADPH oxidase at the phagosome membrane as well (see Fig. 127-3) generating large amounts of superoxide (O₂⁻) from molecular oxygen that, in turn, decomposes to produce hydrogen peroxide (H₂O₂) and singlet oxygen. Myeloperoxidase, a major azurophil granule component, catalyzes the reaction of H₂O₂ with ubiquitously present chloride ions to create hypochlorous acid (HOCl) in the phagosome. Hypochlorous acid is essentially Clorox bleach. H₂O₂ and HOCl are potent microbicidal agents that break down and clear pathogens from sites of infection.

In addition, neutrophils secrete a wide variety of cytokines and chemokines that recruit more neutrophils to fight the infection, attract monocytes and macrophages that possess both microbicidal and scavenger functions, and promote antigen presentation to help initiate the adaptive immune response. Also, the reactive oxidants can inactivate chemotactic factors and may serve to terminate the process of neutrophil influx, thereby attenuating the inflammatory process. Finally, the release of reactive oxygen species, granule proteins, and cytokines can also damage local tissues, leading to the classic signs of inflammation or to more permanent impairment of tissue integrity and function.

Bibliography is available at Expert Consult.
Bibliography


Mononuclear phagocytes (monocytes, macrophages) are distributed across all body tissues and play a central role in maintaining homeostasis. They are essential for innate host defense against infection, tissue repair and remodeling, and the antigen-specific adaptive immune response. No human has been identified as having congenital absence of this cell line, probably because macrophages are required to remove primitive tissues during fetal development as new tissues develop to replace them. Monocytes and tissue macrophages in their several forms (Table 128-1) have variable morphology and surface markers and different transcriptional profiles but common functions, particularly phagocytosis. Dendritic cells (DCs) are specialized derivatives of this system that develop from myeloid-lymphoid cell precursors.

**DEVELOPMENT**

Monocytes develop more rapidly during bone marrow hematopoiesis and remain longer in the circulation than do neutrophils (see Table 127-1). The first recognizable monocyte precursor is the monoblast, followed by the promonocyte with cytoplasmic granules and an indented nucleus, and, finally, the fully developed monocyte with cytoplasm filled with granules containing hydrolytic enzymes. The transition from monoblast to mature circulating monocyte requires about 6 days.

Two major subsets of human blood monocytes can be identified on the basis of surface antigens: CD14++ CD16−, originally termed
Part XIV  Immuno[ly]ogy

Principal Sites of Macrophages in Tissues

Table 128-1

**Liver** (Kupffer cells)  
**Lung** (interstitial and alveolar macrophages)  
**Connective tissue, adipose tissue, and interstitium of major organs and skin**  
**Serosal cavities (pleural and peritoneal macrophages)**  
**Synovial membrane (type A synoviocytes)**  
**Bone (osteoclasts)**  
**Brain and retina (microglial cells)**  
**Spleen, lymph nodes, bone marrow**  
**Intestinal wall**  
**Breast milk**  
**Placenta**  
**Granulomas (multinucleated giant cells)**

Macrophages are found in a variety of locations throughout the body, each with specific functions. These cells play a crucial role in the immune response by phagocytosing particles, presenting antigens to lymphocytes, and releasing cytokines. The liver, lung, and intestinal walls are particularly rich in macrophages.

**FUNCTIONAL ACTIVITIES**

Numerous functions are upregulated when the macrophage is activated in response to infection (see Table 128-2). These include phagocytosis, the ingestion and killing of intracellular pathogens such as mycobacteria, *Listeria*; and, through secretion of cytokines, the activation of lymphocytes. Activated macrophages are examples of a continuum of physiologic functions expressed by these long-lived cells in response to the specific task at hand.

**Activated in Response to Infection**

Table 128-2

**Microbicidal and tumoricidal activity**  
**Phagocytosis (of most particles) and pinocytosis**  
**Phagocytosis-associated respiratory burst (O$_2^−$, H$_2$O$_2$)**  
**Generation of nitric oxide**  
**Chemotaxis**  
**Glucose transport and metabolism**  
**Membrane expression of MHC, CD40, TNF receptor**  
**Antigen presentation**  
**Secretion**  
**Complement components**  
**Lysozyme, acid hydrolases, and cytolytic proteinases**  
**Collagenase**  
**Plasminogen activator**  
**Interleukins, including IL-1, IL-12, and IL-15**  
**TNF-α**  
**Interferons, including IFN-α and IFN-β**  
**Antimicrobial peptides (cathelicidin, defensins)**  
**Angiogenic factors**

| $H_2O_2$, hydrogen peroxide; $i$FN, interferon; IL, interleukin; MHC, major histocompatibility complex; $O_2^−$, superoxide anion; TNF, tumor necrosis factor |

**Activated**

Classical activation refers to a response to infection that is driven by specifically activated T-helper (Th) type 1 (Th1)–type lymphocytes and natural killer cells through their release of interferon-γ (IFN-γ). TNF-α secreted by activated macrophages amplifies their activation, as does bacterial cell wall protein or endotoxin through Toll-like receptors. Alternative activation is driven by Th2–type lymphocytes through release of IL-4 and IL-13, cytokines that regulate antibody responses, allergy, and resistance to parasites. Alternatively activated macrophages may have particular functional advantages, such as in wound healing and immunoregulation. In the traditional context of host defense, the term activated macrophage indicates that the ‘classically activated’ cell has an enhanced capacity to kill microorganisms or tumor cells. These macrophages are larger, with more pseudopods and pronounced ruffling of the plasma membrane, and they exhibit accelerated activity of many functions (Table 128-2). Considering the variety of macrophage activities essential to the maintenance of homeostasis, it seems likely that so-called classically and alternatively activated macrophages are examples of a continuum of physiologic functions expressed by these long-lived cells in response to the specific task at hand.

**FUNCTIONAL ACTIVITIES**

Numerous functions are upregulated when the macrophage is activated in response to infection (see Table 128-2). Obviously important are the ingestion and killing of intracellular pathogens such as mycobacteria, *Listeria*; and, through secretion of cytokines. Activated macrophages are examples of a continuum of physiologic functions expressed by these long-lived cells in response to the specific task at hand.

Classical macrophage activation is accomplished during infection with intracellular pathogens (e.g., mycobacteria, *Listeria*) through crossstalk between Th1 lymphocytes and antigen-presenting macrophages mediated by the engagement of a series of ligands and receptors on the 2 cell types, including CD40 on macrophages and CD40 ligand on Th cells, and through secretion of cytokines. Macrophages encountering microorganisms release IL-12, which stimulates Th cells to release IFN-γ. These interactions constitute the basis of cell-mediated immunity. IFN-γ is an especially important macrophage-activating cytokine; it is currently used as a therapeutic agent.

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Classical macrophage activation is accomplished during infection with intracellular pathogens (e.g., mycobacteria, *Listeria*) through crossstalk between Th1 lymphocytes and antigen-presenting macrophages mediated by the engagement of a series of ligands and receptors on the 2 cell types, including CD40 on macrophages and CD40 ligand on Th cells, and through secretion of cytokines. Macrophages encountering microorganisms release IL-12, which stimulates Th cells to release IFN-γ. These interactions constitute the basis of cell-mediated immunity. IFN-γ is an especially important macrophage-activating cytokine; it is currently used as a therapeutic agent.
as endotoxin, and they do not effectively produce proinflammatory cytokines. They retain, however, the capacity to ingest and kill microbes. They have been modified during evolution to allow the absence of inflammation typical of normal intestinal mucosa in spite of its constant exposure to huge numbers of microbes and their inflammatory by-products.

Macrophages play an essential role in the disposal of damaged and dying cells, helping resolve the inflammatory response and heal wounds. Brain microglia demonstrate these functions particularly well. In conditions such as stroke, neurodegenerative disease, and tumor invasion, these cells can become activated, surround damaged and dead cells, and clear cellular debris. Macrophages lining the sinuses of the spleen are especially important in ingesting aged or autoantibody-coated erythrocytes or platelets; splenectomy is used to manage autoimmune cytopenias. Macrophages in inflammatory sites can recognize changes in phosphatidylserine on the membrane of neutrophils undergoing apoptosis, and these can be removed before they become necrotic and spill their toxic contents into the tissue. Macrophages also remove the extracellular traps exuded by inflammatory neutrophils, thus reducing the risk of autoimmunity. Macrophages can be identified early in fetal development, where they function to remove debris as one maturing embryonic tissue replaces another. They are also important in removing immune complexes, protein fragments, and inorganic particles such as elements of cigarette smoke that enter the alveoli.

Macrophages are integrally involved in the induction and expression of adaptive immune responses, including antibody formation and cell-mediated immunity. This involvement depends on their capacity to break down foreign material in phagocytic and pinocytic vesicles and then present individual antigens on their surface as peptides or poly saccharides bound to class II major histocompatibility complex (MHC) molecules. B lymphocytes and, most effectively, DCs can also present antigens to T cells for the specific immune response. Expression of MHC class II molecules is increased in activated macrophages, and antigen presentation is more effective.

The heightened capacity of activated macrophages to synthesize and release various hydrolytic enzymes and microbialicidal materials (see Table 128-2) probably plays a part in their increased killing capacity, although not every macrophage product is secreted in increased amounts when the cell is activated. The macrophage is an extraordinarily active secretory cell. It has been shown to secrete more than 100 distinct substances, including cytokines, growth factors, and steroid hormones, placing it in a class with the hepatocyte. Because of the profound effect of some of these secretory products on other cells and the large number and widespread distribution of macrophages, this network of cells can be viewed as an important endocrine organ. IL-1 illustrates this point well. Microbes and microbial products, burns, ischemia--reperfusion, and other causes of inflammation or tissue damage stimulate the release of IL-1, mainly by monocytes, macrophages, and epithelial cells. In turn, IL-1 elicits fever, sleep, and release of IL-6, which induces production of acute-phase proteins.

As traumatic damage and infection subside, the macrophage population shifts toward playing an essential role in tissue repair and healing through removal of apoptotic cells and secretion of IL-10, transforming growth factor-β, lipoxins, and omega-3 fatty acid--derived resolvins, protectins, and maresins (macrophage mediators in resolving inflammation).

**DENDRITIC CELLS**

DCs are derived from both myeloid and lymphoid bone marrow progenitors. They are specialized to capture, process, and present antigens to T cells to generate adaptive immunity or tolerance to self-antigens. Human monocytes can be induced to differentiate into DCs in some circumstances, particularly inflammation. DCs express retractable dendritic (branched) extensions and potent endocytic capacity but are a heterogeneous population from the standpoint of location, surface markers, level of antigen-presenting activity, and function. There are 2 major functional types of DCs, conventional DCs, which include Langhans cells in the epithelial surfaces of skin and mucosa, and dermal or interstitial DCs in subepithelial skin and interstitia of solid organs; and plasmacytoid DCs, sentinels for viral infection and principal source of antiviral IFN-α and IFN-β. DCs migrating from the bloodstream enter skin, epithelial surfaces, and lymphoid organs where, as immature cells, they internalize self- and foreign-antigens. Microbial products, cytokines, or molecules exposed in damaged tissue (“danger signals” or “alarmins”) induce DC maturation, with upregulation of cytokine receptors and MHC class II and costimulatory molecules. Stimulated DCs in the periphery migrate to lymphoid organs where they continue to mature. They function there as the most potent cells that present antigens to T lymphocytes and induce their proliferation, activities that are central to the antigen-specific adaptive immune response. Macrophage IL-10 acts to suppress DC maturation during resolution of inflammation.

DCs from cancer patients have been used in an attempt to control their cancer. The patient’s DCs are amplified and matured from blood monocytes or marrow progenitor cells by cytokines, exposed to antigens from the patient’s tumor, then injected into the patient as a “vaccine” against the cancer.

**ABNORMALITIES OF MONOCYTE-MACROPHAGE OR DENDRITIC CELL FUNCTION**

Mononuclear phagocytes, as well as neutrophils, from patients with chronic granulomatous disease exhibit a profound defect of phagocytic killing (see Chapter 130). The inability of affected macrophages to kill ingested organisms leads to abscess formation and characteristic granulomas at sites of macrophage accumulation beneath the skin and in the liver, lungs, spleen, and lymph nodes. IFN-γ is currently used for preventing infection in patients with chronic granulomatous disease and for treating the decreased bone resorption of congenital osteopetrosis, which is caused by decreased function of osteoclasts. Genetic deficiency of the CD11/CD18 complex of membrane adherence glycoproteins (leukocyte adhesion defect-1), which includes a receptor for opsonic complement component 3, results in impaired phagocytosis by monocytes (see Chapter 130).

The monocyte–macrophage system is prominently involved in lipid storage diseases called sphingolipidoses (see Chapter 86.3). In these conditions, the expression in macrophages of a systemic enzymatic defect permits the accumulation of cell debris that is normally cleared. Resistance to infection can be impaired, at least partly because of impairment in macrophage function. Gaucher disease is the prototype for these disorders. In this condition, the enzyme glucocerebroside functions abnormally, thus allowing accumulation of glucocerebrosides from cell membranes in Gaucher cells throughout the body. In all locations, the Gaucher cell is an altered macrophage. These patients can be treated with infusions of the normal enzyme modified to expose mannose residues, which bind to mannose receptors on macrophages.

The cytokine IL-12 is a powerful inducer of IFN-γ production by T cells and natural killer cells. Individuals with inherited deficiency in macrophage receptors for IFN-γ or lymphocyte receptors for IL-12, or in IL-12 itself, suffer a severe, profound, and selective susceptibility to infection by nontuberculous mycobacteria such as Mycobacterium avium complex or bacillus Calmette-Guérin (see Chapter 126). About half of these patients have had disseminated Salmonella infection. These abnormalities are now grouped as defects in the IFN-γ–IL-12 axis.

Monocyte–macrophage function has been shown to be partially abnormal in various clinical conditions. Cultured mononuclear phagocytes of newborns are more readily infected than adult cells by HIV-1 and measles virus. Macrophages from newborns release less granulocyte colony-stimulating factor (G-CSF) than adult cells, and induce their proliferation, activities that are central to the antigen-specific adaptive immune response. Macrophage IL-10 acts to suppress DC maturation during resolution of inflammation.

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would be expected to blunt the newborn’s response to infection by viruses, fungi, and certain bacteria such as *Listeria*.

There are 2 disorders in which macrophage activation is pathologically excessive. **Familial and acquired hemophagocytic lymphohistiocytosis** is characterized by uncontrolled activation of T cells and macrophages, with resultant fever, hepatosplenomegaly, lymphadenopathy, pancytopenia, marked elevation of serum proinflammatory cytokines, and macrophage hemophagocytosis (see Chapter 507). Up to 5% of children with systemic onset juvenile rheumatoid arthritis develop an acute severe complication termed **macrophage activation syndrome**, with persistent fever (rather than typical febrile spikes), hepatosplenomegaly, pancytopenia, macrophage hemophagocytosis, and coagulopathy, which can progress to disseminated intravascular coagulation and death if not recognized (see Chapter 155).

Two genetic autoinflammatory diseases result from dysregulation of the mononuclear phagocyte–produced proinflammatory cytokine IL-1. In **neonatal onset multisystem inflammatory disorder** monocytes overproduce IL-1. In **deficiency of the IL-1-receptor antagonist**, normal activity levels of IL-1 go unopposed. In both conditions patients present in the 1st few days or weeks of life with pustular or urticarial rash, bony overgrowth, sterile osteomyelitis, elevated sedimentation rate, and other evidence of systemic inflammation. The recombinant IL-1-receptor antagonist anakinra is effective treatment for both these disorders.

The term **histiocyte** was originally used to describe cells thought to be macrophages in fixed tissue preparations. Histiocytosis X represents a malignancy-like overgrowth of Langerhans-type DCs (see Chapter 507). Thus, the term **Langerhans cell histiocytosis** better describes this disorder, because histiocyte is a histologic term and not cell specific.

*Bibliography is available at Expert Consult.*
Bibliography

Eosinophils are a source of a number of proinflammatory cytokines, including IL-1, IL-3, IL-4, IL-5, IL-9, IL-13, and granulocyte-macrophage colony-stimulating factor; they can also function as antigen-presenting cells. Thus, eosinophils have considerable potential to initiate and sustain inflammatory response of the innate and acquired immune systems.

Eosinophil migration from the vasculature into the extracellular tissue is mediated by the binding of leukocyte adhesion receptors to their ligands or counterstructures on the postcapillary endothelium. Similar to neutrophils (see Fig. 127-2), transmigration begins as the eosinophil selectin receptor binds to the endothelial carbohydrate ligand in loose association, which promotes eosinophils rolling along the endothelial surface until they encounter a priming stimulus such as a chemotactic mediator. Eosinophils then establish a high-affinity bond between integrin receptors and their corresponding immunoglobulin-like ligand. Unlike neutrophils, which become flattened before transmigrating between the tight junctions of the endothelial cells, eosinophils can use unique integrins, known as VLA-4, to bind to vascular cell adhesion molecule-1, which enhances eosinophil adhesion and transmigration through endothelium. Eosinophils are recruited to tissues in inflammatory states by the chemokine eotaxin. These unique pathways account for selective accumulation of eosinophils in allergic and inflammatory disorders. Eosinophils normally dwell primarily in tissues, especially tissues with an epithelial interface with the environment, including the respiratory, gastrointestinal, and lower genitourinary tracts. The life span of eosinophils may extend for weeks within tissues.

IL-5 selectively enhances eosinophil production, adhesion to endothelial cells, and function. Considerable evidence shows that IL-5 has a pivotal role in promoting eosinophil accumulation. It is the predominant cytokine in allergen-induced pulmonary late-phase reaction, and antibodies against IL-5 block eosinophil infiltration into the lungs in animal models associated with airway hyperresponsiveness following allergen challenge. Eosinophils also bear unique receptors for several chemokines, including RANTES (regulated upon activation, normal T-cell expressed and secreted), eotaxin, and monocyte chemotactic proteins 3 and 4. These chemokines appear to be key mediators in the induction of tissue eosinophilia.

**DISEASES ASSOCIATED WITH EOSINOPHILIA**

The absolute eosinophil count (AEC) is used to quantify eosinophilia. Calculated as the white blood cell count/µL × percent of eosinophils, it is usually <450 cells/µL and varies diurnally, with eosinophil numbers higher in the early morning and diminishing as endogenous glucocorticoid levels rise.

Many diseases with allergic, infectious, hematologic, autoimmune, or idiopathic origins are associated with moderate (AEC 1,500-5,000 cells/µL) or severe (AEC >5,000 cells/µL) eosinophilia in peripheral blood (Table 129-1). These disorders may range from mild and transient to chronic and life-threatening, and, importantly, blood eosinophil numbers do not always reflect the extent of eosinophil involvement in disease-affected tissues. Because prolonged eosinophilia is associated with end-organ damage, especially involving the heart, patients with persistently elevated AECs should undergo a thorough evaluation to search for an underlying cause.

**Allergic Diseases**

Allergy is the most common cause of eosinophilia in children in the United States. Patients with allergic asthma commonly have eosinophils in the blood, sputum, and/or lung tissue. Hypersensitivity drug reactions can elicit eosinophilia, and when associated with organ dysfunction (e.g., DRESS [drug rash with eosinophilia and systemic symptoms]), these reactions can be serious (see Chapter 152). If a drug is suspected of triggering eosinophilia, biochemical evidence of organ dysfunction should be sought and if found, the drug should be discontinued. Various skin diseases have also been associated with eosinophilia, including atopic dermatitis/eczema, pemphigus, urticaria, and toxic epidermal necrolysis.
**Table 129-1 Causes of Eosinophilia**

<table>
<thead>
<tr>
<th>Category</th>
<th>Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ALLERGIC DISORDERS</strong></td>
<td>Allergic rhinitis, Asthma, Acute and chronic urticaria, Pemphigoid</td>
</tr>
<tr>
<td></td>
<td>Hypersensitivity drug reactions (drug rash with eosinophilia and systemic symptoms [DRESS]), Eosinophilic gastrointestinal disorders.</td>
</tr>
<tr>
<td></td>
<td>Intestinal nephritis.</td>
</tr>
<tr>
<td><strong>INFECTIOUS DISEASES</strong></td>
<td>Tissue-Invasive Helminth Infections</td>
</tr>
<tr>
<td></td>
<td>Trichinosis, Toxocariasis, Strongyloides, Ascaris, Filariasis, Schistosomiasis, Echinococcosis, Pneumocystis carinii, Toxoplasmosis, Scarlet fever, Amebiasis, Malaria, Bronchopulmonary aspergillosis, Coccidiodomycosis, Scabies</td>
</tr>
<tr>
<td><strong>MALIGNANT DISORDERS</strong></td>
<td>Brain tumors, Hodgkin disease and T-cell lymphoma, Acute myelogenous leukemia, Myeloproliferative disorders, Eosinophilic leukemia</td>
</tr>
<tr>
<td><strong>GASTROINTESTINAL DISORDERS</strong></td>
<td>Inflammatory bowel disease, Peritoneal dialysis, Chronic active hepatitis, Eosinophilic gastrointestinal disorders: • Eosinophilic esophagitis • Eosinophilic gastroenteritis • Eosinophilic colitis</td>
</tr>
<tr>
<td><strong>RHEUMATOLOGIC DISEASE</strong></td>
<td>Rheumatoid arthritis, Eosinophilic fasciitis, Scleroderma.</td>
</tr>
<tr>
<td><strong>IMMUNODEFICIENCY DISEASE</strong></td>
<td>Hyperimmunoglobulin E syndromes, Wiskott-Aldrich syndrome, Graft-versus-host disease, Omenn syndrome, Severe congenital neutropenia, Hypersensitivity pneumonia</td>
</tr>
<tr>
<td><strong>MISCELLANEOUS</strong></td>
<td>Thrombocytopenia with absent radii, Churg-Strauss syndrome (eosinophilic granulomatosis with vasculitis), Vasculitis, Adrenal insufficiency, Postirradiation of abdomen, Histiocytosis with cutaneous involvement, Hypereosinophilic syndromes, Autoimmune lymphoproliferative syndromes (ALPS), Autoimmune dysregulation, polyendocrinopathy, X-linked (IPEX).</td>
</tr>
</tbody>
</table>

Eosinophilic gastrointestinal diseases are important emerging allergic causes of eosinophilia in tissue and, in some cases, peripheral blood (see Chapter 337). In these conditions, eosinophils are inappropriately recruited to esophagus, stomach, and/or intestine, where they induce tissue inflammation and clinical symptoms such as dysphagia, food aversion, abdominal pain, vomiting, and diarrhea. Treatment options include allergen elimination diets and swallowed topical corticosteroids.

**Infectious Diseases**

Eosinophilia is often associated with invasive infection with multicellular helminthic parasites, which are the most common cause in developing countries. Table 129-1 includes examples of specific organisms. The level of eosinophilia tends to parallel the magnitude and extent of tissue invasion, especially by larvae such as visceral larva migrans (see Chapter 298). Eosinophilia often does not occur in established parasitic infections that are well contained within tissues or are solely intraluminal in the gastrointestinal tract, such as *Giardia lamblia* and *Enterobius vermicularis* infection.

In evaluating patients with unexplained eosinophilia, the dietary history and geographic or travel history may indicate potential exposures to helminthic parasites. It is frequently necessary to examine the stool for ova and larvae at least 3 times. Additionally, the diagnostic parasite stages of many of the helminthic parasites that cause eosinophilia never appear in feces. Thus, normal results of stool examinations do not absolutely preclude a helminthic cause of eosinophilia; diagnostic blood tests or tissue biopsy may be needed. *Toxocara* causes visceral larva migrans usually in toddlers with pica (see Chapter 298). Most young children are asymptomatic, but some develop fever, pneumonia, hepatomegaly, and hypergammaglobulinemia accompanied by severe eosinophilia. Isohagemagglutinins are frequently elevated. Serology can establish the diagnosis.

Two fungal diseases may be associated with eosinophilia: aspergillosis in the form of **allergic bronchopulmonary aspergillosis** (see Chapter 237.1) and coccidioidomycosis (see Chapter 240) following primary infection, especially in conjunction with erythema nodosum. HIV can also be associated with peripheral eosinophilia.

**Hypereosinophilic Syndrome**

The idiopathic hypereosinophilic syndrome is a heterogeneous group of disorders characterized by sustained overproduction of eosinophils. The 3 diagnostic criteria for this disorder are (1) AEC >1,500 cells/µL persisting for 6 mo or longer or at least on 2 occasions or with evidence of tissue eosinophilia; (2) absence of another diagnosis to explain the eosinophilia; and (3) signs and symptoms of organ involvement. The clinical signs and symptoms of hypereosinophilic syndrome can be heterogeneous because of the diversity of potential organ (pulmonary, cutaneous, neurologic, serosal, gastrointestinal) involvement. Loeffler endocarditis, one of the most serious and life-threatening complications, can cause heart failure from endomyocardial thrombosis and fibrosis. Eosinophilic leukemia, a clonal myeloproliferative variant, may be distinguished from idiopathic hypereosinophilic syndrome by demonstrating a clonal interstitial deletion on chromosome 4q12 that fuses the platelet-derived growth factor receptor-α (PDGFRα) and FIP1-like-1 (FIP1L1) genes; this disorder is treated with imatinib mesylate, which helps target the fusion oncoprotein (Fig. 129-1).

Therapy is aimed at suppressing eosinophilia and is initiated with corticosteroids. Imatinib mesylate, a tyrosine kinase inhibitor, may be effective in FIP1L1-PDGFRα-negative patients. Hydroxyurea may be beneficial in patients unresponsive to corticosteroids. Specific anti–IL-5 monoclonal antibodies (mepolizumab) target this cytokine, which has a central role in eosinophil differentiation, mobilization and activity. With therapy, the eosinophil count declines and corticosteroid doses may be reduced. For patients with prominent organ involvement who fail to respond to therapy, the mortality is ~75% after 3 yr.

**Miscellaneous Diseases**

Eosinophilia is observed in many patients with primary immunodeficiency syndromes, especially hyperimmunoglobulin E syndrome (see Chapters 122 and 126), Wiskott-Aldrich syndrome, and Omenn syndrome. Eosinophilia is also frequently present in the syndrome of thrombocytopenia with absent radii and in familial...
Reticuloendotheliosis with eosinophilia. Eosinophilia can be found in patients with Hodgkin disease, as well as in acute lymphoid and myeloid leukemia. Other considerations include gastrointestinal disorders such as ulcerative colitis, Crohn disease during symptomatic phases, chronic hepatitis, Churg-Strauss vasculitis, and adrenal insufficiency.

Bibliography is available at Expert Consult.
Bibliography
Chapter 130
Disorders of Phagocyte Function
Thomas D. Coates

Neutrophils are the first-line of defense against microbial invasion. They arrive at the site of inflammation during the critical 2-4 hr after microbial invasion to contain the infection and prevent hematogenous dissemination. This well-orchestrated process is one of the most interesting stories in modern cell biology. In fact, much of our knowledge about neutrophil function derives from studies done in patients with genetic errors in neutrophil function. These critical functions and their associated disorders are depicted in Figure 127-2. Children with phagocytic dysfunction present at a young age with recurrent infections that are often involve unusual organisms and are poorly responsive to treatment.

Primary defects of phagocytic function comprise fewer than 20% of immunodeficiencies and there is significant overlap in the presenting signs and symptoms between phagocytic disorders and lymphocyte and humeral disorders. Children with phagocytic defects present with deep tissue infection, pneumonia, adenitis, or osteomyelitis rather than blood stream infections (Tables 130-1 and 130-2, and Fig. 130-1). A few clinical features point to phagocyte defects rather than other immunodeficiencies, but correct diagnosis relies on highly specialized laboratory tests.

Chemotaxis, the direct migration of cells into sites of infection, involves a complex series of events (see Chapter 127). Disorders of adhesion or granule abnormalities can have intermediate or profound motility defects and the propensity to infections is related to a combination of these functional deficits. However, studies of a Tongan family with recessively inherited neutrophil actin dysfunction tell us that a pure severe chemotactic defect can result in fatal recurrent infection. Defective in vitro chemotaxis of neutrophils can be detected in children with various clinical conditions. However, unless chemotaxis is essentially absent, it is difficult to establish whether frequent infections arise from a primary chemotactic abnormality or occur as secondary medical complications of the underlying disorder. For example, dental infection with Capnocytophaga is associated with a clear neutrophil motility defect that resolves when the infection is eliminated.

Motility defects present with significant skin and mucosal infections. They can also have tender cutaneous nodular lesions that characteristically do not contain any neutrophils. In fact, presence of a true abscess makes the diagnosis of a significant chemotactic defect less likely.

Laboratory tests of chemotaxis are biologic assays and have high variability except in the most experienced of hands. The assays must be done on freshly obtained blood and are affected by many factors related to blood sampling itself. It is best to assay other features of the suspected disorder, such as surface marker expression, to establish a specific diagnosis.

LEUKOCYTE ADHESION DEFICIENCY
Leukocyte adhesion deficiency 1 (LAD-1), 2 (LAD-2), and 3 (LAD-3) are rare autosomal recessive disorders of leukocyte function. LAD-1 affects about 1 per 10 million individuals and is characterized by...
### Table 130-1  Infections and WBC Defects: Features That Can Be Seen in Phagocyte Disorders

<table>
<thead>
<tr>
<th>SEVERE INFECTIONS</th>
<th>RECURRENT INFECTIONS</th>
<th>SPECIFIC INFECTIONS</th>
<th>UNUSUALLY LOCATED INFECTIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>TYPE OF INFECTION</td>
<td>DIAGNOSIS TO CONSIDER</td>
<td>SITE OF INFECTION</td>
<td>DIAGNOSIS TO CONSIDER</td>
</tr>
<tr>
<td>Cellulitis</td>
<td>Neutropenia, LAD CGD, HIES</td>
<td>Cutaneous</td>
<td>Neutropenia, CGD, LAD, HIES</td>
</tr>
<tr>
<td>Colitis</td>
<td>Neutropenia, CGD</td>
<td>Gums</td>
<td>LAD, neutrophil motility disorders</td>
</tr>
<tr>
<td>Osteomyelitis</td>
<td>CGD, MSMD pathway defects</td>
<td>Upper and lower respiratory tract</td>
<td>Neutropenia, HIES, functional neutrophil disorders (CGD, MSMD pathway defects (salmonella)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gastrointestinal tract</td>
<td>CGD, MSMD pathway defects (mycobacteria)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lymph nodes</td>
<td>CGD, MSMD pathway defects (mycobacteria)</td>
</tr>
</tbody>
</table>

BCG, bacille Calmette-Guérin; CGD, chronic granulomatous disease; HIES, hyperimmunoglobulin E syndrome; LAD, leukocyte adhesion deficiency; MSMD, Mendelian susceptibility to mycobacterial disease; SCID, severe combined immunodeficiency.


### Table 130-2  Clinical Disorders of Neutrophil Function

<table>
<thead>
<tr>
<th>DISORDER</th>
<th>ETIOLOGY</th>
<th>IMPAIRED FUNCTION</th>
<th>CLINICAL CONSEQUENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DEGRANULATION ABNORMALITIES</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chédiak-Higashi syndrome</td>
<td>Autosomal recessive; disordered coalescence of lysosomal granules; responsible gene is CHS1/LYST, which encodes a protein hypothesized to regulate granule fusion</td>
<td>Decreased neutrophil chemotaxis, degranulation, and bactericidal activity; platelet storage pool defect; impaired NK function, failure to disperse melanosomes</td>
<td>Neutropenia; recurrent pyogenic infections, propensity to develop marked hepatosplenomegaly as a manifestation of the hemophagocytic syndrome</td>
</tr>
<tr>
<td>Specific granule deficiency</td>
<td>Autosomal recessive; functional loss of myeloid transcription factor arising from a mutation or arising from reduced expression of Gfi-1 or C/EBPα, which regulates specific granule formation</td>
<td>Impaired chemotaxis and bactericidal activity; bilobed nuclei in neutrophils; defensins, gelatinase, collagenase, vitamin B₁₂–binding protein, and lactoferrin</td>
<td>Recurrent deep-seated abscesses</td>
</tr>
</tbody>
</table>

| **ADHESION ABNORMALITIES**                    |                                                                          |                                                                                 |                                                                                      |
| Leukocyte adhesion deficiency 1              | Autosomal recessive; absence of CD11/CD18 surface adhesive glycoproteins (β₂ integrins) on leukocyte membranes most commonly arising from failure to express CD18 messenger RNA | Decreased binding of C3bi to neutrophils and impaired adhesion to ICAM1 and ICAM2 | Neutrophilia; recurrent bacterial infection associated with a lack of pus formation |
| Leukocyte adhesion deficiency 2              | Autosomal recessive; loss of fucosylation of ligands for selectins and other glycol-conjugates arising from mutations of the GDP-fucose transporter | Decreased adhesion to activated endothelium expressing ELAM | Neutrophilia; recurrent bacterial infection without pus |
| Leukocyte adhesion deficiency 3 (LAD-1 variant syndrome) | Autosomal recessive; impaired integrin function arising from mutations of FERM3 which encodes kindlin-3 in hematopoietic cells; kindlin-3 binds to β₂-integrin and thereby transmits integrin activation | Impaired neutrophil adhesion and platelet activation | Neutrophilia; recurrent infections, bleeding tendency |

*Continued*
### Clinical Disorders of Neutrophil Function—cont’d

<table>
<thead>
<tr>
<th>DISORDER</th>
<th>ETIOLOGY</th>
<th>IMPAIRED FUNCTION</th>
<th>CLINICAL CONSEQUENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DISORDERS OF CELL MOTILITY</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enhanced motile responses; FMF</td>
<td>Autosomal recessive gene responsible for FMF on chromosome 16 which encodes for a protein called pyrin; pyrin regulates caspase-1 and thereby IL-1β secretion; mutated pyrin may lead to heightened sensitivity to endotoxin, excessive IL-1β production, and impaired monocyte apoptosis</td>
<td>Excessive accumulation of neutrophils at inflamed sites, which may be the result of excessive IL-1β production</td>
<td>Recurrent fever, peritonitis, pleuritis, arthritis, and amyloidosis</td>
</tr>
<tr>
<td><strong>DEPRESSED MOTILE RESPONSES</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Defects in the generation of chemotactic signals</td>
<td>IgG deficiencies; C3 and properdin deficiency can arise from genetic or acquired abnormalities; mannose-binding protein deficiency predominantly in neonates</td>
<td>Deficiency of serum chemotaxis and opsonic activities</td>
<td>Recurrent pyogenic infections</td>
</tr>
<tr>
<td>Intrinsic defects of the neutrophil, e.g., LAD, Chêdiak-Higashi syndrome, specific granule deficiency, neutrophil actin dysfunction, neonatal neutrophils</td>
<td>In the neonatal neutrophil there is diminished ability to express β integrins, and there is a qualitative impairment in β-integrin function</td>
<td>Diminished chemotaxis</td>
<td>Propensity to develop pyogenic infections</td>
</tr>
<tr>
<td>Direct inhibition of neutrophil mobility, e.g., drugs</td>
<td>Ethanol, glucocorticoids, cyclic AMP</td>
<td>Impaired locomotion and ingestion; impaired adherence</td>
<td>Possible cause for frequent infections; neutrophilia seen with epinephrine arises from cyclic AMP release from endothelium</td>
</tr>
<tr>
<td><strong>MICROBICIDAL ACTIVITY</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic granulomatous disease</td>
<td>X-linked and autosomal recessive; failure to express functional gp91phox in the phagocyte membrane in p22phox (AR). Other AR forms of CGD arise from failure to express protein p47phox or p67phox</td>
<td>Failure to activate neutrophil respiratory burst leading to failure to kill catalase-positive microbes</td>
<td>Recurrent pyogenic infections with catalase-positive microorganisms</td>
</tr>
<tr>
<td>G6PD deficiency</td>
<td>Less than 5% of normal activity of G6PD</td>
<td>Failure to activate NADPH-dependent oxidase, and hemolytic anemia</td>
<td>Infections with catalase-positive microorganisms</td>
</tr>
<tr>
<td>Myeloperoxidase deficiency</td>
<td>Autosomal recessive; failure to process modified precursor protein arising from missense mutation</td>
<td>H2O2-dependent antimicrobial activity not potentiated by myeloperoxidase</td>
<td>None</td>
</tr>
<tr>
<td>Rac2 deficiency</td>
<td>Autosomal dominant; dominant negative inhibition by mutant protein of Rac2-mediated functions</td>
<td>Failure of membrane receptor–mediated O2− generation and chemotaxis</td>
<td>Neutrophilia, recurrent bacterial infections</td>
</tr>
<tr>
<td>Deficiencies of glutathione reductase and glutathione synthetase</td>
<td>AR; failure to detoxify H2O2</td>
<td>Excessive formation of H2O2</td>
<td>Minimal problems with recurrent pyogenic infections</td>
</tr>
</tbody>
</table>

AMP, adenosine monophosphate; AR, autosomal recessive; C, complement; CD, cluster of differentiation; CGD, chronic granulomatous disease; ELAM, endothelial-leukocyte adhesion molecule; FMF, familial Mediterranean fever; G6PD, glucose-6-phosphate dehydrogenase; GDP, guanosine diphosphate; ICAM, intracellular adhesion molecule; Ig, immunoglobulin; IL-1, interleukin-1; LAD, leukocyte adhesion deficiency; NADPH, nicotinamide adenine dinucleotide phosphate; NK, natural killer.

recurring bacterial and fungal infections and depressed inflammatory responses despite striking blood neutrophilia (Table 130-3). The neutrophils have significant defects in adhesion, motility, and ability to phagocytose bacteria.

**Genetics and Pathogenesis**

LAD-1 results from mutations of the gene on chromosome 21q22.3 encoding CD18, the 95-kDa β2-leukocyte transmembrane integrin subunit. Normal neutrophils express 4 heterodimeric adhesion molecules: LFA-1 (CD11a/CD18), Mac-1 (CD11b/CD18, also known as CR3 or iC3b receptor), p150,95 (CD11c/CD18), and αMβ2 (CD11b/CD18). These 4 transmembrane adhesion molecules are composed of unique extracellular α subunits encoded on chromosome 16 and share a common β subunit (CD18) that links them to the membrane and connects them to intracellular signal transduction machinery. This group of leukocyte integrins is responsible for the tight adhesion of neutrophils to the endothelial cell surface, egress from the circulation, and adhesion to iC3b-coated microorganisms, which promotes phagocytosis and particulate activation of the phagocyte nicotinamide adenine dinucleotide phosphate (NADPH) oxidase. Some mutations of CD11/CD18 allow a low level of assembly and activity of integrin molecules, resulting in retention of some neutrophil integrin adhesion function and a moderate phenotype.

Because of their inability to adhere firmly to intercellular adhesion molecules such as degranulation and oxidative metabolism normally triggered by ic3b binding are also markedly compromised in LAD-1 neutrophils, resulting in impaired phagocytic function and high risk for serious and recurrent bacterial infections.

Monocyte function is also impaired, with poor fibrinogen-binding function, an activity that is promoted by the CD11/CD18 complex. Consequently, such cells are unable to participate effectively in wound healing.

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**Table 130-3  Leukocyte Adhesion Deficiency Syndromes**

<table>
<thead>
<tr>
<th>LEUKOCYTE ADHESION DEFICIENCY (LAD)</th>
<th>TYPE 1 (LAD1)</th>
<th>TYPE 2 (LAD2 OR CDG-IC)</th>
<th>TYPE 3 (LAD3)</th>
<th>E-SELECTIN DEFICIENCY</th>
<th>RAC2 DEFICIENCY</th>
</tr>
</thead>
<tbody>
<tr>
<td>OMIM</td>
<td>116920</td>
<td>266265</td>
<td>612840</td>
<td>131210</td>
<td>602049</td>
</tr>
<tr>
<td>Inheritance pattern</td>
<td>Autosomal recessive</td>
<td>Autosomal recessive</td>
<td>Autosomal recessive</td>
<td>Unknown</td>
<td>Autosomal dominant</td>
</tr>
<tr>
<td>Affected protein(s)</td>
<td>Integrin β2 common chain (CD18)</td>
<td>Fucosylated proteins (e.g., sialyl-LewisA, CD15s)</td>
<td>Kindlin 3</td>
<td>Endothelial E-selectin expression</td>
<td>Rac2</td>
</tr>
<tr>
<td>Neutrophil function affected</td>
<td>Chemotaxis, tight adherence</td>
<td>Rolling, tethering</td>
<td>Chemotaxis, adhesion, superoxide production</td>
<td>Rolling, tethering</td>
<td>Chemotaxis, superoxide production</td>
</tr>
<tr>
<td>Delayed umbilical cord separation</td>
<td>Yes (severe phenotype only)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Leukocytosis/ neutrophilia</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No (mild neutropenia)</td>
<td>Yes</td>
</tr>
</tbody>
</table>

OMIM, Online Mendelian Inheritance in Man.

Children with LAD-2 share the clinical features of LAD-1 but have normal CD11/CD18 integrins. Features unique to LAD-2 include neurologic defects, cranial facial dysmorphism, and absence of the erythrocyte ABO blood group antigen (Bombay phenotype). LAD-2 (also known as congenital disorder of glycosylation IIc) derives from mutations in the gene encoding a specific GDP-L-fucose transporter of the Golgi apparatus. This abnormality prevents the incorporation of fucose into various cell surface glycoproteins, including the carbohydrate structure sialyl Lewis X that is critical for low-affinity rolling adhesion of neutrophils to vascular endothelium. This is an important initial step necessary for subsequent integrin-mediated activation, spreading, and transendothelial migration. Infections in LAD-2 are milder than that in LAD-1.

LAD-3 is characterized by a Glanzmann thrombasthenia-like bleeding disorder, delayed separation of the umbilical cord, and serious skin and soft-tissue infections similar to that seen in LAD-1, and failure of leukocytes to undergo β2- and β1-integrin-mediated adhesion and migration. Mutations in KINDLIN3 affect integrin activation.

**Clinical Manifestations**

Patients with the severe clinical form of LAD-1 express <0.3% of the normal amount of the β2-integrin molecules, whereas patients with the moderate phenotype may express 2-7% of the normal amount. Children with severe forms of LAD present in infancy with recurrent, indolent bacterial infections of the skin, mouth, respiratory tract, lower intestinal tract, and genital mucosa. Significant neutrophilic leukocytosis, often >25,000/mm3, is a prominent feature. They may have a history of delayed separation of the umbilical cord, usually with associated infection of the cord stump. The presence of significant omphalitis is an important feature that distinguishes these rare patients from the 10% of healthy infants who can have cord separation at age 3 wk or later. Skin infection may progress to large chronic ulcers with polymicrobial infection, including anaerobic organisms (Fig. 130-2). The ulcers heal slowly, need months of antibiotic treatment, and often require plastic surgery grafting. Severe gingivitis can lead to early loss of primary and secondary teeth (Fig. 130-3). Infected areas characteristically have very little neutrophil infiltration.

The pathogens infecting patients with LAD-1 are similar to those affecting patients with severe neutropenia (see Chapter 131) and include *Staphylococcus aureus* and enteric Gram-negative organisms such as *Escherichia coli*. These patients are also susceptible to opportunistic infection by fungi such as *Candida* and *Aspergillus*. Typical signs of inflammation, such as swelling, erythema, and warmth, may be absent. Pus does not form, and few neutrophils are identified microscopically in biopsy specimens of infected tissues. Despite the paucity of neutrophils within the affected tissue, the circulating neutrophil count during infection typically exceeds 30,000/µL and can surpass 100,000/µL. During intervals between infections, the peripheral blood neutrophil count may chronically exceed 12,000/µL. LAD-1 genotypes with only moderate, rather than absent, amounts of functional integrins at the surface of the neutrophil, significantly have reduced severity and frequency of infections compared to children with the severe form, although gingival disease is still a prominent feature.

**Laboratory Findings**

The laboratory of LAD-1 is established most readily by flow cytometric measurements of surface CD11b/CD18 in stimulated and unstimulated neutrophils. Neutrophil and monocyte adherence, aggregation, chemotaxis, and IC3b-mediated phagocytosis demonstrate striking abnormalities. However, these assays are not clinically available. Delayed-type hypersensitivity reactions are normal, and most individuals have normal specific antibody synthesis. However, some patients have impaired T-lymphocyte-dependent antibody responses. The diagnosis of LAD-2 is established by flow cytometric measurement of sialyl Lewis X (CD15) on neutrophils. It is important to note that the flow cytometric assays are not done the same as the more common lymphocyte subset analysis and require specialized approaches to detect levels of surface expression, especially to detect milder phenotypes.

**Treatment**

Treatment of LAD-1 depends on the phenotype as determined by the level of expression of functional CD11/CD18 integrins. Early allogeneic hematopoietic stem cell transplantation (HSCT) is the treatment of choice for severe LAD-1 (and LAD-3). Other treatment is largely supportive. Patients can be maintained on prophylactic trimethoprim-sulfamethoxazole and should have close surveillance for logic agent by culture or biopsy is important because of the prolonged antibiotic treatment required in the absence of neutrophil function.

Some LAD-2 patients have responded to fucose supplementation, which induced a rapid reduction in the circulating leukocyte count and appearance of the sialyl Lewis X molecules accompanied by marked improvement in leukocyte adhesion.

**Prognosis**

The severity of infectious complications correlates with the degree of β2-integrin deficiency. Patients with severe deficiency may die in infancy, and those surviving infancy have a susceptibility to severe life-threatening systemic infections. Patients with moderate deficiency have infrequent life-threatening infections and relatively long survival.

**Figure 130-2** Skin infection of a patient with leukocyte adhesion deficiency type 1. Failure to form pus, inability to demarcate the fibrotic skin debris, and limited inflammation. Enterococcus gallinarum was cultured from the wound. (From Rich RR: Clinical immunology principles and practices, ed 4, Philadelphia, 2013, WB Saunders, Fig. 21-3, p. 273.)
CHÉDIAK-HIGASHI SYNDROME

Chédiak-Higashi syndrome (CHS) is a rare autosomal recessive disorder characterized by increased susceptibility to infection caused by defective degranulation of neutrophils, a mild bleeding diathesis, partial ocuolcutaneous albinism, progressive peripheral neuropathy, and a tendency to develop a life-threatening form of hemophagocytic lymphohistiocytosis (see Chapter 507). CHS is caused by a fundamental defect in granule morphogenesis that results in abnormally large granules in multiple tissues. Pigmentary dilution involving the hair, skin, and ocular fundi results from pathologic aggregation of melanosomes. Neurologic deficits are associated with a failure of deconvolution of the optic and auditory nerves. Patients exhibit an increased susceptibility to infection that can be explained only in part by defects in neutrophil function. The patients have progressive neutropenia as well as abnormalities in natural killer (NK) function, again related to granule dysfunction.

Genetics and Pathogenesis

LYST (for lysosomal traffic regulator), the gene mutated in CHS, is located at chromosome 1q2-q44. The LYST/CHS protein is thought to regulate vesicle transport by mediating protein–protein interaction and protein–membrane associations. Loss of function may lead to indiscriminate interactions with lysosomal surface proteins, yielding giant granules through uncontrolled fusion of lysosomes with each other. Almost all cells of patients with CHS show some oversized and dysmorphic lysosomes, storage granules, or related vesicular structures. Melanosomes are oversized, and delivery to the keratinocytes and hair follicles is compromised, resulting in hair shafts devoid of pigment granules. This abnormality in melanosomes leads to the macroscopic impression of hair and skin that is lighter than expected from parental coloration. The same abnormality in melanocytes leads to the partial ocular albinism associated with light sensitivity.

Beginning early in neutrophil development, spontaneous fusion of giant primary granules with each other or with cytoplasmic membrane components results in huge secondary lysosomes with reduced contents of hydrolytic enzymes, including proteinases, elastase, and cathepsin G. This deficiency of proteolytic enzymes may be responsible for the impaired killing of microorganisms by CHS neutrophils.

Clinical Manifestations

Patients with CHS have light skin and silvery hair and frequently complain of solar sensitivity and photophobia that is associated with rotary nystagmus. Other signs and symptoms vary considerably, but frequent infections and neuropathy are common. The infections involve mucous membranes, skin, and respiratory tract. Affected children are susceptible to Gram-positive bacteria, Gram-negative bacteria, and fungi, with S. aureus being the most common offending organism. The neuropathy may be sensory or motor in type, and ataxia may be a prominent feature. Neuropathy often begins in the teenage years and becomes the most prominent problem.

Patients with CHS have prolonged bleeding times with normal platelet counts, resulting from impaired platelet aggregation associated with a deficiency of the dense granules containing adenosine diphosphate and serotonin.

The most life-threatening complication of CHS is the development of an accelerated phase characterized by pancytopenia, high fever, and lymphohistiocytic infiltration of liver, spleen, and lymph nodes. The onset of the accelerated phase, which can occur at any age, is now recognized to be a genetic form of hemophagocytic lymphohistiocytosis. This occurs in 85% of patients and usually results in death.

Laboratory Findings

The diagnosis of CHS is established by finding large inclusions in all nucleated blood cells. These can be seen on Wright-stained blood films and are accentuated by a peroxidase stain. Because of impaired egress from the bone marrow, cells containing the large inclusions may be missed on peripheral blood smear but readily identified on bone marrow examination. The patients have progressive neutropenia and abnormal platelet, neutrophil, and NK function.

Treatment

High-dose ascorbic acid (200 mg/day for infants, 2,000 mg/day for adults) may improve the clinical status of some children in the stable phase. Although controversy surrounds the efficacy of ascorbic acid, given the safety of the vitamin, it is reasonable to administer ascorbic acid to all patients.

The only curative therapy to prevent the accelerated phase is HSCT. Normal stem cells reconstitute hematopoietic and immunologic function, correct the NK cell deficiency, and prevent conversion to the accelerated phase, but cannot correct or prevent the neuropathy. If the patient is in the accelerated phase with active hemophagocytic lymphohistiocytosis, HSCT often fails to prevent death.

MYELOPEROXIDASE DEFICIENCY

Myeloperoxidase (MPO) deficiency is an autosomal recessive disorder of oxidative metabolism and is one of the most common inherited disorders of phagocytes, occurring at a frequency approaching 1 per 2,000 individuals. MPO is a green heme protein located in the azurophilic lysosomes of neutrophils and monocytes and is the basis for the greenish tinge to pus accumulated at a site of infection.

Clinical Manifestations

MPO deficiency is usually clinically silent. Rarely, patients may have disseminated candidiasis, usually in conjunction with diabetes mellitus. Acquired partial MPO deficiency can develop in acute myelogenous leukemia and in myelodysplastic syndromes.

Laboratory Findings

Deficiency of neutrophil and monocyte MPO can be identified by histochemical analysis. Severe MPO deficiency can cause the dihydorhodamine (DHR) flow cytometric assay for chronic granulomatous disease to be falsely positive. Unlike chronic granulomatous disease (CGD), eosinophils in severe MPO deficiency will still reduce DHR and yield a normal reaction.

Treatment

There is no specific therapy. Aggressive treatment with antifungal agents should be provided for candidal infections. The prognosis is usually excellent.

CHRONIC GRANULOMATOUS DISEASE

CGD is characterized by neutrophils and monocytes capable of normal chemotaxis, ingestion, and degranulation, but unable to kill catalase-positive microorganisms because of a defect in the generation of microbicidal oxygen metabolites. CGD is a rare disease with an incidence of 4-5 per 1 million individuals; it is caused by 4 genes, 1 X-linked and 3 autosomal recessive in inheritance.

Genetics and Pathogenesis

Activation of the phagocyte NADPH oxidase requires stimulation of the neutrophils and involves assembly from cytoplasmic and integral membrane subunits (see Fig. 127-3). Oxidase activation initiates with phosphorylation of a cationic cytoplasmic protein, p47phox (47-kDa phagocyte oxidase protein). Phosphorylated p47phox, together with 2 other cytoplasmic components of the oxidase, p67phox and the low-molecular-weight guanosine triphosphatase Rac2, translocates to the membrane where they combine with the cytoplasmic domains of the transmembrane flavocytochrome b558 to form the active oxidase complex (see Fig. 127-3). The flavocytochrome is a heterodimer composed of p22phox and highly glycosylated gp91phox. The gp91phox glycoprotein catalyzes electron transport through its NADPH-binding, flavin-binding, and heme-binding domains. Defects in any of these NADPH oxidase components can lead to CGD.

Approximately 65% of patients with CGD are males who inherit their disorder as a result of mutations in CYBB, an X-chromosome gene encoding gp91phox. Approximately 35% of patients inherit CGD in an autosomal recessive fashion resulting from mutations in the NCF1 gene on chromosome 7, encoding p47phox. Defects in the genes
Granulomatous chronic pathogenesis

Immunology

Aspergillus, Candida albicans, Nocardia, and frequently causing infections include catalase-positive microorganisms such as E. coli, S. aureus, Salmonella, Staphylococcus epidermidis, and Candida albicans, and Aspergillus. When organisms such as E. coli gain entry into CGD neutrophils, they are not exposed to hydrogen peroxide because the neutrophils do not produce it, and the hydrogen peroxide generated by microorganisms themselves is destroyed by their own catalase. When CGD neutrophils ingest streptococci, which lack catalase, the organisms generate enough hydrogen peroxide to result in a microbicidal effect. As indicated (middle), catalase-positive microbes such as E. coli can survive within the phagosome of the CGD neutrophil. (Modified from Boxer LA: Quantitative abnormalities of granulocytes. In Butler E, Lichtman MA, Coller BS, et al, editors: Williams hematology, ed 6, New York, 2001, McGraw-Hill, p. 845.)

Figure 130-4 The pathogenesis of chronic granulomatous disease (CGD). The manner in which the metabolic deficiency of the CGD neutrophil predisposes the host to infection is shown schematically. Normal neutrophils stimulate hydrogen peroxide in the phagosome containing ingested Escherichia coli. Myeloperoxidase is delivered to the phagosome by degranulation, as indicated by the closed circles. In this setting, hydrogen peroxide acts as a substrate for myeloperoxidase to oxidize halide to hypochlorous acid and chloramines that kill the microbes. The quantity of hydrogen peroxide produced by the normal neutrophil is sufficient to exceed the capacity of catalase, a hydrogen peroxide-catabolizing enzyme of many aerobic microorganisms, including Staphylococcus aureus, most Gram-negative enteric bacteria, Candida albicans, and Aspergillus. When organisms such as E. coli gain entry into CGD neutrophils, they are not exposed to hydrogen peroxide because the neutrophils do not produce it, and the hydrogen peroxide generated by microorganisms themselves is destroyed by their own catalase. When CGD neutrophils ingest streptococci, which lack catalase, the organisms generate enough hydrogen peroxide to result in a microbicidal effect. As indicated (middle), catalase-positive microbes such as E. coli can survive within the phagosome of the CGD neutrophil. (Modified from Boxer LA: Quantitative abnormalities of granulocytes. In Butler E, Lichtman MA, Coller BS, et al, editors: Williams hematology, ed 6, New York, 2001, McGraw-Hill, p. 845.)

Laboratory Findings

The diagnosis is most often made by performing flow cytometry using dihydrorhodamine 123 (DHR) to measure oxidant production through its increased fluorescence when oxidized by H2O2. The nitroblue tetrazolium dye test is frequently cited in the literature but is now rarely used clinically. The X-linked carrier state is usually easily diagnosed in the mother by DHR fluorescence by presence of a bimodal response to stimulation. It is important to test the mother as some extremely Lyonized carriers with <50% positive cells may have chronic clinical problems as well. Ideally, at least the first patient in a kindred should have DNA analysis to facilitate prenatal diagnosis and for genetic counseling purposes.

A few individuals have been described with apparent CGD caused by severe glucose-6-phosphate dehydrogenase deficiency, leading to insufficient NADPH substrate for the phagocyte oxidase. The erythrocytes of these patients also lack the enzyme, leading to chronic hemolysis.

Clinical Manifestations

Although the clinical presentation is variable, several features suggest the diagnosis of CGD. Any patient with recurrent pneumonia, lymphadenitis, hepatic or subcutaneous or other abscesses, osteomyelitis at multiple sites, a family history of recurrent infections, or any infection with an unusual catalase-positive organism requires evaluation. Other clinical features include chronic colitis or enteritis, gastric outlet or ureteral obstruction from granulomas, or blood stream infection caused by Salmonella, Burkholderia cepacia, or Candida.

Clinical Manifestations

Although the clinical presentation is variable, several features suggest the diagnosis of CGD. Any patient with recurrent pneumonia, lymphadenitis, hepatic or subcutaneous or other abscesses, osteomyelitis at multiple sites, a family history of recurrent infections, or any infection with an unusual catalase-positive organism requires evaluation. Other clinical features include chronic colitis or enteritis, gastric outlet or ureteral obstruction from granulomas, or blood stream infection caused by Salmonella, Burkholderia cepacia, or Candida.

The onset of clinical signs and symptoms usually occurs in early infancy, though a few patients with very rare subtypes have presented later in life. The attack rate and severity of infections are exceedingly variable thought the infection incidence does decrease in the second decade coincident with maturation of the lymphocyte and humoral immunity. The most common pathogen is S. aureus, although any catalase-positive microorganism may be involved. Other organisms frequently causing infections include Serratia marcescens, E. coli, Aspergillus, Candida albicans, Nocardia, and Salmonella. There may also be increased susceptibility to mycobacterium, including the bacillus Calmette-Guérin vaccine. Pneumonia, lymphadenitis, osteomyelitis, and skin infections are the most common illnesses encountered. Bacteremia or fungemia occurs but is much less common than focal infections and usually only occurs when local infections have been inappropriately treated for long periods of time. Patients may suffer from the sequelae of chronic infection, including anemia of chronic disease, poor growth, lymphadenopathy, hepatosplenomegaly, chronic purulent dermatitis, restrictive lung disease, gingivitis, hydrophobia, esophageal dysmotility, and pyloric outlet narrowing. Perirectal abscesses and recurrent skin infections, including folliculitis, cutaneous granulomas, and discoid lupus erythematosus also suggest the possibility of CGD. Granuloma formation and inflammatory processes are a hallmark of CGD and may be the presenting symptoms that prompt testing for CGD if they cause pyloric outlet obstruction, bladder outlet or ureter obstruction, or rectal fistulas and granulomatous colitis simulating Crohn disease. More than 80% of CGD patients have positive serology for Crohn disease. Persistent fever especially with splenomegaly and cytopenia warrants an evaluation for secondary macrophage activation syndrome. This has been seen in CGD and may require treatment with steroids and discontinuation of interferon-γ treatment.

Management of infection is dramatically different than in normal children. CGD patients are always at risk for deep-seated, indolent bacterial infections that can become widespread if not treated properly. They also develop the same kinds of infections that occur in normal children so determination of the appropriate treatment can be difficult. The erythrocyte sedimentation rate (ESR) can be quite helpful. If the child does not have a deep-seated infection, the ESR will be normal or will normalize within several days with standard management. However, if it does not, a search for deep tissues is warranted, as is consideration of empirical antibiotics. Cultures should be obtained, but are usually negative. Because all neutrophil functions in CGD except killing are normal, there is often an exuberant inflammatory reaction to a very small number of organisms. Thus, blood cultures and direct cultures of biopsy samples are usually negative unless there are a lot of organisms. Most abscesses require surgical drainage for therapeutic treatment.
and diagnostic purposes. Prolonged use of antibiotics is required even for common bacterial infections. A simple pneumonia may require 6-8 wk of parenteral antibiotics. Infections should be treated for at least 1 wk past normalization of the sedimentation rate to prevent recurrence. Severe pneumonias can be cleared completely but may require many months of parenteral antibiotics. Especially because cultures are often not helpful, we support an “antibiotic sensitivity by sedimentation rate response” approach to treatment. The ESR rates are often in the 40-80 mm/hr or more range with severe infection and will drop monotonically over a week or so after starting antibacterial drugs. It is important to check the ESR daily or every other day as there is moderate variability in this test and changes in treatment need to be based on trends rather than individual values. If there is a clear downward trend over 3-6 days, we continue with antibacterials alone. If this is not the case, parenteral voriconazole should be added to cover *Aspergillus*. Failure of the ESR to come down suggests another antimicrobial approach needs to be tried. Because of the rarity of this disorder, it is critical to seek counsel from someone with significant direct experience with management of several CGD patients. Granulocyte transfusions have been used but it is not clear that they are very helpful. The ESR should be regularly monitored in well patients and whenever they appear ill. A high ESR itself is usually not enough to trigger treatment. However, in the presence of symptoms, one should search for sources at least by contrast CT of the sinus, chest, and abdomen. If the patient is unstable or has very high fevers, *B. cepacia* should be considered and empirically covered. This organism can cause septic shock quickly, unlike the usual smoldering infections seen in CGD. We treat with antibiotics until the ESR is normal and radiographic evidence of infection has been cleared, if possible. The overall incidence of infection decreases in the second decade of life as nonneutrophil immunity matures, but increased risk of infection is lifelong.

Corticosteroids may be useful for the treatment of children with antral and urethral obstruction or severe granulomatous colitis. They can also be helpful in pneumonia to shrink granulomas in the lung and promote drainage. We favor short (4-6 days) pulses of 1-2 mg/kg prednisone with rapid taper to avoid long-term side effects and risk of fungus. Pulses can be repeated if clinical effect has not been achieved.

**Genetic Counseling**

Identifying a patient’s specific genetic subgroup by DNA analysis is useful primarily for genetic counseling and prenatal diagnosis. In X-linked CGD, all possibly affected females should be tested by DHR to exclude carrier state. Counseling is best done by a physician who has direct knowledge of the clinical manifestations of CGD.

**Prognosis**

The overall mortality rate for CGD is about 2 patient deaths/yr per 100 cases, with the highest mortality among young children. The development of effective infection prophylactic regimens, close surveillance for signs of infections, and aggressive surgical and medical interventions has improved the prognosis.

*Bibliography is available at Expert Consult.*
Bibliography
Leukopenia refers to an abnormally low number of white blood cells (WBCs) in the circulating blood secondary to a paucity of lymphocytes, granulocytes or both. Because there are marked developmental changes in normal values for WBC counts during childhood (see Chapter 727), normal ranges must be considered in the context of age. For newborns, the mean WBC count at birth is high, followed by a rapid fall beginning at 12 hr through the 1st wk of life. Thereafter, values are stable until 1 yr of age, after which a slow steady decline in the WBC count continues throughout childhood until adult values are reached during adolescence. Evaluation of patients with leukopenia begins with a thorough history, physical examination, and at least 1 confirmatory complete blood count with differential. Further evaluation then depends upon whether the leukopenia represents a decreased number of neutrophils, lymphocytes, or both cell populations (Table 131-1). Treatment depends upon the etiology and clinical manifestations of the leukopenia.

**NEUTROPENIA**

Neutropenia is defined as a decrease in the absolute number of circulating segmented neutrophils and bands in the peripheral blood. The absolute neutrophil count (ANC) is determined by multiplying the total WBC count by the percentage of segmented neutrophils plus bands. Normal neutrophil counts must be stratified for age and race. Neutrophils predominate at birth but rapidly decrease in the 1st few days of life. During infancy, neutrophils constitute 20-30% of circulating leukocyte populations. Near equal numbers of neutrophils and lymphocytes are found in the peripheral circulation at 5 yr of age, and the characteristic 70% predominance of neutrophils that occurs in adulthood is usually attained during puberty. For white children older than 12 mo of age, the lower limit of normal for the ANC is 1,500/µL; for black children older than 12 mo of age the lower limit of normal is 1,200/µL. The relatively lower limit of normal in blacks likely reflects the prevalence of the Duffy negative (Fy−/−) blood group, which is selectively enriched in populations in the malarial belt of Africa and is associated with ANCs 200-600/µL less than those who are Duffy positive.

Neutropenia may be characterized as **mild neutropenia**, with an ANC of 1,000-1,500/µL; **moderate neutropenia**, with an ANC of 500-1,000/µL; or **severe neutropenia**, with an ANC <500/µL. ANC <200 is also termed **agranulocytosis**. This stratification aids in predicting the risk of pyogenic infection in patients who have neutropenia as a result of disorders of bone marrow production as only patients with severe neutropenia have a significantly increased susceptibility to life-threatening infections. Neutropenia associated with monocytopenia, lymphocytopenia, or hypogammaglobulinemia increases the risk for infection compared to isolated neutropenia. Patients with neutropenia caused by increased destruction (e.g., autoimmune) may tolerate very low ANCs without increased frequency of infection.

**Acute neutropenia** evolves over a few days and is often a result of rapid neutrophil use and/or compromised neutrophil production. **Chronic neutropenia** by definition lasts longer than 3 mo and arises from reduced production, increased destruction or excessive splenic sequestration of neutrophils. The etiology of neutropenia can be classified as either an acquired disorder or extrinsic insult (Table 131-2), or, more rarely, an inherited, intrinsic defect (Table 131-3).

**Clinical Manifestations of Neutropenia**

Individuals with neutrophil counts <500/µL are at substantial risk for developing infections, primarily from their endogenous flora as well as from nosocomial organisms. However, some patients with isolated chronic neutropenia may not experience many serious infections, probably because the remainder of the immune system remains intact or because neutrophil delivery to tissues is preserved, as in autoimmune neutropenias. In contrast, children whose neutropenia is secondary to acquired disorders of production such as with cytotoxic therapy, immunosuppressive drugs, or radiation therapy are likely to develop serious bacterial infections because many arms of the immune system are markedly compromised. Neutropenia associated with additional monocytopenia or lymphocytopenia, is more highly associated with serious infection than neutropenia alone. The integrity of skin and mucous membranes, the vascular supply to tissues, and nutritional status also influence the risk of infection.

The most common **clinical presentation of profound neutropenia** includes fever, aphthous stomatitis, and gingivitis. Infections
commonly associated with neutropenia include cellulitis, furunculosis, periarticular inflammation, colitis, sinusitis, and otitis media, as well as more serious infections such as pneumonia, deep tissue abscess, and sepsis. The most common pathogens causing infections in neutropenic patients are *Staphylococcus aureus* and Gram-negative bacteria. Isolated neutropenia does not heighten a patient’s susceptibility to parasitic or viral infections or to bacterial meningitis. The usual signs and symptoms of local infection and inflammation such as exudate, fluctuance, and regional lymphadenopathy may be diminished in the absence of neutrophils because of the inability to form pus, but patients with agranulocytosis still experience fever and feel pain at sites of inflammation.

### Laboratory Findings

Isolated absolute neutropenia has a limited number of causes (Tables 131-2 through 131-5). The duration and severity of the neutropenia greatly influence the extent of laboratory evaluation. Patients with chronic neutropenia since infancy and a history of recurrent fevers and chronic gingivitis should have WBC counts and differential counts determined 3 times/wk for 6-8 wk to evaluate the periodicity suggestive of **cyclic neutropenia**. Bone marrow aspiration and biopsy should be performed on select patients to assess cellularity and myeloid maturation. Additional marrow studies such as cytogenetic analysis and special stains for detecting leukemia and other malignant disorders should be obtained for patients with suspected intrinsic defects in the myeloid progenitors and for patients with suspected malignancy. If malignancy is not a concern, assessing the ANC before and 4-6 hr after a single dose of glucocorticosteroid (usually prednisone 1-2 mg/kg) measures mobilization of the bone marrow reserve pool of mature neutrophils; an increase in the ANC to a normal or only moderately low level indicates “chronic benign” or idiopathic neutropenia, and may render bone marrow examination unnecessary. Selection of further laboratory tests is determined by the duration and severity of the neutropenia and the associated findings on physical examination (see Table 131-1).

### Acquired Neutropenia

**Infection-Related Neutropenia.** Transient neutropenia often accompanies or follows viral infections (see Table 131-4) and is the most frequent cause of neutropenia in childhood. Viruses commonly causing acute neutropenia include influenza A and B, adenovirus, respiratory syncytial virus, enteroviruses, human herpes virus 6, measles, rubella, and varicella. Parvovirus B19 and hepatitides A and B may also cause neutropenia, but are more commonly associated with pure red cell aplasia or multiple cytopenias, respectively. Viral-associated acute neutropenia often occurs during the 1st 24-48 hr of illness and usually persists for 3-8 days, which generally corresponds to the period of viremia. The neutropenia is related to virus-induced redistribution of neutrophils from the circulating to the marginating pool. In addition, neutrophil sequestration may occur after virus-induced tissue damage or splenomegaly. Significant neutropenia also may be associated with severe bacterial, protozoal, rickettsial, and fungal infections (see Table 131-4). Bacterial sepsis is a particularly serious cause of neutropenia, especially among younger infants and
### Table 131-2 Causes of Neutropenia Extrinsic to Marrow Myeloid Cells

<table>
<thead>
<tr>
<th>CAUSE</th>
<th>ETIOLOGIC FACTORS/AGENTS</th>
<th>ASSOCIATED FINDINGS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection</td>
<td>Viruses, bacteria, protozoa, rickettsia, fungi</td>
<td>Clinical features and laboratory findings of the infectious agent</td>
</tr>
<tr>
<td>Drug-induced</td>
<td>Phenothiazines, sulfonamides, anticonvulsants, penicillins, aminopyrine</td>
<td>Usually none; occasional hypersensitivity reaction (fever, lymphadenopathy, rash, hepatitis, nephritis, pneumonitis, aplastic anemia) or antineutrophil antibody</td>
</tr>
<tr>
<td>Immune neutropenia</td>
<td>Alloimmune, autoimmune</td>
<td>Myeloid hyperplasia with left shift in bone marrow (may appear to be “arrest” at metamyelocyte or band stage)</td>
</tr>
<tr>
<td>Reticuloendothelial sequestration</td>
<td>Hypersplenism</td>
<td>Anemia, thrombocytopenia</td>
</tr>
<tr>
<td>Bone marrow replacement</td>
<td>Malignancy (leukemia, lymphoma, metastatic solid tumor, etc.)</td>
<td>Anemia, thrombocytopenia, malignant cells in bone marrow</td>
</tr>
<tr>
<td>Cancer chemotherapy or radiation therapy</td>
<td>Suppression of myeloid cell production</td>
<td>Anemia, thrombocytopenia, bone marrow hypoplasia</td>
</tr>
</tbody>
</table>

### Table 131-3 Acquired Disorders of Myeloid Cells

<table>
<thead>
<tr>
<th>CAUSE</th>
<th>ETIOLOGIC FACTORS/AGENTS</th>
<th>ASSOCIATED FINDINGS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aplastic anemia</td>
<td>Stem cell destruction and depletion</td>
<td>Pancytopenia</td>
</tr>
<tr>
<td>Vitamin B₁₂ or folate deficiency</td>
<td>Malnutrition; congenital deficiency of B₁₂ absorption, transport, and storage; vitamin avoidance</td>
<td>Megaloblastic anemia, hypersegmented neutrophils</td>
</tr>
<tr>
<td>Acute leukemia, chronic myelogenous leukemia</td>
<td>Bone marrow replacement with malignant cells</td>
<td>Pancytopenia, leukocytosis</td>
</tr>
<tr>
<td>Myelodysplasia</td>
<td>Dysplastic maturation of stem cells</td>
<td>Bone marrow hypoplasia with megaloblastoid red cell precursors, thrombocytopenia</td>
</tr>
<tr>
<td>Prematurity with birth weight &lt;2 kg</td>
<td>Impaired regulation of myeloid proliferation and reduced size of postmitotic pool</td>
<td>Maternal preeclampsia</td>
</tr>
<tr>
<td>Chronic idiopathic neutropenia</td>
<td>Impaired myeloid proliferation and/or maturation</td>
<td>None</td>
</tr>
<tr>
<td>Paroxysmal nocturnal hemoglobinuria</td>
<td>Acquired stem cell defect secondary to mutation of PIG-A gene</td>
<td>Pancytopenia, thrombosis</td>
</tr>
</tbody>
</table>

### Table 131-4 Infections Associated with Neutropenia

<table>
<thead>
<tr>
<th>CAUSE</th>
<th>ETIOLOGIC FACTORS/AGENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viral</td>
<td>Cytomegalovirus, dengue, Epstein-Barr virus, hepatitis viruses, HIV, influenza, measles, parvovirus B19, rubella, varicella</td>
</tr>
<tr>
<td>Bacterial</td>
<td>Anaplasma (formerly Ehrlichia) phagocytophilum, brucella, paratyphoid, pertussis, tuberculosis (disseminated), tularemia, typhoid; any form of sepsis</td>
</tr>
<tr>
<td>Fungal</td>
<td>Histoplasmosis (disseminated)</td>
</tr>
<tr>
<td>Protozoan</td>
<td>Malaria, leishmaniasis (kala-azar)</td>
</tr>
<tr>
<td>Rickettsial</td>
<td>Psittacosis, Rocky Mountain spotted fever, typhus, rickettsialpox</td>
</tr>
</tbody>
</table>

### Table 131-5 Forms of Drug-Induced Neutropenia

<table>
<thead>
<tr>
<th>IMMUNOLOGIC</th>
<th>TOXIC</th>
<th>HYPERSENSITIVITY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paradigm drugs</td>
<td>Aminopyrine, propylthiouracil, penicillins</td>
<td>Phenothiazines, clozapine</td>
</tr>
<tr>
<td>Time to onset</td>
<td>Days to weeks</td>
<td>Weeks to months</td>
</tr>
<tr>
<td>Clinical appearance</td>
<td>Acute, often explosive symptoms</td>
<td>Often asymptomatic or insidious onset</td>
</tr>
<tr>
<td>Rechallenge</td>
<td>Prompt recurrence with small test dose</td>
<td>Latent period; high doses required</td>
</tr>
<tr>
<td>Laboratory findings</td>
<td>Antineutrophil antibody may be positive; bone marrow myeloid hyperplasia</td>
<td>Bone marrow myeloid hypoplasia</td>
</tr>
</tbody>
</table>
children. Premature neonates are especially prone to exhausting their marrow reserve and rapidly succumbing to bacterial sepsis.

Chronic neutropenia often accompanies infection with Epstein-Barr virus, cytomegalovirus, or HIV. The neutropenia associated with AIDS probably arises from a combination of viral bone marrow suppression, antibody-mediated destruction of neutrophils, and effects of antiretroviral or other drugs.

**Drug-Induced Neutropenia.** Drugs constitute a common cause of neutropenia (see Table 131-5). The incidence of drug-induced neutropenia in infancy, dramatic at any age; only 10% of cases occur among children and young adults. The majority of cases occur among adults older than age 65 yr, likely reflecting the more frequent use of multiple medications in that age group. Almost any drug can cause neutropenia. The most common offending drug classes are antimicrobial agents, antithyroid drugs, antipsychotics, antipyretics, and antirheumatics. Drug-induced neutropenia has several underlying mechanisms—immunemediated, toxic, idiosyncratic, hypersensitivity, idiopathic—that are distinct from the severe neutropenia that predictably occurs after administration of antineoplastics or radiotherapy.

Drug-induced neutropenia from immune mechanisms usually develops abruptly, is accompanied by fever, and lasts for about 1 wk after the discontinuation of the drug. The process likely arises from effects of drugs, such as propylthiouracil or penicillin, that act as haptons to stimulate antibody formation, or drugs, such as quinine, that induce immune complex formation. Other drugs, including the antipsychotic drugs such as the phenothiazines, can cause neutropenia when given in toxic amounts, but some individuals, such as those with preexisting neutropenia, may be susceptible to levels at the high end of the usual therapeutic range. Late-onset neutropenia can occur after rituximab therapy. Idiosyncratic reactions, for example to chloramphenicol, are unpredictable with regard to dose or duration of use. Hypersensitivity reactions are rare and may involve arene oxide metabolites of aromatic anticonvulsants. Fever, rash, lymphadenopathy, hepatitis, nephritis, pneumonitis, and aplastic anemia are often associated with hypersensitivity-induced neutropenia. Acute hypersensitivity reactions such as those caused by phenytoin or phenobarbital may last for only a few days if the offending drug is discontinued. Chronic hypersensitivity may last for months to years.

Once neutropenia occurs, the most effective therapeutic measure is withdrawal of nonessential drugs, particularly drugs most commonly associated with neutropenia. Usually the neutropenia will resolve soon after withdrawal of the offending drug. If the neutropenia fails to improve with drug withdrawal and the patient is symptomatic with infection or stomatitis, subcutaneous administration of recombinant human granulocyte colony-stimulating factor (filgrastim) 5 \( \mu \)g/kg/day should be considered. Drug-induced neutropenia may be asymptomatic and noted only as an incidental finding or because of regular monitoring of WBC counts during drug therapy. For patients who are asymptomatic, continuation of the suspected offending drug depends on the relative risks of neutropenia vs discontinuation of a possibly essential drug. If the drug is continued, blood counts should be monitored for possible progression to agranulocytosis.

Neutropenia commonly and predictably follows the use of antinecancer drugs or radiation therapy, especially radiation therapy directed at the pelvis or vertebrae, secondary to cytotoxic effects on rapidly replicating myeloid precursors. A decline in the WBC count typically occurs 7-10 days after administration of the anticaner drug and may persist for 1-2 wk. The neutropenia accompanying malignancy or following cancer chemotherapy is frequently associated with compromised cellular immunity and barrier compromise secondary to central venous lines and mucositis, thereby predisposing patients to a much greater risk of infection (see Chapter 178) than found in disorders associated with isolated neutropenia. Patients with chemotherapy/radiation-related neutropenia and fever must be treated aggressively with broad-spectrum antibiotics.

**Nutrition-Related Neutropenia.** Poor nutrition can contribute to neutropenia. Ineffective myelopoiesis may result in neutropenia caused by acquired dietary vitamin \( B_12 \) or folic acid deficiency. In addition, megaloblastic pancytopenia also can result from extended use of antibiotics such as trimethoprim-sulfamethoxazole, which inhibit folic acid metabolism, and from the use of phenytoin, which may impair folate absorption in the small intestine, or from surgical resection of the small intestine. Neutropenia also occurs with starvation and marasmus in infants, with anorexia nervosa, and occasionally among patients receiving prolonged parenteral nutrition without vitamin supplementation.

**Immune-Mediated Neutropenia.** Immune-mediated neutropenia is usually associated with the presence of circulating antineutrophil antibodies, which may mediate neutrophil destruction by complement-mediated lysis or splenic phagocytosis of opsonized neutrophils, or by accelerated apoptosis of mature neutrophils or myeloid precursors.

**Allergic Neutropenia.** Neutropenia occurs after transplacental transfer of maternal alloantibodies directed against antigens on the infant’s neutrophils, analogous to Rh hemolytic disease. Prenatal sensitization induces maternal IgG antibodies to neutrophil antigens on fetal cells. The neutropenia is often severe and infants may present within the 1st 2 wk of life with skin or umbilical infections, fever, and pneumonia caused by the usual microbes that cause neonatal disease. By 7 wk of age, the neutrophil count usually returns to normal, reflecting the decay of maternal antibodies in the infant’s circulation. Treatment consists of supportive care and appropriate antibiotics for clinical infections, plus filgrastim for severe infections without neutrophil recovery.

Mothers with autoimmune disease may give birth to infants who develop transient neutropenia, known as neonatal passive autoimmune neutropenia. The duration of the neutropenia depends on the time required for the infant to clear the maternally transferred circulating immunoglobulin G antibody. It persists in most cases for a few weeks to a few months. Neonates almost always remain asymptomatic.

**Autoimmune Neutropenia (AIN) of infancy** is a benign condition with an annual incidence of approximately 1 per 100,000 among children between infancy and 10 yr of age. Patients usually have severe neutropenia on presentation, with ANC <500/mL, but the total WBC count is generally within normal limits. Monocytosis or eosinophilia may occur but does not impact the low rate of infection. The median age of presentation is 8-11 mo with a range of 2-54 mo. There is a slight female predominance. The diagnosis is often evident when a blood count incidentally reveals neutropenia in a child with a minor infection. Occasionally, children may present with more severe infections, including abscesses, pneumonia, or sepsis. The diagnosis may be established by the presence of antineutrophil antibodies in serum; however, the test has frequent false-negative and false-positive results, so the absence of detectable antibodies does not exclude the diagnosis and a positive result does not exclude other conditions. The diagnosis may also be based clinically on a benign course and normal or hyperplastic myeloid maturation in the bone marrow. There is considerable overlap between AIN of infancy and “chronic benign neutropenia.”

Treatment is not generally necessary because the disease is only rarely associated with severe infection and usually remits spontaneously. Low-dose filgrastim may be useful for severe infections, to promote wound healing following surgery, or to avert emergency room visits or hospitalizations for febrile illnesses. Longitudinal studies of infants with AIN demonstrate median durations of disease ranging from 7-30 mo. Affected children generally have no evidence or risk of other autoimmune diseases.

**AIN in older children** can occur as an isolated process, as a manifestation of other autoimmune diseases, or as a secondary complication of infection, drugs or malignancy. In primary AIN, low circulating neutrophil counts are the only hematologic finding, and associated diseases or other factors that cause neutropenia are absent. Secondary AIN associated with immune dysregulation or other factors is more commonly identified in older children and is less likely to spontaneously remit. AIN is distinguished from other forms of neutropenia by the demonstration of antineutrophil antibodies (with caveats discussed above) and myeloid hyperplasia on bone marrow examination. The
most common antineutrophil antibody targets are human neutrophil antigens 1a, 1b, and 2.

Treatment of AIN relies on management of any underlying disorders. In addition, judicious use of appropriate antibiotics for bacterial infections, and regular dental hygiene is generally beneficial. Infections tend to be less frequent in AIN than with the corresponding degree of neutropenia from other causes, probably because tissue delivery of neutrophils is greater than that in conditions resulting from impaired production. Prophylactic antibiotics may be helpful for the management of recurrent minor infections. For patients with serious or recurrent infections, filgrastim is generally effective at raising the ANC and preventing infection. Very low doses (<1-2 µg/kg/day) are usually effective, and administration of standard doses can lead to severe bone pain as a consequence of marrow expansion.

**Neutropenia Secondary to Bone Marrow Replacement.** Various acquired bone marrow disorders lead to neutropenia, usually accompanied by anemia and thrombocytopenia. Hematologic malignancies, including leukemia, lymphoma, and metastatic solid tumors suppress myelopoiesis by infiltrating the bone marrow with tumor cells. Neutropenia may also accompany aplastic anemia, myelodysplastic disorders or preleukemic syndromes, which are characterized by multiple cytopenias and often macrocytosis. Treatment requires management of the underlying disease.

**Neutropenia Secondary to Reticuloendothelial Sequestration.** Splenic enlargement resulting from intrinsic splenic disease (storage disease), portal hypertension, or systemic causes of splenic hyperplasia (inflammation or neoplasia) can lead to neutropenia. Most often the neutropenia is mild to moderate and is accompanied by corresponding degrees of thrombocytopenia and anemia. The reduced neutrophil survival corresponds to the size of the spleen, and the extent of the neutropenia is inversely proportional to bone marrow compensatory mechanisms. Usually the neutropenia may be corrected by successfully treating the underlying disease. In selected cases, splenectomy may be necessary to restore the neutrophil count to normal, but results in increased risk of infections by encapsulated bacterial organisms. Patients undergoing splenectomy should receive appropriate presplenectomy immunizations and may benefit from antibiotic prophylaxis postsplenectomy to help mitigate the risk of sepsis. Splenectomy should be avoided in patients with common variable immunodeficiency, autoimmune lymphoproliferative disease and other immunodeficiency syndromes because of the higher risk of sepsis.

**Inherited Neutropenia**

Intrinsic disorders of proliferation or maturation of myeloid precursor cells are rare. Table 131-6 presents a classification based on genetics and molecular mechanisms; selected disorders are discussed below.

**Primary Disorders of Granulocytopoiesis.** Cyclic neutropenia is a rare autosomal dominant congenital granulopoietic disorder occurring with an estimated incidence of 0.5-1 cases per 1 million population. The disorder is characterized by regular, periodic oscillations, with the ANC ranging from normal to <200/µL, mirrored by reciprocal cycling of monocytes. Cyclic neutropenia is sometimes termed cyclic hematopoiesis because of the secondary cycling of other blood cells, such as platelets and reticulocytes. The mean oscillatory period of the cycle is 21 days (± 4 days). During the neutropenic nadir, many patients suffer from malaise, fever, oral and genital ulcers, gingivitis, periodontitis, or pharyngitis, and occasionally lymph node enlargement. More serious infections may occasionally occur, including pneumonia, mastoiditis, and intestinal perforation with peritonitis leading to life-threatening clostridial sepsis. Prior to the availability of filgrastim, approximately 10% of patients developed fatal clostridial or Gram-negative infections. Cyclic neutropenia arises from a regulatory abnormality involving early hematopoietic precursor cells and is almost invariably associated with mutations in the neutrophil elastase gene, ELANE, that lead to accelerated apoptosis as a result of abnormal protein folding. Many patients experience abatement of symptoms with age. The cycles tend to become less noticeable in older patients, and the hematologic picture often begins to resemble that of chronic idiopathic neutropenia.

Cyclic neutropenia is diagnosed by obtaining blood counts 3 times/wk for 6-8 wk. The requirement for repeated blood counts is necessary because some of the elastase mutations overlap with those in patients who have severe congenital neutropenia. Demonstrating oscillillation or a lack thereof in the blood counts helps to identify the patients risk for progression to myelodysplastic syndrome (MDS)/acute myelogenous leukemia (AML), a risk that is only associated with severe congenital neutropenia. The diagnosis can be confirmed with genetic studies demonstrating a mutation in the ELANE gene. Affected patients with neutrophil nadirs <200/µL are treated with filgrastim and their cycle of profound neutropenia changes from a 21-day period with at least 3-5 days of profound neutropenia to a 9-11 day interval with 1 day of less-profound neutropenia. The dose needed to maintain nadirs >500/µL is usually 2-4 µg/kg/day administered daily or every other day.

**Severe congenital neutropenia (SCN) is a rare, genetically heterogeneous, congenital granulopoietic disorder with an estimated incidence of 1-2 cases per 1 million population. The disorder is characterized by an arrest in myeloid maturation at the promyelocyte stage in the bone marrow, resulting in ANCs consistently <200/µL and may occur sporadically, with autosomal dominant or recessive inheritance. The dominant form is caused most often by mutations in the ELANE gene, which accounts for 60-80% of SCN cases, while recessive forms arise from mutations in HAX1 (the form also known as Kostmann disease) or G6P1C3 (encoding a myeloid-specific isoform of glucose-6-phosphate). HAX1 mutations may be associated with neurologic deficits, and G6P1C3 with heart defects, urogenital abnormalities, and venous angiectasias. In addition to severe neutropenia, peripheral blood counts generally show monocytoysis and many also exhibit eosinophilia; chronic inflammation may lead to secondary anemia and thrombocytopenia. Patients who have SCN experience frequent episodes of fever, skin infections (including omphalitis), oral ulcers, gingivitis, perinatal and perirectal abscesses, typically appearing in the 1st few mo of life. Infections often disseminate to the blood, meninges and periarticular, and are usually caused by S. aureus, Escherichia coli, and Pseudomonas species. Prior to the current era of filgrastim therapy, most patients died of infectious complications within the 1st 1-2 yr of life despite prophylactic antibiotics. More than 95% of SCN patients respond to filgrastim treatment with an increase in the ANC and a decrease in infections. Doses required to achieve an ANC >1000/µL vary greatly. A starting dose of filgrastim 5 µg/kg/day is recommended; the dose should be gradually increased, if necessary, as high as 100 µg/kg/day to attain an ANC of 1000-2000/µL. The 5% of patients who do not respond to filgrastim or who require high doses (>8 µg/kg/day) should be considered for hematopoietic stem cell transplantation. Besides infections, patients with SCN are at risk for developing MDS associated with monosomy 7 and AML. For this reason, regular monitoring with blood counts and yearly bone marrow surveillance, including karyotyping and fluorescence in situ hybridization, should be performed on all SCN patients. Although clonal cytogenetic abnormalities may spontaneously remit, their appearance should be considered a strong indication for hematopoietic stem cell transplantation, which is much more likely to be successful prior to progression to MDS/AML.

**Disorders of Molecular Processing.** Shwachman-Diamond syndrome (SDS) is an autosomal recessive disorder classically characterized by neutropenia, pancreatic insufficiency, and short stature with skeletal abnormalities. SDS is caused by proapoptotic mutations of the SBDS gene, which encodes a protein that plays a role in ribosome biogenesis and RNA processing. The initial symptoms are usually steatorrhea and failure to thrive because of malabsorption, which usually develops by 4 mo of age, although the gastrointestinal symptoms may be subtle in some patients and go unrecognized. Patients have also been reported to have respiratory problems with frequent otitis media, pneumonia and eczema. Virtually all patients with SDS have neutropenia, with the ANC periodically <1000/µL. Some children have defects in chemotaxis or in the number or function of B, T, and natural killer (NK) cells that may contribute to the increased susceptibility to pyogenic infection. The diagnosis of SDS is based on clinical
**Table 131-6**  Intrinsic Disorders of Myeloid Precursor Cells

<table>
<thead>
<tr>
<th>SYNDROME</th>
<th>INHERITANCE (GENE)</th>
<th>CLINICAL FEATURES (INCLUDING STATIC NEUTROPIA UNLESS OTHERWISE NOTED)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRIMARY DISORDERS OF MYELOPOIESIS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyclic neutropenia</td>
<td>AD (ELANE)</td>
<td>Periodic oscillation (21-day cycles) in ANC</td>
</tr>
<tr>
<td>Severe congenital neutropenia</td>
<td>AD (primarily ELANE, also GFI and others) AR (G6PC3, HAX1) (HAX1 = Kostmann syndrome) XL (WAS)</td>
<td>Risk of MDS/AML G6PC3: cardiac and urogenital anomalies, venous angiectasias; HAX1: neurologic abnormalities, risk of MDS/AML Neutropenic variant of Wiskott-Aldrich syndrome</td>
</tr>
<tr>
<td>DISORDERS OF MOLECULAR PROCESSING</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shwachman-Diamond syndrome</td>
<td>Ribosomal defect: AR (SBDS)</td>
<td>Pancreatic insufficiency, metaphysical dysostosis, bone marrow failure, MDS/AML</td>
</tr>
<tr>
<td>Dyskeratosis congenita</td>
<td>Telomerase defects: XL (DKC1), AD (TERC), AR (TERT)</td>
<td>Nail dystrophy, leukoplakia, abnormal and carious teeth, lacy reticulated hyperpigmentation of the skin, bone marrow failure</td>
</tr>
<tr>
<td>DISORDERS OF VESICULAR TRAFFICKING</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chédiak-Higashi syndrome</td>
<td>AR (LYST)</td>
<td>Partial albinism, giant granules in myeloid cells, platelet storage pool defect, impaired natural killer cell function, HLH</td>
</tr>
<tr>
<td>Griscelli syndrome, type II</td>
<td>AR (RAB27a)</td>
<td>Partial albinism, impaired natural killer cell function, neurological impairment, HLH</td>
</tr>
<tr>
<td>Cohen syndrome</td>
<td>AR (COH1)</td>
<td>Partial albinism, pigmentary retinopathy, developmental delay, facial dysmorphism</td>
</tr>
<tr>
<td>Hermansky-Pudlak syndrome, type II</td>
<td>AR (AP3P1)</td>
<td>Cyclic neutropenia, partial albinism, HLH</td>
</tr>
<tr>
<td>p14 deficiency</td>
<td>Probable AR (MAPBPIP)</td>
<td>Partial albinism, decreased B and T cells</td>
</tr>
<tr>
<td>VPS45 defects</td>
<td>AR (VPS45)</td>
<td>Neutrophil dysfunction, bone marrow fibrosis, nephromegaly</td>
</tr>
<tr>
<td>DISORDERS OF METABOLISM</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glycogen storage disease, type 1b</td>
<td>AR (G6PT1)</td>
<td>Hepatic enlargement, growth retardation, impaired neutrophil motility</td>
</tr>
<tr>
<td>Barth syndrome</td>
<td>XL (TAZ1)</td>
<td>Episodic neutropenia, dilated cardiomyopathy, methylglutaconic aciduria</td>
</tr>
<tr>
<td>Pearson syndrome</td>
<td>Mitochondrial (DNA deletions)</td>
<td>Episodic neutropenia, pancytopenia; defects in exocrine pancreas, liver, and kidneys</td>
</tr>
<tr>
<td>NEUTROPIA IN DISORDERS OF IMMUNE FUNCTION</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Common variable immunodeficiency</td>
<td>Familial, sporadic (TNFRSF13B) AR, XL (multiple loci)</td>
<td>Hypogammaglobulinemia, other immune system defects</td>
</tr>
<tr>
<td>IgA deficiency</td>
<td></td>
<td>Decreased IgA</td>
</tr>
<tr>
<td>Severe combined immunodeficiency</td>
<td>XL (HIPM1)</td>
<td>Absent humoral and cellular immune function</td>
</tr>
<tr>
<td>Hyper-IgM syndrome</td>
<td>AD (CXCR4)</td>
<td>Absent IgG, elevated IgM, autoimmune cytopenias</td>
</tr>
<tr>
<td>WHIM syndrome</td>
<td>AR (RMKP)</td>
<td>Warts, hypogammaglobulinemia, infections, myelokathexis</td>
</tr>
<tr>
<td>Cartilage-hair hypoplasia</td>
<td></td>
<td>Lymphopenia, short-limbed dwarfism, metaphyseal chondrodysplasia, fine sparse hair</td>
</tr>
<tr>
<td>Schimke immunoosseous dysplasia</td>
<td>Probable AR (SMARCAL1)</td>
<td>Lymphopenia, pancytopenia, spondyloepiphyseal dysplasia, growth retardation, renal failure</td>
</tr>
<tr>
<td>X-linked agammaglobulinemia</td>
<td>BTK</td>
<td>Agammaglobulinemia, neutropenia in ~25%</td>
</tr>
</tbody>
</table>

AD, autosomal dominant; AML, acute myelogenous leukemia; ANC, absolute neutrophil count; AR, autosomal recessive; HLH, hemophagocytic lymphohistiocytosis; Ig, immunoglobulin; MDS, myelodysplasia; XL, X-linked; BTK, Britton tyrosine kinase.

- phenotype: approximately 90% of patients have mutations identified in the SBDS gene. SDS may progress to bone marrow hypoplasia or to MDS/AML; cytogenetic abnormalities, particularly isochromosome i(7q) and del(20q), often precede conversion to MDS, so bone marrow monitoring is warranted. Treatment includes pancreatic enzyme replacement, plus filgrastim in patients with severe neutropenia.

- **Dyskeratosis congenita**, a disorder of telomerase activity, most often presents as bone marrow failure rather than isolated neutropenia. The classical phenotype also includes nail dystrophy, leukoplakia, malformed teeth, and reticulated hyperpigmentation of the skin, although many patients, particularly young ones, do not exhibit these clinical features.

- **Vesicular Trafficking Disorders.** This group of very rare primary immunodeficiency syndromes (see Table 131-6) derives from autosomal recessive defects in the biogenesis or trafficking of lysosomes and related endosomal organelles. As a result, the syndromes share phenotypic characteristics including defects in melanosomes contributing to partial albinism, abnormal platelet function, and immunologic defects involving not only neutrophil number, but also the function of neutrophils, B lymphocytes, NK cells, and cytotoxic T lymphocytes. The syndromes share a high risk of hemophagocytic lymphohistiocytosis (HLH) as a result of defects in T and NK cells.

- **Chédiak-Higashi syndrome**, best known for the characteristic giant cytoplasmic granules in neutrophils, monocytes, and lymphocytes, is a disorder of subcellular vesicular dysfunction caused by mutations in the LYST gene, with resultant giant granules in all granule-bearing cells. Patients have increased susceptibility to infections, mild bleeding diathesis, progressive peripheral neuropathy, and predisposition to life-threatening HLH. The only curative treatment is hematopoietic stem cell transplantation.

- **Griscelli syndrome type II** also features neutropenia, partial albinism, and a high risk of HLH, but peripheral blood granulocytes do not show giant granules. Patients often have hypogammaglobulinemia. The disorder is caused by mutations in RAB27a, which encodes a small guanosine triphosphatase that regulates granule secretory pathways. The only curative treatment is hematopoietic stem cell transplantation.

- **Disorders of Metabolism.** Recurrent infections with neutropenia are a distinctive feature of glycogen storage disease (GSD).
type Ib. As in classic von Gierke disease (GSDIa), glycogen storage in GSDIb causes massive hepatomegaly and severe growth retardation (see Chapter 87.1). Mutations in glucose-6-phosphate transporter 1, G6PT1, inhibit glucose transport in GSDIb, resulting in both defective neutrophil motility and increased apoptosis associated with neutropenia and recurrent bacterial infections. Treatment with filgrastim can correct the neutropenia but does not correct the underlying functional neutrophil defects.

### Neutropenia in Disorders of Immune Dysfunction

Congenital immunologic disorders that have severe neutropenia as a clinical feature include X-linked agammaglobulinemia, common variable immunodeficiency, the severe combined immunodeficiencies, autoimmunemediated lymphoproliferative syndrome, hyperimmunoglobulin M syndrome, WHIM (warts, hypogammaglobulinemia, infections, myelokathexis) syndrome, and a number of even rarer immunodeficiency disorders (see Table 131-6).

**Unclassified Neutropenic Disorders.** Chronic benign neutropenia of childhood represents a common group of disorders characterized by mild to moderate neutropenia that does not lead to an increased risk of pyogenic infections. Spontaneous remissions are often reported, although these may represent misdiagnosis of AIN of infancy, in which remissions occur commonly during childhood. Chronic benign neutropenia may be sporadic or inherited in either a dominant or recessive form. Because of the relatively low risk of serious infection, patients usually do not require any form of therapy.

Idiopathic chronic neutropenia is characterized by the onset of neutropenia after 2 yr of age, with no identifiable etiology. Patients with an ANC persistently <500/µL may be afflicted with recurrent pyogenic infections involving the skin, mucous membranes, lungs, and lymph nodes. Bone marrow examination reveals variable patterns of myeloid formation with arrest generally occurring between the myelocyte and band forms. The diagnosis overlaps with chronic benign and AINs.

### Treatment

The management of acquired transient neutropenia associated with malignancies, myelosuppressive chemotherapy, or immunosuppressive chemotherapy differs from that of congenital or chronic forms of neutropenia. In the former situation, infections sometimes are heralded only by fever, and sepsis is a major cause of death. Early recognition and treatment of infections may be lifesaving (see Chapter 178). Therapy of severe chronic neutropenia is dictated by the clinical manifestations. Patients with benign neutropenia and no evidence of repeated bacterial infections or chronic gingivitis require no specific therapy. Superficial infections in children with mild to moderate neutropenia may be treated with appropriate oral antibiotics. In patients who have invasive or life-threatening infections, broad-spectrum intravenous antibiotics should be started promptly.

Subcutaneously administered filgrastim can provide effective treatment of severe chronic neutropenia including SCN, chronic symptomatic idiopathic neutropenia, and cyclic neutropenia. Treatment leads to dramatic increases in neutrophil counts, resulting in marked attenuation of infection and inflammation. Doses range from 2-5 µg/kg/day for cyclic, idiopathic, and autoimmune neutropenias, to 10-100 µg/kg/day for SCN. The long-term effects of filgrastim therapy include a propensity for the development of moderate splenomegaly, thrombocytopenia, and, rarely, vasculitis; only patients with SCN are at risk for MDS/AML.

Patients with SCN or SDs who develop MDS or AML respond only to hematopoietic stem cell transplantation; chemotherapy is ineffective. Hematopoietic stem cell transplantation is also the treatment of choice for aplastic anemia or HLH.

### LYMPHOPENIA

The definition of lymphopenia, like neutropenia, is age-dependent and can be from acquired or inherited causes. The absolute lymphocyte count (ALC) is determined by multiplying the total WBC count by the percentage of total lymphocytes. For children younger than 12 mo old, lymphopenia is defined as an ALC <3,000 cells/µL. For older children and adults, an ALC <1,000 cells/µL is considered lymphopenia. In isolation, mild to moderate lymphopenia is generally a benign condition often detected only in the evaluation of other illnesses. However, severe lymphopenia can result in serious, life-threatening illness. Lymphocyte subpopulations can be measured by flow cytometry, which uses the pattern of lymphocyte antigen expression to quantitate and classify T, B, and NK cells.

### Acquired Lymphopenia

Acute lymphopenia is most often a consequence of infection and/or is iatrogenic from lymphocyte-toxic medications and treatments (Table 131-7). Microbial causes include viruses (e.g., respiratory syncytial virus, cytomegalovirus, influenza, measles, and hepatitis) bacterial infections (e.g., tuberculosis, typhoid fever, histoplasmosis, and brucellosis) and malaria. The mechanisms behind infection-associated lymphopenia are not fully elucidated but probably include lymphocyte redistribution and accelerated apoptosis. Corticosteroids are a common cause of medication-induced lymphopenia, as are lymphocyte-specific immunosuppressive agents (e.g., antilymphocyte globulin, alemtuzumab, and rituximab) chemotherapy drugs, and radiation. In most cases, infectious and iatrogenic causes of acute lymphopenia are reversible, although full lymphocyte recovery from chemotherapy and lymphocyte-specific immunosuppressive agents may take several months to years. Prolonged lymphopenia (Table 131-7) may be caused by recurrent infection; persistent infections, mostly notably HIV; malnutrition; mechanical loss of lymphocytes through protein-losing enteropathy or thoracic duct leaks; or systemic diseases such as lupus erythematosus, rheumatoid arthritis, sarcoidosis, renal failure, lymphoma, and aplastic anemia.

### Inherited Lymphopenia

Primary immunodeficiencies and bone marrow failure syndromes are the main cause of inherited lymphopenia in children (see Table 131-7). Primary immunodeficiency may result in a severe quantitative defect, as in X-linked agammaglobulinemia and severe combined immunodeficiency (SCID), or a qualitative or progressive defect as in Wiskott-Aldrich syndrome and common variable immunodeficiency. X-linked agammaglobulinemia is characterized by a near absence of mature B cells because of a mutation in BTK that results in a dysfunctional tyrosine kinase. SCIDs are a genetically heterogenous group of disorders characterized by abnormalities of thymopoiesis and T-cell maturation. Newborn screening for severe T-cell deficiency, via analysis of T-cell receptor excision circles from dried blood spot Guthrie cards, is available in many states to aid in the rapid identification and treatment of infants with SCID and other T-cell disorders. Quantitative defects in lymphocytes can also be appreciated in select forms of inherited bone marrow failure such as reticular dysgenesis, SCN secondary to GFI1 mutation, and dyskeratosis congenita.

**Bibliography** is available at Expert Consult.
Bibliography
Leukocytosis is an elevation in the total leukocyte or white blood cell (WBC) count that is 2 SD above the mean count for a particular age (see Chapter 727). To evaluate the patient with leukocytosis, it is critical to determine which class of WBC is elevated in conjunction with the duration and extent of the leukocytosis. For discussion of WBC elevation caused by immature leukocytes in acute and chronic leukemias, see Chapter 495.

A WBC count exceeding 50,000/µL is termed a leukemoid reaction because of the similarity to some features of leukemia. Leukemoid reactions are usually neutrophilic, and unlike true leukemia, show only small proportions of immature myeloid cells, consisting primarily of band forms, occasional metamyelocytes, and progressively rarer myelocytes, promyelocytes, and blasts. The process is most frequently associated with septicemia and severe bacterial infections, including shigellosis, salmonellosis, and meningococcemia.

A proportion of immature neutrophil cells >5%, termed a left shift, indicates rapid release of cells from the bone marrow, consisting primarily of band forms, which usually constitute 1-5% of circulating neutrophilic cells, or metamyelocytes and myelocytes, which are not usually found in the peripheral circulation. Higher degrees of left shift with more immature neutrophil precursors are indicative of serious bacterial infections and may be a dire sign of depletion of the bone marrow reserve pool of neutrophils. Marked left shift may occasionally be encountered with trauma, burns, surgery, acute hemolysis, or hemorrhage.

**NEUTROPHILIA**

Neutrophilia is an increase in the total number of blood neutrophils that is 2 SD above the mean count for age (see Chapter 727). Elevated absolute neutrophil counts represent disturbances of the normal equilibrium involving bone marrow neutrophil production, movement out of the marrow compartments into the circulation, and neutrophil destruction. Neutrophilia may arise either alone or in combination with enhanced mobilization into the circulating pool from either the bone marrow storage compartment or the peripheral blood maturing pool, by impaired neutrophil egress into tissues, or by expansion of the circulating neutrophil pool secondary to increased granulopoiesis. Myelocytes are not released to the blood except under extreme circumstances.

**Acute Acquired Neutrophilia**

Neutrophilia is usually an acquired, secondary finding associated with inflammation, infection, injury, or stress (Table 132-1). Acute or chronic bacterial infections, trauma, and surgery are among the most common causes encountered in clinical practice. Neutrophilia may also be associated with heatstroke, burns, diabetic ketoacidosis, or any other acute stress. Drugs commonly associated with neutrophilia include epinephrine, corticosteroids, and recombinant growth factors such as recombinant human granulocyte colony-stimulating factor (G-CSF; filgrastim) and recombinant human granulocyte-macrophage colony-stimulating factor.

Epinephrine causes release into the circulation of a sequestered pool of neutrophils that normally mature along the vascular endothelium. Corticosteroids accelerate the release of neutrophils and bands from a large storage pool within the bone marrow and impair the migration of neutrophils from the circulation into tissues. Acute neutrophilia in response to inflammation and infections occurs because of release of neutrophils from the marrow storage pool. The postmitotic marrow neutrophil pools are approximately 10 times the size of the blood neutrophil pool, and about half of these cells are bands and segmented neutrophils. In neutrophil production disorders, such as those associated with malignancies and cancer chemotherapy, the size of this pool may be reduced and the capacity to develop neutrophilia remains impaired. Exposure of blood to foreign substances such as hemodialysis membrane activates the complement system and causes transient neutropenia followed by neutrophilia because of release of bone marrow neutrophils. G-CSF and granulocyte-macrophage colony-stimulating factor cause acute and chronic neutrophilia by mobilizing cells from the marrow reserves and by stimulating neutrophil production.

**Chronic Acquired Neutrophilia**

Chronic acquired neutrophilia is usually associated with continued stimulation of neutrophil production resulting from persistent inflammatory reactions or chronic infections (e.g., tuberculosis), vasculitis, postsplenectomy states, Hodgkin disease, chronic myelogenous leukemia, chronic blood loss, sickle cell disease, some chronic hemolytic anemias, and prolonged administration of corticosteroids (see Table 132-1). Chronic neutrophilia can arise after expansion of cell production secondary to stimulation of cell divisions within the mitotic precursor pool, which consists of promyelocytes and myelocytes. Subsequently, the size of the postmitotic pool increases. These changes lead to an increase in the marrow reserve pool, which can be readily mobilized for release of neutrophils into the circulation. The neutrophil production rate can increase greatly in response to exogenously administered hematopoietic growth factors, such as G-CSF, with a maximum response taking at least 1 wk to develop.

**Lifelong Neutrophilia**

Congenital or acquired asplenia is associated with lifelong neutrophilia. Uncommon genetic disorders that present with neutrophilia include leukocyte function disorders such as leukocyte adhesion deficiencies, periodic fever syndromes. Subsequently, the size of the postmitotic pool increases. These changes lead to an increase in the marrow reserve pool, which can be readily mobilized for release of neutrophils into the circulation. The neutrophil production rate can increase greatly in response to exogenously administered hematopoietic growth factors, such as G-CSF, with a maximum response taking at least 1 wk to develop.

<table>
<thead>
<tr>
<th>Type</th>
<th>Cause</th>
<th>Example</th>
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<td>Acute acquired</td>
<td>Bacterial infections</td>
<td>Burns, diabetic ketoacidosis, heat stroke, postneutropenia rebound, exercise</td>
</tr>
<tr>
<td></td>
<td>Surgery</td>
<td>Corticosteroids, epinephrine, hematopoietic growth factors, lithium</td>
</tr>
<tr>
<td>Chronic acquired</td>
<td>Chronic inflammation</td>
<td>Inflammatory bowel disease, rheumatoid arthritis, vasculitis</td>
</tr>
<tr>
<td></td>
<td>Persistent infection</td>
<td>Tuberculosis</td>
</tr>
<tr>
<td></td>
<td>Persistent stress</td>
<td>Chronic blood loss, hypoxia, sickle cell and other chronic hemolytic anemias</td>
</tr>
<tr>
<td>Drugs</td>
<td>Corticosteroids, lithium; rarely ranitidine, quinidine</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>Postsplenectomy, tumors, Hodgkin disease</td>
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</tr>
</tbody>
</table>

**Table 132-1** Causes of Neutrophilia
Evaluation of persistent neutrophilia requires a careful history, physical examination, and laboratory studies to search for infectious, inflammatory, and neoplastic conditions. The leukocyte alkaline phosphatase score of circulating neutrophils can differentiate chronic myelogenous leukemia, in which the level is uniformly near zero, from reactive or secondary neutrophilia, which feature normal to elevated levels.

**MONOCYTOSIS**

The average absolute blood monocyte count varies with age, which must be considered in the assessment of monocytosis. Given the role of monocytes in antigen presentation and cytokine secretion and as effectors of ingestion of invading organisms, it is not surprising that many clinical disorders give rise to monocytosis (Table 132-2). Most commonly, monocytosis occurs in patients recovering from myelosuppressive chemotherapy and is a harbinger of the return of the neutrophil count to normal. Monocytosis is occasionally a sign of an acute bacterial, viral, protozoal, or rickettsial infection, and may also occur in some forms of chronic neutropenia and postsplenectomy states. Chronic inflammatory conditions can stimulate sustained monocytosis, as can preleukemia, chronic myelogenous leukemia, lymphomas, and occasionally Hodgkin disease.

<table>
<thead>
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<th>CAUSE</th>
<th>EXAMPLE</th>
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</tr>
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<td>Brucellosis, subacute bacterial endocarditis, syphilis, tuberculosis</td>
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<td>Typhoid</td>
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<tr>
<td>Nonbacterial infections</td>
<td>Fungal infections, kala-azar, malaria, Rocky Mountain spotted fever, typhus</td>
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<td>Hematologic disorders</td>
<td>Congenital and acquired neutropenias, hemolytic anemias</td>
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<tr>
<td>Malignant disorders</td>
<td>Acute myelogenous leukemia, chronic myelogenous leukemia, juvenile myelomonocytic leukemia, Hodgkin disease, non-Hodgkin lymphomas, preleukemia</td>
</tr>
<tr>
<td>Chronic inflammatory diseases</td>
<td>Inflammatory bowel disease, polyarteritis nodosa, rheumatoid arthritis, sarcoidosis, systemic lupus erythematosus</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>Cirrhosis, drug reaction, postsplenectomy, recovery from bone marrow suppression</td>
</tr>
</tbody>
</table>

Evaluation of persistent neutrophilia requires a careful history, physical examination, and laboratory studies to search for infectious, inflammatory, and neoplastic conditions. The leukocyte alkaline phosphatase score of circulating neutrophils can differentiate chronic myelogenous leukemia, in which the level is uniformly near zero, from reactive or secondary neutrophilia, which feature normal to elevated levels.

**Lymphocytosis**

The most common cause of lymphocytosis is an acute viral illness, as part of the normal T-cell response to the infection. In infectious mononucleosis, the B cells are infected with the Epstein-Barr virus and the T cells react to the viral antigens present in the B cells, resulting in atypical lymphocytes with characteristic large, vacuolated morphology. Other viral infections classically associated with lymphocytosis are cytomegalovirus and viral hepatitis. Chronic bacterial infections such as tuberculosis and brucellosis may lead to a sustained lymphocytosis. Pertussis is accompanied by marked lymphocytosis in approximately 25% of infants infected before 6 mo of age. Thyrotoxicosis and Addison disease are endocrine disorders associated with lymphocytosis. Persistent or pronounced lymphocytosis suggests acute lymphocytic leukemia.

**Basophilia**

Basophilia is defined as an absolute basophil count >120 cells/µL. Basophilia is a nonspecific sign of a wide variety of disorders and is usually of limited diagnostic importance. Basophilia is most often present in hypersensitivity reactions and frequently accompanies the leukocytosis of chronic myeloid leukemia.

_Bibliography is available at Expert Consult._
Bibliography
Complement (C) was originally defined as the nonspecific, heat-labile complementary principal required with specific antibody to lyse bacteria. The 1st 4 components were numbered in the order of their discovery and are termed the classical pathway. Unfortunately, the components fix to the immune complex in a different order, C1423. Beyond this confusing start, complement is a logical, exquisitely balanced, and highly influential system that is fundamental to the clinical expression of host defense and inflammation. In addition, it is evolutionarily ancient, and as it coevolved with other physiologic systems, it developed the capacity to perform functions beyond just host defense. Among these, it promotes phagocytic removal of dying body cells, molecular debris, and synapses during brain formation. But it can also cause harm and has been implicated in more than 30 illnesses.

The complement system, an essential component of innate immunity, is broadly conceptualized as the classical, lectin, and alternative pathways, which interact and depend on each other for their full activity; the membrane attack complex (C5b6789), formed from activity of any pathway; cell membrane receptors that bind complement components or fragments to mediate complement activity; and a large array of serum and membrane regulatory proteins (Table 133-1).
After C1423, complement nomenclature is logical and consists of only a few rules. Fragments of components resulting from cleavage by other components acting as enzymes are assigned lowercase letters (a, b, c, d, e); with the exception of C2 fragments, the smaller piece that is released into surrounding fluids is assigned the lowercase letter a, and the major part of the molecule, bound to other components or to some part of the immune complex, is assigned letter b—for example, C3a and C3b. Components of the alternative pathway, B and D, have been assigned uppercase letters, as have the control proteins I and H, which downregulate both pathways. C3, and especially its major fragment C3b, is a component of both the classical and alternative pathways.

Complement is a system of interacting proteins. The biologic functions of the system depend on the interactions of individual components, which occur in sequential, cascade fashion. Activation of each component, except the 1st, depends on activation of the prior component or components in the sequence. Interaction occurs along 3 pathways (Fig. 133-2): the classical pathway, in the order antigen–antibody–C142356789; the lectin (carbohydrate-binding) pathway, in the order microbial carbohydrate–lectin (mannose-binding lectin [MBL] or ficolin)–MBL-associated serine protease–C42356789; and the alternative pathway, in the order activator–C3bBD–C56789. Antibody accelerates the rate of activation of the alternative pathway, but activation can occur on appropriate surfaces in the absence of antibody. The classical and the alternative pathways interact with each other through the ability of both to activate C3.

Activation of the early-acting components of complement (C1423) results in the generation of a series of active enzymes, C1, C42, and C423, on the surface of the immune complex or underlying cell. These enzymes cleave and activate the next component in the sequence. In contrast, the interaction among C5b, C6, C7, C8, and C9 is nonenzymatic and depends on changes in molecular configuration.

**CLASSICAL AND LECTIN PATHWAYS**

The classical pathway sequence begins with fixation of C1, by way of C1q, to the Fc, non–antigen-binding part of the antibody molecule after antigen–antibody interaction. The C1 tricomplex changes

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**Figure 133-1** The complement cascade. The classical pathway is activated primarily by antibody while the mannose-binding lectin and alternative pathways are activated directly by pathogens. In each case, the activation arm leads to cleavage of C3. (From Leung DYM, editor: Pediatric allergy principles and practice, ed 2, Philadelphia, 2010, WB Saunders, Fig. 11-1, p. 121.)

**Figure 133-2** Sequence of activation of the components of the classical and lectin pathways of complement and interaction with the alternative pathway. Activation of C3 is the essential target. Functional activities generated during activation are enclosed in boxes. The multiple sites at which inhibitory regulator proteins (not shown) act are indicated by asterisks, emphasizing the delicate balance between action and control in this system that is essential for host defense yet capable of profound damage to host tissues. Ab, antibody (immunoglobulin G or M class); Ag, antigen (bacterium, virus, tumor or tissue cell); B, D, I, P, factors B, D, I, and properdin; C-CRP, carbohydrate–carbohydrate-reactive protein; C4-bp, C4-binding protein; MASP, MBL-associated serine protease; MBL, mannose-binding lectin.
configuration and the C1s subcomponent becomes an active enzyme, “C1 esterase.” Certain bacteria, Mycoplasma, RNA viruses, and the lipid A component of bacterial endotoxin can activate C1q directly and trigger the full complement cascade.

As part of the innate immune response, broadly reactive “natural” antibodies and C-reactive protein, which reacts with carbohydrate from microorganisms and with dying cells, can substitute for specific antibody in the fixation of C1q and initiate reaction of the entire sequence. Endogenous agents, including uric acid crystals, amyloid deposits, DNA, and components of damaged cells such as apoptotic blebs and mitochondrial membranes, can activate C1q directly. But in this case, the ligand–C1q complex interacts strongly with the inhibitors C4-binding protein and factor H, allowing some C3-mediated opsonization and phagocytosis, but limiting the full inflammatory response typically triggered by microbes. C1q synthesized in the brain and retina enables the complement-dependent pruning of synapses that is essential for normal nervous system development.

There are 4 recognition molecules in the lectin pathway: MBL and ficolins 1, 2, and 3. MBL is the prototype of the collectin family of carbohydrate-binding proteins (lectins) that are believed to play an important part in innate, nonspecific immunity; its structure is homologous to that of C1q. These lectins, in association with MBL-associated serine proteases 1, 2, and 3 (MASPs 1/2/3), can bind to mannose, lipoteichoic acid, and other carbohydrates on the surface of bacteria, fungi, parasites, and viruses. MASPs then function there like C1s to cleave C4 and C2 and activate the complement cascade. The peptide C4a has weak “anaphylatoxin” activity and reacts with mast cells to release the chemical mediators of immediate hypersensitivity, including histamine. C3a and C5a, released later in the sequence, are potent anaphylatoxins, and C5a is also an important chemotactic factor. Fixation of C4b to the complex permits it to adhere to neutrophils, macrophages, B cells, dendritic cells, and erythrocytes. MASP-2 can activate clotting by generating thrombin from prothrombin, which could prevent microbial spread.

Cleavage of C3 and generation of C3b is the next step in the sequence. The serum concentration of C3 is the highest of any component, and its activation is the most crucial step in terms of biologic activity. Cleavage of C3 can be achieved through the C3 convertase of the classical pathway, C142, or of the alternative pathway, C3bBb. Once C3b is fixed to a complex or dead or dying host cell, it can bind to cells with receptors for C3b (complement receptor 1 [CR1]), including B lymphocytes, erythrocytes, and phagocytic cells (neutrophils, monocytes, and macrophages). Efficient phagocytosis of most microorganisms in vitro, especially by neutrophils, requires binding of C3 to the microbe. The severe pyogenic infections that commonly occur in C3-deficient patients indicate that phagocytosis in vivo is also inefficient without C3. The biologic activity of C3b is controlled by cleavage by factor I to iC3b, which promotes phagocytosis on binding to the iC3b receptor (CR3) on phagocytes. Further degradation of iC3b by factor I and proteases yields C3dg, then C3d; C3d binds to CR2 on B lymphocytes and thereby serves as a costimulator of antigen-induced B-cell activation.

**ALTERNATIVE PATHWAY**

The alternative pathway can be activated by C3b generated through classical pathway activity or proteases from neutrophils or the clotting system. It can also be activated by a form of C3 created by low-grade, spontaneous reaction of native C3 with a molecule of water, a “tick-over” that occurs constantly in plasma. Once formed, C3b or the hydrolyzed C3 can bind to any nearby cell or to factor B. Factor B attached to C3b in the plasma or on a surface can be cleaved to Bb by the protease factor D. The complex C3bBb becomes an efficient C3 convertase, which generates more C3b through an amplification loop. Properdin can bind to C3bBb, increasing stability of the enzyme and protecting it from inactivation by factors I and H, which modulate the loop and the pathway.

Certain “activating surfaces” promote alternative pathway activation if C3b is fixed to them, including bacterial teichoic acid or endotoxin, virally infected cells, antigen–immunoglobulin A complexes, and cardiopulmonary bypass and renal dialysis membranes. These surfaces act by protecting the C3bBb enzyme from the control otherwise exercised by factors I and H. Rabbit red blood cell membrane is such a surface, which serves as the basis for an assay of serum alternative pathway activity. Sialic acid on the surface of microorganisms or cells prevents formation of an effective alternative pathway C3 convertase by promoting activity of factors I and H. Nevertheless, significant activation of C3 can occur through the alternative pathway, and the resultant biologic activities are qualitatively the same as those achieved through activation by C142 (see Fig. 133-2).

**MEMBRANE ATTACK COMPLEX**

The sequence leading to cytolysis begins with the attachment of C5b to the C5-activating enzyme from the classical pathway, C4b2a3b, or from the alternative pathway, C3bBb3b. C6 is bound to C5b without being cleaved, stabilizing the activated C5b fragment. The C5b6 complex then dissociates from C423 and reacts with C7. C5b67 complexes must attach promptly to the membrane of the parent or a bystander cell, or they lose their activity. Next, C8 binds, and the C5b678 complex then promotes the addition of multiple C9 molecules. The C9 polymer of at least 3-6 molecules forms a transmembrane channel, and lysis ensues.

**CONTROL MECHANISMS**

Without control mechanisms acting at multiple points, there would be no effective complement system, and unbridled consumption of components would generate severe, potentially lethal damage to the host. At the 1st step, C1 inhibitor (C1 INH) inhibits C1r and C1s enzymatic activity and, thus, the cleavage of C4 and C2. C1 INH also inhibits MASP-2, factors Xla and XIIa of the clotting system, and kallikrein of the contact system. Activated C2 has a short half-life, and this relative instability limits the effective life of C42 and C423. The alternative pathway enzyme that activates C3, C3bBb, also has a short half-life, though it can be prolonged by the binding of properdin (P) to the enzyme complex. P can also bind directly to microbes and promote assembly of the alternative pathway C3 convertase.

Serum contains the enzyme carboxypeptidase N, which cleaves the N-terminus arginine from C4a, C3a, and C5a, thereby limiting their biologic activity. Factor I inactivates C4b and C3b; factor H accelerates inactivation of C3b by factor I; and an analogous factor, C4-binding protein (C4-bp), accelerates C4b cleavage by factor I, thus limiting assembly of the C3 convertase. Three protein constituents of cell membranes, CR1, membrane cofactor protein (MCP), and decay-accelerating factor (DAF), promote the disruption of C3 and C5 convertases assembled on those membranes. Another cell membrane-associated protein, CD59, can bind C8 or both C8 and C9 and thereby interfere with insertion of the membrane attack complex (C5b6789). The serum proteins vitronectin and clusterin can inhibit attachment of the C5b67 complex to cell membranes; bind C8 or C9 in a full membrane attack complex, or otherwise interfere with the formation or insertion of this complex. Vitronectin also promotes macrophage uptake of dying neutrophils. The genes for the regulatory proteins factor H, C4-bp, MCP, DAF, CR1, and CR2 are clustered on chromosome 1.

**PARTICIPATION IN HOST DEFENSE**

Neutralization of virus by antibody can be enhanced with C1 and C4 and further enhanced by the additional fixation of C3b through the classical or alternative pathway. Complement may, therefore, be particularly important in the early phases of a viral infection when antibody is limited. Antibody and the full complement sequence can also eliminate infectivity of at least some viruses by the production of typical complement “holes,” as seen by electron microscopy. Fixation of C1q can opsonize (promote phagocytosis) through binding to the C1q receptor.

C4a, C3a, and C5a can bind to mast cells and thereby trigger release of histamine and other mediators, leading to vasodilation and the swelling and redness of inflammation. C5a can enhance macrophage phagocytosis of C3b-opsonized particles and induce macrophages to release the cytokines tumor necrosis factor and interleukin 1. C5a is a major chemotactic factor for neutrophils, monocytes, and eosinophils, which can efficiently phagocytize microorganisms opsonized with C3b.
or cleaved C3b (iC3b). Further inactivation of cell-bound C3b by cleavage to C3d and C3dg removes its opsonizing activity, but it can still bind to B cells. Fixation of C3b to a target cell can enhance its lysis by natural killer cells or macrophages.

Insoluble immune complexes can be solubilized if they bind C3b, apparently because C3b disrupts the orderly antigen-antibody lattice. Binding C3b to a complex also allows it to adhere to C3 receptors (CR1) on red blood cells, which then transport the complexes to hepatic and splenic macrophages for removal. This phenomenon may at least partially explain the immune complex disease found in patients who lack C1, C4, C2, or C3.

The complement system serves to link the innate and adaptive immune systems. C4b or C3b coupled to immune complexes promotes their binding to antigen-presenting macrophages, dendritic cells, and B cells. Coupling of antigen to C3d allows binding to CR2 on B cells, which markedly reduces the amount of antigen needed to trigger an antibody response.

Neutralization of endotoxin in vitro and protection from its lethal effects in experimental animals require C1 INH and later-acting components of complement, at least through C6. Finally, activation of the entire complement sequence can result in lysis of virus-infected cells, tumor cells, and most types of microorganisms. Bactericidal activity of complement has not appeared to be important to host defense, except for the occurrence of Neisseria infections in patients lacking later-acting components of complement (see Chapter 134).

Bibliography is available at Expert Consult.
Bibliography


134.1 Evaluation of the Complement System

Richard B. Johnston Jr.

Testing for total hemolytic complement activity (CH50) effectively screens for most of the common diseases of the complement system. A normal result in this assay depends on the ability of all 11 components of the classical pathway and membrane attack complex to interact and lyse antibody-coated sheep erythrocytes. The dilution of serum that lyses 50% of the cells determines the end point. In congenital deficiencies of C1 through C8, the CH50 value is 0 or close to 0; in C9 deficiency, the value is approximately half-normal. Values in the acquired deficiencies vary with the type and severity of the underlying disorder. This assay does not detect deficiency of mannose-binding lectin (MBL), factors D or B of the alternative pathway, or properdin (Fig. 134-1). Deficiency of factors I or H permits consumption of C3, with partial reduction in the CH50 value. When clotted blood or serum sits at room temperature or warms, CH50 activity begins to decline, which leads to values that are falsely low but not zero. It is important to separate the serum and freeze it at −70°C (−94°F) by no more than 1 hr after blood draw.

In hereditary angioedema, depression of C4 and C2 during an attack significantly reduces the CH50. Typically, C4 is low and C3 normal or slightly decreased. Concentrations of C1 inhibitor protein will be normal in 15% of cases; but C1 acts as an esterase, and the diagnosis can be established by showing increased capacity of patients’ sera to hydrolyze synthetic esters.

A decrease in serum concentration of both C4 and C3 suggests activation of the classical pathway by immune complexes. Decreased C3 and normal C4 levels suggest activation of the alternative pathway. This difference is particularly useful in distinguishing nephritis secondary to immune complex deposition from that caused by NeF (nephritic factor). In the latter condition and in deficiency of factor I or H, factor B is consumed and C3 serum concentration is low. Alternative pathway activity can be measured with a relatively simple and reproducible hemolytic assay that depends on the capacity of rabbit erythrocytes to serve as both an activating (permissive) surface and a target of alternative pathway activity. This assay (AP50) detects deficiency of properdin, factor D, and factor B. Immunochemical methods can be used to quantify individual components of all 3 pathways, guided by results of the screening hemolytic assays. It is possible to analyze the genes encoding most of the components.

A defect of complement function should be considered in any patient with recurrent angioedema, autoimmune disease (especially systemic lupus erythematosus [SLE]), chronic nephritis, hemolytic-uremic syndrome, or partial lipodystrophy, or with recurrent pyogenic infections, disseminated meningococcal or gonococcal infection, or a second episode of bacteremia at any age. A previously well adolescent or young adult with meningococcal meningitis caused by an uncommon serotype (not A, B, or C) should undergo screening for a late-component or alternative pathway deficiency with CH50 and AP50 assays.

Bibliography is available at Expert Consult.

134.2 Genetic Deficiencies of Complement Components

Richard B. Johnston Jr.

Congenital deficiencies of all 11 components of the classical-membrane attack pathway and of factor D and properdin of the alternative pathway are described in Table 134-1. All of the components of the
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C1q deficiency represents absence of both gene products. Complete deficiency of only C4A, present in approximately 1% of the population, also predisposes to SLE, although C4 levels are only partially reduced. Patients with only C4B deficiency may be predisposed to infection. A few patients with C5, C6, C7, or C8 deficiency have SLE, but recurrent meningococcal infections are much more likely to be the major problem.

There are at least 2 possible reasons for the concurrence of complement component deficiencies, especially C1r, C1s, combined C1r/C1s, C4, C2, or C3 deficiency also have a high incidence of autoimmune syndromes (see Table 134-1), especially SLE or an SLE-like syndrome without an elevated antinuclear antibody level.

Classical and alternative pathways except properdin are inherited as autosomal recessive codominant traits. Each parent transmits a gene that codes for synthesis of half the serum level of the component. Deficiency results from inheritance of 1 null gene from each parent; the hemizygous parents typically have low normal CH50 levels and no consequences of the partial deficiency. Properdin deficiency is transmitted as an X-linked trait.

Most patients with primary C1q deficiency have SLE; some have an SLE-like syndrome without typical SLE serology, a chronic rash with underlying vasculitis, or membranoproliferative glomerulonephritis (MPGN). Some C1q-deficient children have serious infections, including septicemia and meningitis. Individuals with C1r, C1s, combined C1r/C1s, C4, C2, or C3 deficiency also have a high incidence of autoimmune syndromes (see Table 134-1), especially SLE or an SLE-like syndrome without an elevated antinuclear antibody level.
 Individuals with C2 deficiency carry the risk of life-threatening septicemic illnesses, most commonly caused by pneumococci. However, most have not had problems with increased susceptibility to infection, presumably because of the protective function of the alternative pathway. The genes for C2, factor B, and C4 are situated close to each other on chromosome 6, and a partial depression of factor B levels can occur in conjunction with C2 deficiency. Persons with a deficiency of both proteins may be at particular risk.

Because C3 can be activated by C1r2 or by the alternative pathway, a defect in the function of either pathway can be compensated for, at least to some extent. Without C3, however, opsonization of bacteria is inefficient, and the chemotactic fragment from C5 (C5a) is not generated. Some organisms must be well opsonized in order to be cleared, and genetic C3 deficiency has been associated with recurrent, severe pyogenic infections caused by pneumococci, *Haemophilus influenzae*, and meningococci.

More than half of the individuals reported to have congenital C5, C6, C7, or C8 deficiency have had meningococcal meningitis or extragenital gonococcal infection. Patients with C9 deficiency, which is most often reported in individuals of Japanese descent, retain about one-third normal CH50 titers; some of these patients have also had *Neisseria* disease. In studies of patients 10 yr of age and older with systemic meningococcal disease, 3-15% have had a genetic deficiency of C5, C6, C7, C8, C9, or C9r. Among patients with infections caused by the uncommon *Neisseria meningitidis* serogroups (X, Y, Z, W135, 29E, or nongroupable; not A, B, or C), 33-45% have an underlying complement deficiency. It is not clear why patients with a deficiency of 1 of the late-acting components suffer a particular predisposition to Neisseria infections. It may be that serum bacteriolysis is uniquely important in defense against this organism. Many persons with such a deficiency have no significant illness.

A few individuals have been identified with deficiency of factor D of the alternative pathway, all with recurrent infections, most often neisserial. Hemolytic complement activity and C3 levels in their serum were normal, but alternative pathway activity was markedly deficient or absent.

Mutations in the structural gene encoding MBL or polymorphisms in the promoter region of the gene result in pronounced interindividual variation in the level of circulating MBL. More than 90% of individuals with MBL deficiency do not express a predisposition to infection. Those with a very low level of MBL have a predisposition to recurrent respiratory infections in infancy and to serious pyogenic and fungal infections if there is another underlying defect of host defense. MBL-associated serine protease (MASP)-2 deficiency has been reported with SLE-like symptoms and recurrent pneumococcal pneumonia. Homozygous ficolin-3 deficiency is associated with repeated pneumonia since early childhood, cerebral abscesses, and bronchiectasis.

**Bibliography is available at Expert Consult.**

### 134.3 Deficiencies of Plasma, Membrane, or Serosal Complement Control Proteins

**Richard B. Johnston Jr.**

Congenital deficiencies of 5 plasma complement control proteins have been described (see Table 134-1). Factor I deficiency was reported originally as a deficiency of C3 resulting from hypercatabolism. The first patient described had suffered a series of severe pyogenic infections similar to those associated with agammaglobulinemia or congenital deficiency of C3. Factor I is an essential regulator of both pathways. Its deficiency permits prolonged existence of C3b as a part of the C3 convertase of the alternative pathway, C3bBb. This results in constant activation of the alternative pathway and cleavage of more C3 to C3b, in circular fashion. Intravenous infusion of plasma or purified factor I induced a prompt rise in serum C3 concentration in the patient and a return to normal of in vitro C3-dependent functions such as opsonization.

The effects of factor H deficiency are like those of factor I deficiency because factor H also assists in dismantling the alternative pathway C3 convertase. A trigger event such as infection initiates uninhibited continuous activation of the alternative pathway, which consumes C3, factor B, total hemolytic activity, and alternative pathway activity. Patients have sustained systemic infections due to pyogenic bacteria, particularly *N. meningitidis*. Many have had glomerulonephritis or atypical hemolytic uremic syndrome (aHUS) (see Chapter 518). Mutations in genes encoding membrane cofactor protein (MCP; CD46), factors I or B, C3, or the endothelial antiinflammatory protein thrombomodulin, or autoantibodies to factors H or B, also are associated with aHUS. The majority of patients with factor I deficiency and aHUS, typically younger than 2 yr of age, develop end-stage renal disease or die. The few patients thus far reported as having C4-binding protein deficiency have approximately 25% of the normal levels of the protein and no typical disease presentation, although 1 had angioedema and Behçet disease.

Persons with properdin deficiency have a striking predisposition to *N. meningitidis* meningitis. All reported patients have been male. The predisposition to infection in these patients demonstrates clearly the need for the alternative pathway in defense against bacterial infection. Serum hemolytic complement activity is normal in these patients, and if the patient has specific antibacterial antibody from immunization or prior exposure, the need for the alternative pathway and properdin is greatly reduced. Several patients have had dermal vasculitis or discoid lupus.

Hereditary angioedema occurs in persons unable to synthesize normal levels of active C1 inhibitor (C1 INH). In 85% of affected families, the patient has markedly reduced concentrations of inhibitor, averaging 30% of normal; the other 15% have normal or elevated concentrations of an immunologically cross-reacting but nonfunctional protein. Both forms of the disease are transmitted as autosomal dominant traits. C1 INH suppresses the complement proteases C1r and MASP-2 and the activated proteases of the contact and fibrinolysis systems. In doing so, C1 INH is consumed as a “suicide inhibitor.” In the absence of full C1 INH function, activation of any of these proteases tips the balance toward the protease. This activation leads to uncontrolled C1 and kallikrein activity with breakdown of C4 and C2 and release of bradykinin, which interacts with vascular endothelial cells to cause vasodilation, which produces localized, nonpitting edema. The biochemical triggers that induce attacks of angioedema in these patients are not well understood.

Swelling of the affected part progresses rapidly, without urticaria, itching, discoloration, or redness and often without severe pain. Swelling of the intestinal wall, however, can lead to intense abdominal cramping, sometimes with vomiting or diarrhea. Concomitant subcutaneous edema is often absent, and patients have undergone abdominal surgery or psychiatric examination before the true diagnosis was established. Laryngeal edema can be fatal. Attacks last 2-3 days and then gradually abate. They may occur at sites of trauma, especially dental, after vigorous exercise, or with menses, fever, or emotional stress. Attacks begin in the 1st yr of life in almost half of patients, but are usually not severe until late childhood or adolescence. Acquired C1 INH deficiency can occur in association with B-cell cancer or autoantibody to C1 INH. SLE and glomerulonephritis have been reported in patients with the congenital disease.

Three of the membrane complement control proteins—CR1, MCP (CD46), and decay-accelerating factor (DAF)—prevent the formation of the full C3-cleaving enzyme, C3bBb, which is triggered by C3b deposition. CD59 (membrane inhibitor of reactive lysis) prevents the full development of the membrane attack complex that creates the “hole.” Paroxysmal nocturnal hemoglobinuria (PNH) is a hemolytic anemia that occurs when DAF and CD59 are not expressed on the erythrocyte surface. The condition is acquired as a somatic mutation in a hematopoietic stem cell of the PIG-A gene on the X chromosome. The product of this gene is required for normal synthesis of a
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Circulating immune complexes and decreased C3 have been reported. Complementemia secondary to activation of the classical pathway may occur in the syndrome of recurrent urticaria, angioedema, eosinophilia, and hypokidneys and skin; depressed synthesis of C3 is also noted. The synthesis of chemotactic activity in serum from full-term newborns is depressed in these conditions, and serum from some patients with combined immunodeficiency disease or hypogammaglobulinemia, apparently secondary to the deficiency of immunoglobulin (Ig) G, which normally binds reversibly to C1q and prevents its rapid catabolism.

Partial deficiency of C1q has occurred in patients with severe combined immunodeficiency disease or hypogammaglobulinemia, apparently secondary to the deficiency of immunoglobulin (Ig) G, which normally binds reversibly to C1q and prevents its rapid catabolism.

Chronic MPGN can be caused by NeF, an IgG autoantibody to the C3–cleaving enzyme of the alternative pathway, C3bBb, which protects the enzyme from inactivation and promotes over activation of the alternative pathway. The result is increased consumption of C3 and decreased concentration of serum C3. Pyogenic infections, including meningitis, may occur if the serum C3 level drops to <10% of normal. This disorder has been found in children and adults with partial lipodystrophy. Adipocytes are the main source of factor D and synthesize C3 and factor B; exposure to NeF induces their lysis. An IgG NeF that binds to and inhibits the C422, the classical pathway C3 convertase, has been described in acute postinfectious nephritis and in SLE. The consumption of C3 that characterizes poststreptococcal nephritis and SLE could be caused by this factor, by complement activation by immune complexes, or by both.

Newborn infants have mild to moderate reductions in all plasma components of the complement system. Opsonization and generation of chemotactic activity in serum from full-term newborns can be markedly deficient through either the classical or alternative pathway. Complement activity is even lower in preterm infants. Patients with severe chronic cirrhosis of the liver, hepatic failure, malnutrition, or anorexia nervosa can have significant deficiency of complement components and functional activity. Synthesis of components is depressed in these conditions, and serum from some patients with malnutrition also contains immune complexes that could accelerate depletion.

Patients with sickle cell disease have normal activity of the classical pathway, but some have defective function of the alternative pathway in opsonization of pneumococci, in bacteriolysis and opsonization of Salmonella, and in lysis of rabbit erythrocytes. Deoxygenation of erythrocytes from patients with sickle cell disease alters their membranes to increase exposure of phospholipids that can activate the alternative pathway and consume its components. This activation is accentuated during painful crisis. Children with nephrotic syndrome may have decreased serum levels of factors B and D and subnormal serum opsonizing activity.

Immune complexes initiated by microorganisms or their by-products can induce complement consumption. Activation occurs primarily through fixation of C1 and initiation of the classical pathway. Formation of immune complexes and consumption of complement have been demonstrated in lepromatous leprosy, bacterial endocarditis, infected ventriculojugular shunts, malaria, infectious mononucleosis, dengue hemorrhagic fever, and acute hepatitis B. Nephritis or arthritides can develop as a result of deposition of immune complexes and activation of complement in these infections. In SLE, immune complexes activate C142, and C3 is deposited at sites of tissue damage, including kidneys and skin; depressed synthesis of C3 is also noted. The syndrome of recurrent urticaria, angioedema, eosinophilia, and hypocomplementemia secondary to activation of the classical pathway may be due to autoantibody to C1q and circulating immune complexes. Circulating immune complexes and decreased C3 have been reported in some patients with dermatitis herpetiformis, celiac disease, primary biliary cirrhosis, and Raye syndrome.
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patient and close household contacts should be immunized against *H. influenzae*, *Streptococcus pneumoniae*, and *N. meningitidis*. High titers of specific antibody might opsonize effectively without the full complement system, and immunization of household members could reduce the risk of exposing patients to these particularly threatening pathogens. Repeat immunization of patients is advisable since complement deficiency can be associated with a blunted or shorter-lived antibody response than normal.

Considering the many conditions in which complement is a central mediator of disease, there is an intensive effort to develop therapeutic complement inhibitors. These include soluble CR1 and inhibitors of C5 convertase and C3a and C5a binding. Heparin, which inhibits both classical and alternative pathways, has been used to prevent “post-pump syndrome.”

_Bibliography is available at Expert Consult._
Bibliography
Protocols for allogeneic HSCT consist of 2 parts: the preparative regimen and transplantation itself. During the preparative conditioning regimen, chemotherapy, often associated with irradiation, is administered to destroy the patient's hematopoietic system and to suppress the immune system, especially T cells, so that graft rejection is prevented. In patients with malignancies, the preparative regimen also serves to significantly reduce the tumor burden. The patient then receives an intravenous infusion of hematopoietic cells from the donor. Less-aggressive conditioning regimens, known as reduced intensity conditioning regimens, are also used in pediatric patients. These regimens are mainly immune-suppressive and aim at inducing a state of reduced immune competence of the recipient permitting to avoid the rejection of donor cells.

The immunology of HSCT is distinct from that of other types of transplant because, in addition to stem cells, the graft contains mature blood cells of donor origin, including T cells, B cells, natural killer cells, and dendritic cells. These cells repopulate the recipient's lymphohematopoietic system and give rise to a new immune system, which helps eliminate residual leukemia cells that survive the conditioning regimen. This effect is known as the graft-versus-leukemia (GVL) effect.

The donor immune system exerts its T-cell-mediated GVL effect through alloreactions directed against not shared recipient histocompatibility antigens displayed on recipient leukemia cells. Because some of these histocompatibility antigens are also displayed on tissues, however, T-cell-mediated alloreactions may ensue. Specifically, donor alloreactive cytotoxic CD8+ effector T cells may attack recipient tissues—in particular, the skin, gastrointestinal tract, and liver—causing acute graft-versus-host disease (GVHD), a condition of varying severity, that, in some cases, can be life-threatening or even fatal (see Chapter 137). Although the main benefit for allogeneic HSCT recipients with leukemia derives from the GVL effect displayed by immune-competent cells, disease recurrence remains the main cause of treatment failure. The risk of failing to eradicate leukemia is influenced by many variables, including disease phase, molecular lesions of tumor cells, and disparity for major or minor histocompatibility antigens in the donor/recipient pairs. Strategies for rescuing patients experiencing disease recurrence are mainly based on either second transplantation or infusion of donor leukocytes. To overcome the hurdle of tumor elusion caused by HLA-loss on malignant cells, the use of non-HLA–restricted chimeric antigen receptors (CARs) has been envisaged. This therapeutic strategy is based on genetic reprogramming of T cells through artificial immune receptors that reproducibly and efficiently redirect the antigen specificity of polyclonal T lymphocytes toward target antigens expressed by leukemic cells. When expressed by T cells, CARs mediate antigen recognition and tumor cytolysis in an major histocompatibility complex (MHC)—unrestricted fashion, and can target any molecule (protein, carbohydrate, or glycolipid) expressed on the surface of tumor cells, thus bypassing one of the major tumor escape mechanisms based on the down regulation of MHC molecules. CARs are composed of an extracellular specific antigen-binding moiety, obtained from the variable regions of a monoclonal antibody, linked together to form a single-chain antibody (scFv), and of an intracellular signaling component derived from the ζ chain of the T-cell–receptor–CD3 complex. The addition to the CAR gene construct of costimulation signals and cytokines promoting T-cell expansion and/or survival improves the antitumor efficiency of the engineered T cells and their survival in the tumor milieu. Gamma retrovirus and lentiviruses are usually used to transduce CARs into T lymphocytes to be employed in the clinical setting. These vectors have been shown to efficiently infect T lymphocytes, integrate into the host genome and produce robust expression of the gene in human T cells and their progeny.

The success of allogeneic HSCT is undermined by diversity between donors and recipients in major and minor histocompatibility antigens. MHC molecules, the HLA-A, HLA-B, and HLA-C MHC class I molecules, present peptides to CD8+ T cells, while the HLA-DR, HLA-DQ, and HLA-DP MHC class II molecules present peptides to CD4+ T cells. There are hundreds of variant forms of each class I and class II molecule, and even small differences can elicit alloreactive T-cell
responses that mediate graft rejection and/or GVHD. Disparities for HLA-A, -B, -C, or -DRB1 alleles in the donor–recipient pair are independent risk factors for both acute and chronic GVHD.

Minor histocompatibility antigens derive from differences between the HLA-matched recipient and donor in peptides that are presented by the same HLA allotype. They are a result of polymorphisms of non-HLA proteins, of differences in the level of expression of proteins, or of genetic differences between males and females. An example of the latter is represented by the H-Y antigens encoded by the Y chromosome, which can stimulate GVHD when a female donor is employed to transplant an HLA-identical male recipient. Thus, from this evidence, it is clear that GVHD may occur even when the donor and recipient are HLA identical.

The optimal donor for any patient undergoing HSCT is an HLA-identical sibling. Because polymorphic HLA genes are closely linked and usually constitute a single genetic locus, any pair of siblings has a 25% chance of being HLA identical. Thus, also in view of the limited family size in the developed countries, less than 25-30% of patients in need of an allograft can receive their transplant from an HLA-identical sibling. This percentage is even lower in patients with inherited disorders.

HEMATOPOIETIC STEM CELL TRANSPLANTATION FROM AN HLA-IDENTICAL SIBLING DONOR

Allogeneic HSCT from an HLA-compatible sibling is the treatment of choice for children with hematologic malignancies and congenital diseases (Table 135-1). Best results are achieved in patients with congenital or acquired non-malignant disorders because the risk of disease recurrence is low and the cumulative transplantation-related mortality is lower than in children receiving transplants for hematologic malignancies.

ACUTE LYMPHOBLASTIC LEUKEMIA

Allogeneic HSCT is used for pediatric patients with acute lymphoblastic leukemia (ALL), either in the first complete remission when a child is considered to be at high risk of leukemia recurrence (such as, e.g., those carrying poor-risk cytogenetic characteristics or with high levels of minimal residual disease), or in second or further complete remission after previous marrow relapse. ALL is the most common indication for HSCT in childhood. Several patient-, donor-, disease-, and transplant-related variables may influence the outcome of patients with ALL given an allogeneic HSCT. The long-term probabilities of event-free survival for patients with ALL transplanted in the 1st or 2nd complete remission is 60–70% and 40–60%, respectively. Inferior results are obtained in patients receiving transplants in more advanced disease phases. The use of radiotherapy, total body irradiation, during the preparative regimen offers an advantage in terms of better event-free survival for patients with ALL transplanted during the chronic phase from an HLA-identical sibling. This percentage is even lower in patients with inherited disorders.

ACUTE MYELOID LEUKEMIA

Allogeneic HSCT from an HLA-identical sibling is largely employed as postremission treatment of pediatric patients with acute myeloid leukemia (AML). In fact, many studies show that children with AML in 1st complete remission who are given allogeneic HSCT as consolidation therapy have a better probability of event-free survival than those treated with either chemotherapy alone or with autologous transplantation. Results obtained in patients given HSCT from an HLA-identical sibling after either a total body irradiation–containing or a chemotherapy-based preparative regimen are similar, the probability of event-free survival being in the order of 70%. Children with acute promyelocytic leukemia in molecular remission at the end of treatment with chemotherapy and all-trans-retinoic acid, or with AML and either translocation t(8;21) or inversion of chromosome 16 (inv16) are no longer considered eligible for allogeneic HSCT in 1st complete remission in view of their excellent prognosis with alternative treatments. Studies suggest restricting the use of HSCT to those patients with poor molecular lesions, such as FLT3-internal tandem duplication, or mixed lineage leukemia abnormalities, or with high levels of minimal residual disease at time the end of induction therapy. Approximately 40% of pediatric patients with AML in the second complete remission can be rescued by an allograft from an HLA-identical sibling.

CHRONIC MYELOGENOUS LEUKEMIA

For many yr, allogeneic HSCT has been considered to be the only proven curative treatment for children with Philadelphia-positive (Ph+) chronic myelogenous leukemia. Leukemia-free survival of chronic myelogenous leukemia patients after an allograft is 45-80%, the phase of disease (chronic phase, accelerated phase, blast crisis), recipient age, type of donor employed (either related or unrelated), and time interval between diagnosis and HSCT being the main factors influencing the outcome. The best results are obtained in children transplanted during the chronic phase from an HLA-identical sibling within 1 year from diagnosis. Treatment with the specific BCR-ABL tyrosine protein kinase inhibitors (imatinib mesylate, dasatinib,
patients transplanted from an alternative donor is slightly lower. It is still unclear whether patients with myelodysplastic syndromes and a blast percentage >20% benefit from pretransplantation chemotherapy. HSCT from an HLA-identical sibling is also the preferred treatment for all children with refractory cytopenia. Transplantation from an alternative donor is also employed in children with refractory cytopenia associated with monosomy 7, complex karyotype, life-threatening infections, profound neutropenia, or transfusion-dependency. For children with refractory cytopenia, the probability of event-free survival after HSCT may be as high as 80%, disease recurrence being rarely observed. This observation has provided the rationale for testing reduced-intensity regimens in these patients.

NON-HODGKIN LYMPHOMA AND HODGKIN DISEASE

Childhood non-Hodgkin lymphoma (NHL) and Hodgkin disease (HD) are quite responsive to conventional chemoradiotherapy, but some of these patients are at high risk for relapse. HSCT can cure a proportion of patients with relapsed NHL and HD and should be offered early after relapse, while the disease is still sensitive to therapy. If an HLA-identical sibling is available, allogeneic transplantation should be offered to patients with NHL to take advantage of the GVL effect. Patients with sensitive disease and limited tumor burden have favorable outcomes, with event-free survival rates of 50-60%. Studies also suggest that patients with HD can benefit from a GVL effect when given an allograft.

ACQUIRED APLASTIC ANEMIA

HSCT from an HLA-identical sibling is the treatment of choice for children with the severe form of acquired aplastic anemia, defined as 2 of the following: platelet count <20,000/mm³, absolute neutrophil count <500/mm³, or reticulocyte count <1% when anemia is present, together with hypoplastic bone marrow (<20% total cellularity). The probability of survival with sustained donor engraftment for these patients is <85-90%, younger patients having even better outcomes. Every child diagnosed with severe acquired aplastic anemia should undergo HLA-typing as early as possible in order to identify a suitable HLA-compatible family donor. Graft rejection represents the most important cause of treatment failure. Blood transfusion should be avoided whenever possible because sensitization to blood products increases the likelihood of graft rejection. GVHD prophylaxis combining cyclosporine and short-term methotrexate is associated with a better outcome as compared to cyclosporine alone (Fig. 135-2). Some studies suggest that the addition of antithymocyte globulin to the classical conditioning regimen consisting of cyclophosphamide (200 mg/kg) can reduce the risk of graft rejection, particularly in patients with previous heavy sensitization to blood products. The use of granulocyte colony-stimulating factor mobilized peripheral blood progenitors has provided inferior results with respect to the infusion of bone marrow cells, since it is associated with an increased risk of chronic GVHD.

CONSTITUTIONAL APLASTIC ANEMIA

Fanconi anemia and dyskeratosis congenita are genetic disorders associated with a high risk of developing pancytopenia. Fanconi anemia is an autosomal recessive disease characterized by spontaneous chromosomal fragility, which is increased after exposure of peripheral blood lymphocytes to DNA crosslinking agents, including clastogenic compounds, such as diepoxybutane, mitomycin C, and melphalan. Patients with Fanconi anemia, besides being at risk of pancytopenia, show a high propensity to develop clonal disorders of hematopoiesis, such as myelodysplastic syndromes and AML. HSCT can rescue aplastic anemia and prevent the occurrence of clonal hematopoietic disorders. In view of their defects in DNA repair mechanisms, which are responsible for the chromosomal fragility, Fanconi anemia patients have an exquisite sensitivity to alkylating agents. Thus, they must be prepared for the allograft with reduced doses of cyclophosphamide. Many patients were once successfully transplanted after receiving low-dose cyclophosphamide and thoracoabdominal irradiation. However, the use of this regimen is associated with an increased incidence of nilotinib), targeting the enzymatic activity of the BCR-ABL fusion protein, could modify the natural history of the disease and, thus, the indications for transplantation. Infusion of donor leukocytes can re-induce a state of complete remission in a large proportion of patients experiencing leukemia relapse.

JUVENILE MYELOMONOCYTIC LEUKEMIA

This is a rare hematopoietic malignancy of early childhood, representing 2–3% of all pediatric leukemias. Juvenile myelomonocytic leukemia (JMML) is characterized by ineffective hematopoiesis leading to peripheral organ infiltration, with excessive proliferation of cells of monocytic and granulocytic lineages. Hypersensitivity to granulocyte-macrophage colony-stimulating factor and pathologic activation of the RAS-RAF-MAP (mitogen-activated protein) kinase signaling pathway play an important role in the pathophysiology. JMML usually runs an aggressive clinical course, with a median duration of survival for untreated children of <12 mo from diagnosis. Rare patients with CBL-1 or N-RAS mutations can survive for years without an allograft. HSCT is able to cure approximately 50-60% of patients with JMML. Patients who receive a transplant from an unrelated donor have comparable outcome to those given HSCT from an HLA-compatible related donor. Cord blood transplantation represents a suitable alternative option for those patients with either a related or an unrelated donor. Leukemia recurrence is the main cause of treatment failure in children with JMML after HSCT, the relapse rate being as high as 40-50%. Because children with JMML frequently have massive spleen enlargement, splenectomy has been performed before transplantation. Spleen size at the time of HSCT and splenectomy before HSCT do not appear to affect the post-transplantation outcome. Although donor leukocyte infusion is not effective whenever possible because sensitization to blood products increases the likelihood of graft rejection, GVHD prophylaxis combining cyclosporine and short-term methotrexate is associated with a better outcome as compared to cyclosporine alone (Fig. 135-2). Some studies suggest that the addition of antithymocyte globulin to the classical conditioning regimen consisting of cyclophosphamide (200 mg/kg) can reduce the risk of graft rejection, particularly in patients with previous heavy sensitization to blood products. The use of granulocyte colony-stimulating factor mobilized peripheral blood progenitors has provided inferior results with respect to the infusion of bone marrow cells, since it is associated with an increased risk of chronic GVHD.

MYELODYSPlastic SYNdromes OTHER THAN JUVENILE MYELOMONOCYTIC LEUKEMIA

Myelodysplastic syndromes are a heterogeneous group of clonal disorders characterized by ineffective hematopoiesis leading to peripheral blood cytopenia and a propensity to evolve toward AML. HSCT is the treatment of choice for children with refractory anemia with excess of blasts (RAEB) and for those with RAEB in transformation (RAEB-t). The probability of survival without evidence of disease for these children is 60% if the donor is an HLA-identical sibling, whereas that of patients transplanted from an alternative donor is slightly lower. It is still unclear whether patients with myelodysplastic syndromes and a blast percentage >20% benefit from pretransplantation chemotherapy. HSCT from an HLA-identical sibling is also the preferred treatment for all children with refractory cytopenia. Transplantation from an alternative donor is also employed in children with refractory cytopenia associated with monosomy 7, complex karyotype, life-threatening infections, profound neutropenia, or transfusion-dependency. For children with refractory cytopenia, the probability of event-free survival after HSCT may be as high as 80%, disease recurrence being rarely observed. This observation has provided the rationale for testing reduced-intensity regimens in these patients.

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HSCT from an HLA-identical sibling is the treatment of choice for children with the severe form of acquired aplastic anemia, defined as 2 of the following: platelet count <20,000/mm³, absolute neutrophil count <500/mm³, or reticulocyte count <1% when anemia is present, together with hypoplastic bone marrow (<20% total cellularity). The probability of survival with sustained donor engraftment for these patients is <85-90%, younger patients having even better outcomes. Every child diagnosed with severe acquired aplastic anemia should undergo HLA-typing as early as possible in order to identify a suitable HLA-compatible family donor. Graft rejection represents the most important cause of treatment failure. Blood transfusion should be avoided whenever possible because sensitization to blood products increases the likelihood of graft rejection. GVHD prophylaxis combining cyclosporine and short-term methotrexate is associated with a better outcome as compared to cyclosporine alone (Fig. 135-2). Some studies suggest that the addition of antithymocyte globulin to the classical conditioning regimen consisting of cyclophosphamide (200 mg/kg) can reduce the risk of graft rejection, particularly in patients with previous heavy sensitization to blood products. The use of granulocyte colony-stimulating factor mobilized peripheral blood progenitors has provided inferior results with respect to the infusion of bone marrow cells, since it is associated with an increased risk of chronic GVHD.

CONSTITUTIONAL APLASTIC ANEMIA

Fanconi anemia and dyskeratosis congenita are genetic disorders associated with a high risk of developing pancytopenia. Fanconi anemia is an autosomal recessive disease characterized by spontaneous chromosomal fragility, which is increased after exposure of peripheral blood lymphocytes to DNA crosslinking agents, including clastogenic compounds, such as diepoxybutane, mitomycin C, and melphalan. Patients with Fanconi anemia, besides being at risk of pancytopenia, show a high propensity to develop clonal disorders of hematopoiesis, such as myelodysplastic syndromes and AML. HSCT can rescue aplastic anemia and prevent the occurrence of clonal hematopoietic disorders. In view of their defects in DNA repair mechanisms, which are responsible for the chromosomal fragility, Fanconi anemia patients have an exquisite sensitivity to alkylating agents. Thus, they must be prepared for the allograft with reduced doses of cyclophosphamide. Many patients were once successfully transplanted after receiving low-dose cyclophosphamide and thoracoabdominal irradiation. However, the use of this regimen is associated with an increased incidence of
posttransplantation head and neck cancers. Either reduced doses of cyclophosphamide alone or low-dose cyclophosphamide with fludara- bine are currently employed for preparing Fanconi anemia patients to the allograft. Using these regimens, the success rate of HSCT from an HLA-identical sibling is on the order of 70-80%. Results of unrelated donor allograft have markedly improved over time and rival with those obtained using an HLA-identical sibling donor.

Allogeneic HSCT remains the only potentially curative approach for severe bone marrow failure associated with dyskeratosis congenita, a rare congenital syndrome characterized also by atrophy and reticular pigmentation of the skin, nail dystrophy, and leukoplakia of mucous membranes. Results of allograft in these patients have been relatively poor, due to occurrence of both early and late complications, reflecting increased sensitivity of endothelial cells to radiotherapy and alkylating agents.

THALASSEMIA
Conventional treatment (i.e., regular blood transfusion and iron- chelation therapy) has dramatically improved both the survival and quality of life of patients with thalassemia, changing a previously fatal disease with early death to a chronic, slowly progressive disease compatible with prolonged survival. However, HSCT remains the only curative treatment for patients with thalassemia. In patients with thalassemia, the risk of dying from transplant-related complications is primarily dependent on patient age, iron overload, and concomitant hepatic viral infections. Adults, especially when affected by chronic active hepatitis, have a poorer outcome than children. Among children, 3 classes of risk have been identified on the basis of 3 parameters, namely regularity of previous iron chelation, liver enlargement, and presence of portal fibrosis. In pediatric patients without liver disease who have received regular iron chelation (class 1 patients), the probability of survival with transfusion independence is >90%, whereas for patients with low compliance with iron chelation and signs of severe liver damage (class 3 patients), the probability of survival is 60% (Fig. 135-3). As in other nonmalignant disorders the most effective pharmacologic combinations (such as that including cyclosporine and methotrexate) should be employed to prevent GVHD. The outcome of patients transplanted from an unrelated donor has been reported to be similar to that of HLA-identical sibling recipients.

SICKLE CELL DISEASE
Disease severity varies greatly among patients with sickle cell disease, with 5-20% of the overall population suffering significant morbidity from vasoocclusive crises and pulmonary, renal, or neurologic damage. Despite the fact that hydroxyurea, an agent favoring the synthesis of fetal hemoglobin, reduces the frequency and severity of vasoocclusive crises and improves the quality of life for patients with sickle cell disease, allogeneic HSCT is the only curative treatment for this disease. Although HSCT can cure homozygous hemoglobin S disease, selecting appropriate candidates for transplantation is difficult. Patients with sickle cell disease may survive for decades, but some patients have a poor quality of life, with repeated hospitalizations for painful vasoocclusive crises and central nervous system infarcts. The main indications for performing HSCT in patients with sickle cell disease are history of strokes, magnetic resonance imaging of central nervous system lesions associated with impaired neuropsychologic function, failure to respond to hydroxyurea as shown by recurrent acute chest syndrome, and/or recurrent vasoocclusive crises and/or severe anemia and/or osteonecrosis. The results of HSCT are best when performed in children with an HLA-identical sibling, with a probability of cure of 80-90%. The use of antithymocyte globulin during the preparative regimen improves patient outcome, dramatically reducing the risk of graft failure.

IMMUNODEFICIENCY DISORDERS
HSCT is the treatment of choice for children affected by severe combined immunodeficiency, as well as for other inherited immunodeficiencies, including Wiskott-Aldrich Syndrome, leukocyte adhesion deficiency, and chronic granulomatous disease (see also Table 135-1 for details), among others. With an HLA-identical sibling, the probability of survival approaches 100%, with less-favorable results for patients transplanted from an HLA-partially matched related. Some children with severe combined immunodeficiency, mainly those without residual natural killer activity or maternal T-cell engraftment, may be transplanted without receiving any preparative regimen, the donor lymphoid cells usually being the only elements that engraft. Sustained donor engraftment is more difficult to achieve in children with Omenn syndrome, hemophagocytic lymphohistiocytosis, or leukocyte adhesion deficiency. Life-threatening opportunistic fungal and viral infections occurring before the allograft adversely affect the patient’s outcome after HSCT. Patients with the most severe immunodeficiencies must be transplanted as early as possible.

Bibliography is available at Expert Consult.
Bibliography


Two-thirds of patients who need allogeneic hematopoietic stem cell transplantation (HSCT) do not have an available human leukocyte antigen (HLA)-identical sibling. Alternative donor/sources of hematopoietic stem cells are being increasingly used and include: matched unrelated donors, unrelated umbilical cord blood (UCB), and HLA-haploidentical relatives. Each of these 3 options has advantages and limitations, but rather than being considered competing alternatives, they should be regarded as complementary strategies to be chosen after a careful evaluation of the relative risks and benefits in the patient's best interest. The choice of the donor will depend on various factors related to urgency of transplantation, patient-, disease-, transplant-related factors and center experience. Physician preference is expected to influence this choice as well.

**UNRELATED DONOR TRANSPLANTS**

One of the most widely used strategies for children who need an allograft and do not have an available HLA-identical sibling is to identify an unrelated HLA-matched donor in a registry. Today, worldwide international registries include more than 20 million HLA-typed volunteer donors. HLA-A, -B, -C class I loci, and the DRB1 class II locus are the HLA loci most influencing outcome after HSCT from an unrelated volunteer. The roles played by other class II loci (namely, DQB1 and DP1 loci) on patient outcome remain controversial.

Data on serologic typing of HLA classes IA and IB loci are available for all donors, and there is information on DRB1 typing for approximately one-third of donors. Although in the past serologic (low-resolution) typing was used for HLA-A and -B loci, currently, the unrelated donors are selected using high-resolution (allelic) molecular typing of loci HLA-A, -B, -C, and -DRB1. The chance of finding an HLA-matched donor depends on the frequency of the HLA phenotype, which is closely linked to the ethnic origin of the registry donors and ranges from 60-70% for white patients to 10% for persons of other ethnic groups (Hispanic, black, etc).

Identifying a suitable unrelated donor is a complicated and lengthy process, the median time elapsing from the start of search to transplantation being 3–4 mo. During this period, a patient with acute leukemia may relapse and require further therapy, accumulating organ toxicity that unfavorably affects outcome. Moreover, for various different reasons, a relevant proportion of donors (sometimes reaching 10-20%) are either no longer available or refuse donation. Despite these limitations, many thousands of matched unrelated donor transplantations have been performed.

Initially, HLA polymorphism and the intrinsic limitations of conventional (i.e., serologic) HLA-typing techniques unfavorably affected the accuracy of matching, thus increasing rejection rates and the incidence of acute and chronic graft-versus-host disease (GVHD). Consequently, because the event-free survival of recipients of an unrelated donor allograft was worse than that observed when the donor was a compatible sibling transplant, there is no consensus on the use of unrelated donor transplants for nonmalignant diseases, such as thalassemia or primary immune deficiency syndromes other than severe combined immunodeficiency (SCID). DNA-based (i.e., high-resolution molecular) techniques for HLA typing have revealed an impressive number of new alleles within antigens that were previously defined by serology only. Matching by high-resolution DNA typing reduces the risk of immune complications, namely graft rejection and GVHD, but also the chance of finding a suitable donor. Nevertheless, the advent of both high-resolution molecular HLA classes I and II loci-typing coupled with progress in the prophylaxis and treatment of GVHD has resulted in a reduction of transplantation-related mortality and improvement of outcome. Indeed, outcomes from a fully matched unrelated volunteer donor are now similar to those of HSCT from an HLA-identical sibling, as indicated by results of unrelated donor transplantation in children with acute lymphoblastic leukemia in second complete remission, juvenile myelomonocytic leukemia, or thalassemia (Fig. 136-1).

Although a single locus disparity in patients with leukemia does not markedly affect the probability of event-free survival as the increased risk of toxic death may be compensated for by a reduction in the relapse rate, in patients with nonmalignant disorders optimal results are obtained only when a donor matched at the allelic level with the recipient is selected. In general, a single HLA disparity in the donor–recipient pair, irrespective of whether antigenic or allelic in nature, predicts a greater risk of nonleukemia mortality; multiple allelic disparities at different HLA loci have an additive detrimental effect and are associated with an even worse outcome. To reduce the risk of acute GVHD, *ex vivo T-cell depletion of the graft* has been employed, but has not significantly affected patient outcome, which is similar to that of patients given an unmanipulated graft and pharmacologic prophylaxis for GVHD.

The analyses on the outcome of unrelated donor HSCT include only patients who are transplanted; these numbers do not take into account patients for whom a donor is not found. For patients who urgently need a transplant, the time required to identify a suitable donor from a potential panel, establish eligibility, and harvest the cells may lead to relapse and failure to transplant. For patients who do not have a matched donor or who urgently need a transplant, attention has focused on unrelated cord blood and HLA-haploidentical, mismatched family donors.

**UMBILICAL CORD BLOOD TRANSPLANTS**

UCB transplantation (UCBT) is a viable option for children who need allogeneic HSCT. To date, several hundred children have been cured according to the type of donor used, matched family donor (MFD) or unrelated donor (UD). Matched family donor was superior (55% EFS and 10% TRM) compared to unrelated donor (49% EFS and 16% TRM). (From Locatelli F, Nolite P, Zecca M, et al: Hematopoietic stem cell transplantation [HSCT] in children with juvenile myelomonocytic leukemia [JMML]: results of the EWOG-MDS/EBMT trial. Blood 105:410–419, 2005.)
through transplantation of either related or unrelated UCB units. UCBT offers the advantages of absence of risks to donors, reduced risk of transmitting infections, and, for transplants from unrelated donors, immediate availability of cryopreserved cells, the median time elapsing from start of search to transplantation being only 3-4 wk. In comparison to bone marrow transplantation (BMT), the advantages of UCBT are also represented by lower incidence and severity of GVHD, easier procurement and prompter availability of cord blood cells, and the possibility of using donors showing HLA disparities with the recipient. Despite these advantages, the large experience gained over the last 2 decades has clearly demonstrated that UCBT patients may be exposed to an increased risk of early fatal complications, mainly because of a lower engraftment rate of donor hematopoiesis, delayed kinetics of neutrophil recovery, and lack of adoptive transfer of pathogen-specific memory T-cells. In fact, transfer of donor-derived, memory T-cells significantly contributes to early immunologic reconstitution of children after unmanipulated allogeneic bone marrow or peripheral blood stem cell transplantation.

Concerning the issues of engraftment and hematopoietic recovery, it has been unquestionably shown that an inverse correlation between the number of nucleated cord blood cells infused per kilogram recipient body weight and the risk of dying for transplantation-related causes exists. In particular, engraftment is a major concern when the nucleated cells are $<$2.5 x 10$^9$/kg of recipient body weight. As a cord blood unit usually contains between 1 x 10$^9$ and 1.8 x 10$^9$ cells, it is not surprising that UCB transplantation has been less frequently employed for adolescents or adults with body weight $>$40 kg. Indeed, it can be estimated that only 30% of the UCB units available in the bank inventory could suffice for a 75 kg patient according to the recommended threshold old cell dose (namely more than 2.5 x 10$^9$ total nucleated cells/kg recipient body weight before thawing the unit). In view of these findings, it is not surprising that efforts have been focused on approaches capable of increasing the number of UCB cells to be transplanted. Selection of the richest cord blood units, infusion of 2 units in the same recipient (i.e., double UCBT), and transplantation of ex vivo expanded progenitors have contributed to improve the results of UCBT, opening new scenarios for a wider application of the procedure. In particular, double UCBT is largely employed as it was demonstrated to be effective in adults, significantly increasing the engraftment rate, as compared to single-unit UCBT. In the majority of double UCBT, the 2 UCB units are partially HLA-matched with the recipient, as well as with each other, and sustained hematopoiesis after double UCBT is usually derived from a single donor. This technique is of interest to pediatricians for extending the applicability of UCBT also to adolescents or to patients with a body weight exceeding 40-50 kg. Direct intrabone transplantation of UCB cells is also a feasible and safe approach, able to overcome the problem of graft failure, even when low numbers of HLA-mismatched cord-blood cells are transplanted, and to guarantee prompt platelet recovery.

Despite the low incidence of acute and chronic GVHD observed after UCBT transplantation, the risk of recurrence of leukemia is not increased. The long-term results of UCBT transplants are similar to those after transplantation from other sources of hematopoietic stem cells. In particular, several published reports have compared the outcome of UCBT and BMT from unrelated donors in children with hematologic malignancies. Recipients of UCBT were transplanted from donors with greater HLA-disparities, received 1-log fewer nucleated cells, had delayed neutrophil and platelet recovery, and showed reduced incidence of GVHD as compared to children given BMT. Nevertheless, both the relapse rate and the overall survival probability did not differ in unrelated UCBT or BMT pediatric recipients. The outcome of patients receiving a fully matched UCBT unit is reported to be even better than that of patients who receive a transplant from an HLA-identical, unrelated volunteer. Thus, today, there is no doubt that, in the absence of an HLA-identical family donor, unrelated UCBT can be considered a suitable option for children with malignant and non-malignant disorders. Results of UCBT have been of particular interest in children with Hurler syndrome or Krabbe disease transplanted with cord blood cells from an unrelated donor, as well as in children with hemoglobinopathies given a related UCB transplantation. It has to be emphasized that the lower risk of GVHD associated with UCBT is of particular importance in patients affected by nonmalignant disorders.

Approximately 5% of patients receiving UCBT transplantation develop an autoimmune disorder. These disorders include autoimmune hemolytic anemia, autoimmune thrombocytopenia, Evans syndrome, and immune neutropenia. Less frequently, patients have developed Graves disease, glomerulonephritis, rheumatoid arthritis, or thyroiditis. Treatment for these post-UCB transplant-related autoimmune diseases has included steroids, rituximab, and cyclosporine, with only varying degrees of success.

**HAPLOIDENTICAL TRANSPLANTS**

HSCT from an HLA-haploidentical (haplo-HSCT) donor offers an immediate source of hematopoietic stem cells to almost all leukemia patients who fail to find a matched donor, whether related or unrelated, or a suitable cord blood unit. Indeed, almost all children have at least 1 haploidentical-3 loci mismatched family member who is promptly available as donor. Moreover, the few patients who reject the haploidentical transplant have the advantage of another immediately available donor within the family.

Efficient T-cell depletion of the graft has been demonstrated to prevent acute and chronic GVHD even when using haploidential parental bone marrow differing at the 3 major HLA loci. The benefits of T-cell depletion were first demonstrated in transplantation of children with SCID. More than 300 transplants in SCID patients using haploidential donors have been performed worldwide, with a high rate of long-term partial or complete immune reconstitution. As patients with acute leukemia have a high chance of rejecting a haploidential bone marrow graft, a "megadose" of granulocyte colony-stimulating factor–mobilized peripheral blood stem cells has been demonstrated to be crucial for overcoming the barrier of HLA incompatibility in the donor–recipient pair and for eluding residual antidonor cytotoxic T-lymphocyte precursor activity in the recipient. Indeed, in leukemia patients, the combination of high-intensity immune-suppressive/myeloablative conditioning regimens with the infusion of great numbers of highly purified, peripheral blood CD34+ cells has been demonstrated capable to (1) guarantee the successful and sustained engraftment of donor haematopoiesis across the HLA barrier, and (2) guarantee a very low incidence of grades II-IV acute GVHD without the need for any posttransplantation immune suppression as prophylaxis. The physical elimination of mature T cells from the graft, necessary for preventing GVHD occurrence in a context of great immune genetic disparity, leads to the consequence that recipients cannot benefit from the adoptive transfer of donor memory T lymphocytes that, through their peripheral expansion, are the main factor responsible for protection from infections in the 1st few mo after transplantation. A state of profound immune deficiency lasts for at least 4-6 mo after transplantation in haplo-HSCT recipients. Sophisticated strategies of adoptive infusions of T-cell lines or clones specific for the most common and life-threatening pathogens (namely Epstein-Barr virus, human cytomegalovirus, Aspergillus, and adenovirus) have been envisaged and successfully tested in a few pilot trials to protect the recipients in the early posttransplantation period. Selective approaches of graft manipulation have also been developed. In particular, promising results have been obtained through a negative depletion of T lymphocytes carrying the α/β chains of the T-cell receptor. B-lymphocytes are also depleted to prevent the occurrence of Epstein-Barr virus–related lymphoproliferative disease. Through this approach the patient can benefit from the adoptive transfer of committed hematopoietic progenitors, mature natural killer (NK) cells and γ/δ T cells, which can confer a protection against life-threatening infections.

The outcomes of haplo-HSCT have been more extensively reported in adults than in children. The reported probability of survival at 3-4 yr after a haplo-HSCT in children with acute leukemia ranged from 18-48%. Survival was influenced by many factors, the most important being the state of remission at time of transplantation, with poorer outcomes in children with myeloid leukemias than in those with lymphoid leukemia. It has been reported that in haplotype mismatched
parent-to-child HSCT, patients with acute leukemia grafted from the mother had reduced relapse rates as compared with recipients of paternal grafts, translating into better event-free survival.

For many years the absence of the T-cell mediated graft-versus-leukemia (GVL) effect has been considered rendering the recipients of a T-cell depleted allograft more susceptible to leukemia relapse. However, it has been demonstrated that a GVL effect displayed by donor NK cells can compensate for this lack of T-specific alloreactivity when an HLA-disparate NK alloreactive relative is employed as a donor.

**DONOR VERSUS RECIPIENT NATURAL KILLER–CELL ALLOREACTIVITY**

Donor vs recipient NK-cell alloreactivity is a biologic phenomenon that is unique to the mismatched transplant. It derives from a mismatch between donor NK clones, carrying specific inhibitory receptors for self-major histocompatibility complex (MHC) class I molecules, and MHC class I ligands on recipient cells. NK cells are primed to kill by several activating receptors, which play an important role in the NK cell-mediated GVL effect. Human NK cells discriminate allelic forms of MHC molecules via killer cell immunoglobulin-like receptors (KIRs), which are clonally distributed with each cell in the repertoire bearing at least 1 receptor that is specific for self-MHC class I molecules. Because NK cells coexpress inhibitory receptors for self-MHC class I molecules, autologous cells are not killed. When faced with mismatched allogeneic targets, NK cells sense the missing expression of self–class I alleles and mediate alloreactions. In mismatched transplants, there are many donor recipient pairs in which the donor NK inhibitory cells do not recognize the recipient’s class I alleles as self. Consequently, the donor NK cells are not blocked and are activated to lyse the recipient’s lymphohematopoietic cells.

Haplo-HSCT trials demonstrate that MHC class I mismatches, which generate an alloreactive NK cell response in the graft-versus-host direction, eradicate leukemia cells, improve engraftment, and protect from T-cell–mediated GVHD. Lack of an NK-alloreactive donor is the strongest independent risk factor for leukemia relapse after adjustment for disease status at transplantation. The potential for donor vs recipient NK cell alloreactivity, which can be predicted by standard HLA typing, is recommended when selecting the donor of choice from among the mismatched family members.

The chance of finding a “perfect mismatch” NK-alloreactive donors in the family is on the order of 50%. From a practical point of view, first, the transplantation candidate is HLA typed. Candidates expressing class I alleles belonging to the 3 class I groups recognized by KIRs (HLA-C group 1, HLA-C group 2, and HLA-Bw4 alleles) will block all NK cells from every donor and belong to the one-third of the population that is resistant to allosreactive NK killing. Patients who express only 1 or 2 of these allele groups may find NK-alloreactive donors.

Donor HLA typing identifies family members who do not express the class I group(s) expressed by the patient and, therefore, have the potential for NK alloreactivity. Not all inhibitory KIRs are present in 100% of the population. KIR2DL2/3, the receptor for HLA-C group 1, is present in all persons; KIR2DL1, the receptor for HLA-C group 2, is present in 97% of persons; and KIR3DL1, the receptor for HLA-Bw4 alleles, is present in ~90%. Donor KIR genotyping ensures that the donor expresses the relevant NK cells.

In HLA-Bw4 mismatches, even when the KIR3DL1 gene is present, NK repertoire studies show allosreactive NK cells in approximately two-thirds of individuals. This may be because they occur in highly variable frequencies or because allelic KIR3DL1 variants may not allow receptor expression at the cell membrane. Therefore, for HLA-Bw4 mismatches, direct assessment of the donor NK repertoire is necessary.

**AUTOLOGOUS HEMATOPOIETIC STEM CELL TRANSPLANTATION**

Autologous transplantation, using the patient’s own stored marrow, is associated with a low risk of life-threatening transplant-related complications, although the main cause of failure is disease recurrence resulting from a lack of the immune-mediated GVL effect. Bone marrow was once the only source of stem cells employed in patients given an autograft; in the past few years, the vast majority of patients treated with autologous HSCT receive hematopoietic progenitors mobilized in peripheral blood by either cytokines alone (mainly granulocyte colony-stimulating factor) or by cytokines plus cytotoxic agents. A CXCR4 antagonist (plerixafor) can be extremely effective in mobilizing hematopoietic progenitors in the periphery. When compared to bone marrow, the use of peripheral blood progenitors is associated with a faster hematopoietic recovery and a comparable outcome. A major concern in patients with malignancies given autologous HSCT is represented by the risk of reinfusing malignant cells with the graft; tumor progenitors contained in the graft can contribute to recurrence of the original malignant disease. This observation has provided the rational for **tumor purging** using elaborated strategies aimed at reducing or eliminating tumor contamination of the graft.

Autologous HSCT is employed primarily to prevent relapse in patients with acute myelogenous leukemia (AML) who achieve complete remission after induction therapy, and also for selected children with relapsed lymphomas and selected solid tumors (Table 136-1).

<table>
<thead>
<tr>
<th>Table 136-1</th>
<th>Indications to Autologous Hematopoietic Stem Cell Transplantation for Pediatric Diseases</th>
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</thead>
<tbody>
<tr>
<td>- Acute lymphoblastic leukemia after an isolated extramedullary relapse</td>
<td></td>
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<tr>
<td>- Relapsed Hodgkin or non-Hodgkin lymphoma</td>
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<tr>
<td>- Stage IV or relapsed neuroblastoma</td>
<td></td>
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<tr>
<td>- High-risk, relapsed, or resistant brain tumors</td>
<td></td>
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<tr>
<td>- Stage IV Ewing sarcoma</td>
<td></td>
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<tr>
<td>- Life-threatening autoimmune diseases resistant to conventional treatments</td>
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</table>

Randomized studies have not shown an advantage in terms of event-free survival for patients with AML in the 1st complete remission given an autologous HSCT as compared to those treated with chemotherapy alone. The probability of event-free survival for children with AML in the 1st complete remission given autologous HSCT is reported to range from 40-60%. Ex vivo purging of bone marrow cells with mafosfamide has been shown to reduce the risk of disease recurrence in children with AML in the 1st complete remission given an autologous transplantation.

Patients with sensitive lymphomas and little tumor burden have favorable outcomes after autologous HSCT, with disease-free survival rates of 50-60%, whereas high-risk patients with bulky tumor or poorly responsive disease have a dismal outcome, with survival rates of 10-20%.

Some studies suggest that, as compared to conventional chemotherapy and radiotherapy, autologous HSCT may offer an advantage in terms of event-free survival to children with acute lymphoblastic leukemia in the second complete remission after an isolated extramedullary relapse (i.e., central nervous system, testicular relapse).

Autologous HSCT in patients with high-risk neuroblastoma is associated with a better outcome compared to conventional chemotheraphy. In these patients, posttransplantation infusion of a monoclonal antibody directed against a molecule (GD2) expressed on the surface of neuroblastoma cells confers a protection against the risk of tumor recurrence.

For children with brain tumors at high risk of relapse, or resistant to conventional chemotherapy and irradiation, the dose-limiting toxicity for intensifying therapy is myelosuppression, thus providing a role for stem cell rescue. Several studies provide encouraging results for patients with different histologic types of brain tumors treated with autologous HSCT.

Bibliography is available at Expert Consult.
Bibliography
Clinical Staging and Grading of Graft-Versus-Host Disease

Bilirubin 6-15

T cells, which, together with macrophages, in turn, kill recipient cells and further disrupt tissues.

Acute GVHD usually develops from 2-8 wk posttransplantation. The primary manifestations are an erythematous maculopapular rash, persistent anorexia, vomiting and/or diarrhea, and liver disease with increased serum levels of bilirubin, alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase (Table 137-1). Diagnosis may benefit from skin, liver, or gastrointestinal biopsy for confirmation. Endothelial damage and lymphocytic infiltrates are seen in all affected organs. The epidermis and hair follicles of the skin are damaged, the hepatic small bile ducts show segmental disruption, and there is destruction of the crypts and mucosal ulceration of the gastrointestinal tract. Grade I acute GVHD (skin rash alone) has a favorable prognosis and often does not require treatment (Fig. 137-1). Grade II GVHD is a moderately severe multiorgan disease requiring immunosuppressive therapy. Grade III GVHD is a severe multiorgan disease, and grade IV GVHD is a life-threatening, often fatal condition. The standard pharmacologic prophylaxis of GVHD after an unmanipulated allograft relies mainly on posttransplant administration of immunosuppressive drugs, such as cyclosporine or tacrolimus or combinations of either with methotrexate or prednisone, anti-T-cell antibodies, mycophenolate mofetil, and other immunosuppressive agents. Infusion of cyclophosphamide on days +3 and +5 after transplantation has been proposed as a strategy to delete alloreactive donor T lymphocytes that become activated, and thus cycling, after exposure to recipient antigens. Pretransplantation infusion of either antithymocyte globulin or monoclonal antibodies such as alemtuzumab is largely used to modulate alloreactivity of donor T cells, in particular in patients given the allograft from either an unrelated donor or a partially matched relative. An alternative approach, which has been widely used in clinical practice, is the removal of T lymphocytes from the graft (T-cell depletion). Any form of GVHD prophylaxis in itself may impair posttransplantation immunologic reconstitution, increasing the risk of infection-related deaths. T-cell depletion of the graft is also associated with an increased risk of leukemia recurrence in patients transplanted from a human leukocyte antigen (HLA)-identical sibling or an unrelated volunteer.

Despite prophylaxis, significant acute GVHD develops in ≈30% of recipients of HSCT from matched siblings and in as many as 60% of HSCT recipients from unrelated donors. The risk of acute GVHD is increased by factors such as diagnosis of malignant disease, older donor and recipient ages, and, in patients given an unmanipulated allograft, GVHD prophylaxis including only 1 drug. However, the most important risk factor for acute GVHD is the present of disparities for HLA-molecules in the donor–recipient pair. Acute GVHD is usually initially treated with glucocorticoids; approximately 40-50% of patients show a complete response to steroids. The risk of transplantation-related mortality is much higher in patients who do not respond to

### Table 137-1

<table>
<thead>
<tr>
<th>STAGE</th>
<th>SKIN</th>
<th>LIVER</th>
<th>INTESTINAL TRACT</th>
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<td>+</td>
<td>Maculopapular rash &lt;25% of body surface</td>
<td>Bilirubin 2-3 mg/dL</td>
<td>&gt;500 mL diarrhea/day</td>
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<tr>
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<td>Maculopapular rash 25%-50% of body surface</td>
<td>Bilirubin 3-6 mg/dL</td>
<td>&gt;1,000 mL diarrhea/day</td>
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<tr>
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<td>Generalized erythroderma</td>
<td>Bilirubin 6-15 mg/dL</td>
<td>&gt;1,500 mL diarrhea/day</td>
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<tr>
<td>++++</td>
<td>Generalized erythroderma with bullous formation and desquamation</td>
<td>Bilirubin &gt;15 mg/dL</td>
<td>Severe abdominal pain with or without ileus</td>
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<table>
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<tr>
<th>GVHD GRADE</th>
<th>SKIN STAGE</th>
<th>LIVER STAGE</th>
<th>INTESTINAL TRACT STAGE</th>
<th>DECREASE IN CLINICAL PERFORMANCE</th>
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<td>0</td>
<td>None</td>
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<tr>
<td>II</td>
<td>+ to +++</td>
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<tr>
<td>III</td>
<td>++ to +++</td>
<td>++ to +++</td>
<td>++ to +++</td>
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<td>++ to +++</td>
<td>++ to +++</td>
<td>++ to +++</td>
<td>Extreme</td>
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</tbody>
</table>

steroids than in those showing a complete response. Mofetil mycophenolate, extracorporeal photopheresis, pentostatin, or monoclonal antibodies targeting either molecules expressed on T cells or cytokines released during the inflammatory cascade, which underlies the pathophysiology of GVHD, have been used in patients with steroid-resistant acute GVHD. There are no clear data showing the superiority of one of these approaches over the others. Promising results in children with steroid-resistant acute GVHD have been obtained using mesenchymal stromal cells, which are able to blunt the inflammatory response associated with acute GVHD.

**CHRONIC GRAFT-VERSUS-HOST DISEASE**

Chronic GVHD develops or persists >3 mo posttransplantation and is the most frequent late complication of allogeneic HSCT with an incidence of ≈25% in pediatric patients. Chronic GVHD is the major cause of nonrelapse mortality and morbidity in long-term HSCT survivors. Acute GVHD is recognized as the most important factor predicting the development of the chronic form of the disease. The use of matched unrelated volunteers as donors, and of peripheral blood as the stem cell source, has increased the incidence and severity of chronic GVHD. Other factors that predict occurrence of chronic GVHD include older donor and recipient ages, female donor for male recipient, diagnosis of malignancy, and use of total-body irradiation as part of the preparative regimen.

Chronic GVHD is a disorder of immune regulation characterized by autoantibody production, increased collagen deposition and fibrosis, and clinical symptoms similar to those seen in patients with autoimmune diseases. The predominant cytokines involved in the pathophysiology of chronic GVHD are usually type II cytokines such as IL-4, IL-5, and IL-13. IL-4 and IL-5 contribute to eosinophilia, B-cell hyperactivity with elevated immunoglobulin (Ig) M, IgG, and IgE titers. Associated monoclonal gammapathies indicate clonal dysregulation. Chronic GVHD is dependent on the development and persistence of donor T cells that are not tolerant to the recipient. Maturation of transferred stem cells within a damaged thymus could lead to errors in negative selection and production of cells that have not been tolerant to recipient antigens and are, therefore, autoreactive or, more accurately, recipient reactive. This ongoing immune reactivity results in clinical features resembling a systemic autoimmune disease with lichenoid and sclerodermatous skin lesions, malar rash, sicca syndrome, arthritis, joint contractures, obliterative bronchiolitis, and biliary duct degeneration with cholestasis.

Patients with chronic GVHD involving only the skin and liver have a favorable course (Fig. 137-2). Extensive multiorgan disease may be associated with a very poor quality of life, recurrent infections associated with prolonged immunosuppressive regimens to control GVHD, and a high mortality rate. Morbidity and mortality are highest in patients with a progressive onset of chronic GVHD that directly follows acute GVHD, intermediate in those with a quiescent onset after resolution of acute GVHD, and lowest in patients with de novo onset in the absence of acute GVHD. Single-agent prednisone is standard treatment at present, although other agents, including extracorporeal photopheresis, mofetil mycophenolate, anti-CD20 monoclonal antibody, and pentostatin, have been employed with variable success. Treatment with imatinib mesylate, which inhibits the synthesis of collagen, has been shown to be effective in patients with chronic GVHD and sclerotic features. As a consequence of prolonged immunosuppression, patients with chronic GVHD are particularly susceptible to infections and should receive appropriate antibiotic prophylaxis, including trimethoprim-sulfamethoxazole. Chronic GVHD resolves in most pediatric patients but may require 1-3 yr of immunosuppressive therapy before the drugs can be withdrawn without the disease recurring. Chronic GVHD promotes also the development of secondary neoplasms, in particular in patients with Fanconi anemia.

Graft failure is a serious complication exposing patients to a high risk of fatal infection. **Primary graft failure** is defined as failure to achieve a neutrophil count of 0.2 × 10⁹/L by 21 days posttransplantation. **Secondary graft failure** is loss of peripheral blood counts following initial transient engraftment of donor cells. Causes of graft failure after autologous and allogeneic transplantation include transplantation of an inadequate stem cell dose (more frequently observed in children given cord blood transplantation), and viral infections such as with cytomegalovirus or human herpesvirus type 6, which are often associated with activation of recipient macrophages. Graft failure after allogeneic transplantation, however, is mainly caused by immunologically mediated rejection of the graft by residual recipient-type T cells that survive the conditioning regimen. **Diagnosis** of graft failure resulting from immunologic mechanisms is based on examination of peripheral blood and marrow aspirate and biopsy, along with molecular analysis of chimerism status. Persistence of lymphocytes of host origin in allogeneic transplant recipients with graft failure indicates immunologic...
rejection. The risk of immune-mediated graft rejection is higher in patients given HLA-disparate, T-cell–depleted grafts, reduced-intensity conditioning regimens, and transplantation of low numbers of stem cells, and in recipients who are sensitized toward HLA antigens or, less frequently, minor histocompatibility antigens. Allosensitization develops as a consequence of preceding blood product transfusions and is observed particularly in recipients with aplastic anemia, sickle cell disease, and thalassemia. In HSCT for nonmalignant diseases, such as mucopolysaccharidoses, graft failure is also facilitated by the absence of previous treatment with cytotoxic and immunosuppressive drugs. In thalassemia, graft failure is promoted by expansion of recipient hematopoietic cells. GVHD prophylaxis with methotrexate, an antimetabolite, and antiinfective prophylaxis with trimethoprim-sulfamethoxazole or ganciclovir may also delay engraftment.

**Treatment** of graft failure usually requires removing all potentially myelotoxic agents from the treatment regimen and attempting a short trial of hematopoietic growth factors, such as granulocyte colony-stimulating factor. A second transplant, usually preceded by a highly immune-suppressive regimen, is frequently employed to rescue patients experiencing graft failure. High-intensity regimens are generally tolerated poorly if administered within 100 days from a 1st transplant because of cumulative toxicities.

**VENOOCCLUSIVE DISEASE**

Hepatic venoocclusive disease, also known as sinusoidal obstruction syndrome, presents with hepatomegaly, right upper quadrant tenderness, jaundice, and weight gain from fluid retention and ascites. Onset is usually within 30 days of transplantation, with an incidence of approximately 15%, depending on the intensity of the conditioning protocol. Risk factors include young age, prior hepatic disease (fibrosis, cirrhosis), abdominal radiation, repeated transplantations, neuroblastoma, osteopetrosis and familial hemophagocytic lymphohistiocytosis. The severe form of venoocclusive disease has a high mortality rate; treatment results for severe disease are poor.

Prophylaxis has traditionally used heparin and ursodeoxycholic acid; however, only defibrotide has demonstrated some efficacy in preventing venoocclusive disease. Defibrotide is a combination of porcine oligodeoxyribonucleotides that reduces procoagulant activity and enhances fibrinolytic properties of endothelial cells.

*Bibliography is available at Expert Consult.*
Bibliography

Chapter 138  Infectious Complications of Hematopoietic Stem Cell Transplantation

Andrea Velardi and Franco Locatelli

Hematopoietic stem cell transplantation (HSCT) recipients experience a transient but profound state of immune deficiency. Immediately after transplantation, because neutrophils are absent or markedly reduced, patients are particularly susceptible to bacterial and fungal infections. Consequently, most centers start prophylactic antibiotic or antifungal treatment during the conditioning regimen. Despite these prophylactic measures, most patients will develop fever and signs of infection in the early posttransplantation period. The common pathogens include enteric bacteria and fungi such as Candida and Aspergillus. An indwelling central venous line, routinely employed in all children given HSCT, is a significant risk factor for bacterial and fungal infections, staphylococcal species and Candida being the most frequent pathogens in catheter-related infections (see Chapter 178). Emergence of multidrug resistant strains of Pseudomonas aeruginosa and Klebsiella pneumoniae has become a serious problem, being associated with a high case: fatality ratio.

HSCT recipients remain at increased risk of developing severe infections even after the neutrophil count has normalized, because T-cell number and function remain below normal for months after transplantation. Unrelated donor transplant recipients are at increased risk of developing graft-versus-host disease (GVHD), which is itself an additional risk factor for fungal and viral opportunistic infections, as are the associated immunosuppressive treatments. After cord blood transplantation, infections are the consequence of both the slow neutrophil engraftment and donor T-cell naïveté. In haploidentical transplantation, the increased risk of infection observed in the 1st 4-6 mo after the allograft is the consequence of T-cell depletion of the graft. Indeed, patients given this type of transplantation, as well as those receiving cord blood transplantation, cannot benefit from the adoptive transfer of donor-derived, antigen-experienced T cells.

Among HSCT recipients, invasive aspergillosis, cytomegalovirus (CMV) infection, disseminated adenovirus infections, and Epstein-Barr virus (EBV)-related lymphoproliferative disorders represent peculiar, life-threatening complications that significantly affect patient's outcome.

Invasive aspergillosis remains a significant cause of infectious morbidity and mortality in HSCT recipients. Despite prompt and aggressive administration of potent antifungal agents, proven cases of aspergillosis remain difficult to treat, with case-fatality rates of 80-90%. The annual incidence of invasive aspergillosis has risen with use of stem cells from alternative sources. The incidence is 7.3% in recipients of an human leukocyte antigen (HLA)-matched related donor transplant and 10.5% in patients given the allograft from either an HLA-mismatched family donor or an unrelated donor volunteer. Most cases of aspergillosis are diagnosed from 40-180 days after HSCT, with 30% diagnosed <40 days before and 17% more than 6 mo after transplantation. The risk of developing aspergillosis is mainly influenced by the duration of neutropenia, GVHD occurrence, use of corticosteroid therapy, posttransplant CMV infection, viral respiratory tract infections, advanced disease status, older age, and T-cell depletion of the graft. Patients with a previous history of invasive aspergillosis are at particular risk.

Aspergillus infection often originates from the upper airway mucosa. Early lesions in the nose should be sought in patients with neutropenia who have fever and minimal epistaxis. Rapid extension into the adjacent paranasal sinuses, orbit, or face is usual, with or without the appearance of lung lesions. In the lung, invasive aspergillosis generally presents as an acute, rapidly progressive, densely consolidated pulmonary infiltrate. Infection progresses by direct extension across tissue and by hematogenous dissemination to brain and other organs. The earliest CT finding is one or more small pulmonary nodules. As a nodule enlarges, the dense central core of infarcted tissue becomes surrounded by edema or hemorrhage, forming a hazy rim, the halo sign. This rim disappears in a few days as the dense core enlarges. In neutropenic patients, when bone marrow function recovers, the infarcted central core cavitates, creating the crescent sign. Repeated positivity for serum galactomannan represents a useful biomarker for confirming/suspecting a diagnosis of invasive aspergillosis. Antifungal prophylaxis includes isolation of the patient in a laminar air flow or positive pressure room. Liposomal amphotericin B, azole compounds (itraconazole, voriconazole, posaconazole) and echinocandins (caspofungin, micafungin, anidulafungin) are useful for both preventing and treating the fungal infection. Voriconazole represents the treatment of choice for patients with invasive pulmonary and brain aspergillosis. However, often, aspergillosis does not respond satisfactorily to antifungal agents alone, and patients remain at risk until T-cell counts and function recover. This observation provides the rationale...
for developing strategies to accelerate the recovery of pathogen-specific immune responses.

**CMV infection** remains the most common and potentially severe viral complication in patients given allogeneic HSCT. Seropositivity for CMV is an independent risk factor for mortality, even in recipients of matched sibling or unrelated donor transplants. CMV is itself immunosuppressive, as it impairs dendritic cell and T-lymphocyte function. Moreover, ganciclovir, the most frequently used anti-CMV agent, may cause leukopenia and T-cell immune suppression.

The period of maximal risk for CMV infection is 1-4 mo after transplantation. Until CMV-specific T-cell responses develop months after transplant, CMV infection may result in a variety of syndromes including fever, leukopenia, thrombocytopenia, hepatitis, pneumonitis, retinitis, esophagitis, gastritis, and colitis. CMV pneumonia, the most life-threatening complication related to viral infection, has been reported to occur in up to 15-20% of bone marrow transplant recipients, with a case fatality rate of 85%. The risk is greatest between 5 and 13 wk after transplantation. Risk factors include T-cell depletion of the graft, donor seronegative status together with recipient seropositive status, acute GVHD, and patient older age.

Tachypnea, hypoxia, and unproductive cough signals respiratory involvement. Chest x-ray often reveals bilateral interstitial or reticulonodular infiltrates, which begin in the periphery of the lower lobes and spread centrally and superiorly. The differential diagnosis includes infection with *Pneumocystis jiroveci* or other viral, bacterial, or fungal pathogens, pulmonary hemorrhage, and injury secondary to irradiation or to treatment with cytotoxic drugs. Gastrointestinal CMV involvement may lead to ulcers of the esophagus, stomach, small intestine, and colon that may result in bleeding or perforation.

Fatal CMV infections are often associated with persistent viremia and multiorgan involvement. In the 1980s, antiviral treatment was deferred until overt clinical symptoms of CMV infection developed, which led to a high incidence of fatal events. CMV disease has largely been prevented through prophylaxis and a preemptive approach. Prophylaxis is based on administration of antiviral drugs to all transplanted patients for a median duration of 3 mo after transplantation. The major drawbacks of this approach refer to drug toxicity, occurrence of late CMV disease, mainly pneumonia, after withdrawal of prophylaxis, treatment of patients who do not need antiviral therapy as they would not have reactivated CMV infection, and low cost-effectiveness. Preemptive, or presymptomatic, therapy aims at treating only patients who experience CMV reactivation and, thus, are at risk of developing overt disease; it starts only upon detection of CMV in blood by any assay. The most widely used assay is CMV detection of CMV DNA in blood, which have been used to decide inception of treatment when it either becomes positive or reaches a predetermined threshold. Although in the past treatment usually started after this assay became positive, nowadays therapy is usually initiated when a certain viral load is reached. Moreover, quantification of CMV DNA in blood provides a reliable approach for deciding interruption of treatment. The major drawback of this strategy is the need of serial monitoring that is required for the period in which patients are at risk of developing CMV disease. In this regard, approaches to reliably prove the restoration of virus-specific immunity have been developed. Generally, ganciclovir, or less frequently foscarnet, is usually used for prophylaxis and preemptive treatment of CMV infection. Treatment is usually discontinued when repeated negative controls have been obtained.

**Disseminated adenovirus infection** is a life-threatening complication of HSCT recipients. Clinical manifestations include fever, hepatitis, enteritis, meningoencephalitis, and pneumonia. Young children are at particular risk of developing this complication. Diagnosis is based on the demonstration of high levels of adenovirus DNA in blood or on recovery of virus in tissue biopsies. Pharmacologic treatment of adenovirus infections is based on the use of cidofovir, which has significant renal toxicity and sometimes is unable to control viral replication. Recovery of immune system function is associated with a greater chance to survive adenovirus disseminated infection.

**EBV-related lymphoproliferative disease** (EBV-LPD) is a major complication in HSCT and solid-organ transplantation. In patients given HSCT, selective procedures of T-cell-depletion–sparing B lymphocytes, as well as the use of HLA partially matched family and unrelated donors, are risk factors for the development of EBV-LPD. These disorders usually present in the 1st 4-6 mo after transplantation as high-grade diffuse large-cell B-cell lymphomas, which are oligoclonal or monoclonal, express the full array of EBV antigens, and are of donor origin. High levels of EBV-DNA in blood and in vitro spontaneous growth of EBV-lymphoblastoid cell lines predict development of EBV-LPD.

In immunocompromised hosts, EBV-LPD originates from a deficiency of virus-specific cytotoxic T lymphocytes (CTLs), which control outgrowth of EBV-infected B cells. This finding provided the rationale for developing strategies of adoptive cell therapy to restore EBV-specific immune competence. Unselected donor leukocyte infusion, the first attempt at EBV-directed adoptive immunotherapy in humans, can induce EBV-LPD remission but exposes patients to a high risk of developing clinically relevant GVHD and is not suitable for patients transplanted from an HLA-mismatched donor. A safer approach is infusion of in vitro generated EBV-specific CTL lines of donor origin containing both CD8+ and CD4+ T lymphocytes. These CTL lines prevent lymphoproliferative disorders in patients considered at high risk, such as patients given T-cell depleted HSCT from HLA-disparate donors, and cure clinically overt LPD. Infusion of EBV-specific CTLs from third-party donors sharing HLA-class I molecules with the recipient can be also useful. In recent years, use of monoclonal antibodies directed against CD20, a molecule expressed on B cells, has significantly contributed to reduce the incidence and severity of EBV-related LPD, although it can be associated with the emergence of neoplasms in which cells are CD19+ but CD20 negative, thus rendering patients no longer susceptible to the treatment with the monoclonal antibody.
Late Effects of Hematopoietic Stem Cell Transplantation
Andrea Velardi and Franco Locatelli

Many children given hematopoietic stem cell transplantation (HSCT) become long-term survivors. Besides chronic graft-versus-host disease (GVHD), long-term complications that may develop in pediatric transplant recipients include impaired growth, neuroendocrine dysfunction, delayed puberty, infertility, second malignancies, cataracts and other ocular complications, leukoencephalopathy, and cardiac and pulmonary dysfunction.

Children given HSCT before puberty may develop growth impairment, precluding achievement of the genetic target for adult height. The decrease in growth velocity is similar for boys and girls and is more frequently observed in patients given total-body irradiation (TBI) as part of the preparative regimen. Fractionation of irradiation has a less-adverse impact on height than does single-dose TBI, whereas the use of craniospinal radiotherapy before transplantation plays a synergistic detrimental role with TBI in favoring growth impairment. A study of 175 children younger than 6 yr of age, 6-12 yr of age, or 12-15 yr of age receiving TBI-based regimens and not treated with growth hormone reported a mean final adult height of 3.49, 1.92, and 0.37 SD below average, respectively. Chronic GVHD and its treatment with corticosteroids may also contribute to growth impairment. Serial studies of children given a busulfan-based preparative regimen indicate busulfan
has much less impact on growth but produces the same gonadal failure as TBI-based regimens. Preparative regimens using only cyclophosphamide for children transplanted for aplastic anemia have little, if any, detrimental effect on growth and development.

Growth impairment of patients given TBI is mainly a result of direct damage of cartilage plates and to the effect of TBI on the hypothalamic–pituitary axis, which leads to an inappropriately low production of growth hormone (GH). GH deficiency is susceptible to at least partial correction through administration of hormonal replacement therapy. Annual growth evaluation should be performed in all children after HSCT. Children showing a decreased growth velocity should be further investigated through evaluation of bone age and secretion of GH in response to pharmacologic stimulus. Current studies are aimed at identifying children with GH deficiencies at an earlier age and administering hormonal replacement therapy. Initial concerns about potential risks of favoring disease recurrence or promoting development of second malignancies in GH substitute therapy have not been confirmed and GH replacement therapy is widely employed.

The use of TBI during the preparative regimen involves the thyroid gland in the irradiation field and may result in hypothyroidism. Some children who have received single-dose TBI develop either compensated (28-56%) or overt (9-13%) hypothyroidism. The use of fractionated TBI reduces the incidence of both compensated (10-14%) and overt (<5%) hypothyroidism. Children younger than 7 yr old at the time of allograft are at greater risk of developing hypothyroidism. Chemotherapy-only preparative regimens have far fewer adverse effects on normal thyroid function. The site of injury by irradiation is at the level of the thyroid gland rather than at the pituitary or hypothalamus. Therapy with thyroxine is very effective for overt hypothyroidism, but treatment of compensated hypothyroidism is more controversial, although there is evidence that hormonal replacement therapy may reduce the risk of thyroid carcinoma through a suppression of thyroid-stimulating hormone. Despite treatment of hypothyroidism, the incidence of thyroid carcinoma is not negligible. An annual echo of the thyroid gland is indicated for timely identification of nodules in the thyroid gland suspected to be of neoplastic origin. When a nodule with echo characteristics suggestive for a carcinoma is identified, a needle biopsy is indicated to clarify the histologic nature of the nodule. The cumulative incidence of hypothyroidism increases over time, underscoring the importance of annual thyroid function studies.

Gonadal hormones are essential for normal pubertal growth, as well as for development of secondary sexual characteristics. A significant proportion of patients receiving TBI-containing preparative regimens show delayed development of secondary sexual characteristics, resulting from primary ovarian or testicular failure. Laboratory evaluation of these patients reveals elevated follicle-stimulating hormone and luteinizing hormone levels with depressed estradiol and testosterone serum levels. These patients benefit from careful follow-up with evaluation of annual Tanner scores and endocrine function. Supplementation of gonadal hormones is useful for primary gonadal failure and is administered with GH to promote pubertal growth. The incidence of sex hormone deficiency is lower in patients given a busulfan-based regimen, while infertility during adulthood is a common problem of these children, as well as of those prepared to the allograft with TBI. The use of reduced-intensity regimens can have the advantage of sparing fertility in a large proportion of patients.

The overall risk of developing a secondary form of cancer is significantly higher after HSCT than in the general population. Although few studies have specifically analyzed pediatric patients, available evidence indicates that the cumulative incidence of second malignancies shows a slight, but continuous, tendency to increase over time. Several types of secondary tumors have been identified in patients given HSCT. The most frequently diagnosed neoplasms are thyroid carcinoma, brain tumors, and epithelial cancers. Young age, male gender, use of TBI during the preparative regimen, chronic GVHD, and an intrinsic genetic predisposition to develop cancer (Fanconi anemia) have been reported to be risk factors for development of secondary malignancies after HSCT.

Cataracts mainly occur in children given a radiotherapy-based preparative regimen. The incidence of cataracts is particularly high if TBI is delivered as a single-fraction (800-1,000 cGy). The introduction of fractionated TBI has led to a marked reduction of this complication to ≈10-20% of patients, one-third of whom require surgical intervention. Corticosteroids, frequently employed for treating GVHD, also promote development of cataracts. A dry eye syndrome, or keratoconjunctivitis sicca, may also affect HSCT recipients. It is often related to chronic GVHD and postradiotherapy fibrosis of the lacrimal gland and is treated with artificial tears and lubricants.

Bibliography is available at Expert Consult.

KEY ELEMENTS OF ALLERGIC DISEASES

Allergens

Allergens are almost always proteins, but not all proteins are allergens. For a protein antigen to display allergenic activity, it must induce IgE production, which must lead to a type 1 hypersensitivity response upon subsequent exposure to the same protein. Biochemical properties of the allergen, stimulating factors of the innate immune response around the allergen substances at the time of exposure, stability of the allergen in the tissues, digestive system, skin, or mucosa, and the dose and time of stay in lymphatic organs during the interaction with the immune system are all factors that may cause an antigen to become an allergen. This is distinguished from general antigen responses, which induce a state of immune responsiveness without associated IgE production.

Most allergens are proteins of 10-70 kDa molecular weight; molecules <10 kDa do not bridge adjacent IgE antibody molecules on the surfaces of mast cells or basophils; most molecules >70 kDa do not pass through mucosal surfaces, a feature needed to reach antigen-presenting cells (APCs) for stimulation of the immune system. Allergens frequently contain proteases, which promote barrier dysfunction and increase allergen penetration into host tissues. Low-molecular-weight moieties, such as drugs, can become allergens by reacting with serum proteins or cell membrane proteins to be recognized by the immune system. Carbohydrate structures can also be allergens and are most relevant with the increasing use of biologics in clinical practice; patients with cetuximab-induced anaphylaxis have IgE antibodies specific for galactose-α-1,3-galactose (see Chapter 151).

T Cells

Everyone is exposed to potential allergens. Atopic individuals respond to allergen exposure with rapid expansion of T-helper type 2 (Th2) cells that secrete cytokines, such as interleukin (IL)-4, IL-5, and IL-13, favoring IgE synthesis and eosinophilia. Allergen-specific IgE antibodies associated with atopic response are detectable by serum testing or positive immediate reactions to allergen extracts on prick skin testing (see Chapter 141). The Th2 cytokines IL-4 and IL-13 play a key role in immunoglobulin isotype switching to IgE (Fig. 140-1). IL-5 and IL-9 are important in differentiation and development of eosinophils. The combination of IL-3, IL-4, and IL-9 contributes to mast cell activation. Th2 cytokines are important effector molecules in the pathogenesis of asthma and allergic diseases; acute allergic reactions are characterized by infiltration of Th2 cells into affected tissues. In addition, IL-25, IL-33, and thymic stromal lymphopoietin (TSLP) contribute to Th2 response and eosinophilia.

A fraction of the immune response to allergen results in proliferation of T helper type 1 (Th1) cells. Th1 cells are typically involved in the eradication of intracellular organisms, such as mycobacteria, because of the ability of Th1 cytokines to activate phagocytes and promote the production of opsonizing and complement-fixing antibodies. The Th1 component of allergen-specific immune response contributes to chronicity and the effector phase in allergic disease. Activation and apoptosis of epithelial cells induced by Th1 cell–secreted interferon-γ (IFN-γ), tumor necrosis factor-α (TNF-α), and Fas ligand constitute an essential pathogenic event for the formation of eczematous lesions in atopic dermatitis and bronchial epithelial cell shedding in asthma.

Chronic lesions of allergic reactions are characterized by infiltration of Th1 and Th17 cells. This is important because Th1 cytokines such as IFN-γ can potentiate the function of allergic inflammatory effector cells such as eosinophils and thereby contribute to disease severity. Th17 and Th22 cells link the immune response to tissue inflammation; IL-17A and IL-17F and IL-22 are their respective prototype cytokines. Although both T-helper cell subsets play roles in immune defense to extracellular bacteria, IL-17 augments inflammation, whereas IL-22 plays a tissue-protective role. Cytokines in the IL-17 family act on multiple cell types, including epithelial cells and APCs, to cause the release of chemokines, antimicrobial peptides, and proinflammatory cytokines to enhance inflammation and antimicrobial responses. In addition, recently identified Th9 cells produce IL-9, but not other typical Th1, Th2, and Th17 cytokines, and constitute a distinct population of effector T cells that promotes tissue inflammation. Figure 140-2 depicts the complex cytokine cascades involving Th1, Th2, Th9, Th17 and Th22 cells.

T-regulatory (Treg) cells are a subset of T cells thought to play a critical role in expression of allergic and autoimmune diseases. These cells have the ability to suppress effector T cells of either the Th1 or Th2 phenotypes (Fig. 140-3). Treg cells express CD4+CD25+ surface molecules and immunosuppressive cytokines such as IL-10 and transforming growth factor-β (TGF-β). The forkhead box/winged-helix transcription factor gene FOXP3 is expressed specifically by CD4+CD25+ Treg cells and programs their development and function. Adoptive transfer of Treg cells inhibits the development of airway eosinophilia and protects against airway hyperreactivity in animal models of asthma. T-cell response to allergens in healthy individuals shows a wide range, from no detectable response to involvement of active peripheral tolerance mechanisms mediated by different subsets of Treg cells. Individuals who are not allergic even though they are exposed to high doses of allergens, such as beekeepers and cat owners, show a detectable allergen-specific IgG4 response accompanied by IL-10–producing Treg cells. It is thought that CD4+CD25+ Treg cells play an important role in mitigating the allergic immune response and that the lack of such cells may predispose to the development of allergic diseases. Patients with mutations in the human FOXP3 gene lack CD4+CD25+ Treg cells and develop severe immune dysregulation, with polyendocrinopathy, food allergy, and high serum IgE levels (XLAAD/
Allergy and the Immunologic Basis of Atopic Disease

IPEX disease) (see Chapter 126). In addition to Treg cells, IL-10 secreting and allergen-specific Breg cells that increase during allergen-specific immunotherapy, and may play a role in allergen tolerance were recently demonstrated.

**Antigen-Presenting Cells**

Dendritic cells, Langerhans cells, monocytes, and macrophages have the ability to present allergens to T cells and thereby modulate allergic inflammation by controlling the type of T-cell development. APCs are a heterogeneous group of cells that share the property of antigen presentation in the context of the major histocompatibility complex (MHC) and are found primarily in lymphoid organs and the skin. Dendritic cells (DCs) and Langerhans cells are unique in their ability to prime naïve T cells and are responsible for the primary immune response, or the sensitization phase of allergy. Monocytes and macrophages are thought to contribute to activating memory T-cell responses upon reexposure to allergen, which characterizes the elicitation phase of allergy.

Peripheral DCs residing in sites such as the skin, intestinal lamina propria, and lung are relatively immature. These immature DCs take up antigens in tissues and then migrate to the T-cell areas in locally draining lymph nodes. The DCs undergo phenotypic and functional changes during migration, characterized by increased expression of MHC class I, MHC class II, and costimulatory molecules that react with CD28 expressed on T cells. In the lymph nodes, they directly present processed antigens to resting T cells to induce their proliferation and differentiation.

Mature DCs have been designated as myeloid DC or plasmacytoid DC on the basis of their ability to favor Th1 or Th2 differentiation, respectively. The critical factor for polarization to Th1 cells is the level of IL-12 produced by myeloid DC. By contrast, plasmacytoid DC have low levels of IL-12. Plasmacytoid DC particularly play a role in antiviral immunity by rapid production of high amounts of interferon.

**Figure 140-1** Role of Th2 cytokines in allergic cascade. DC, dendritic cell; EOS, eosinophil; GM-CSF, granulocyte-macrophage colony-stimulating factor; IL, interleukin; Th2, T-helper type 2 cell.

**Figure 140-2** Effector T-cell subsets. Following antigen presentation by dendritic cells (DCs), naïve T cells differentiate into Th1, Th2, Th9, Th17, Th22, and follicular helper TFH effector subsets. Their differentiation requires cytokines and other cofactors that are released from dendritic cells and also expressed in the micromilieu. T-cell activation in the presence of interleukin-4 (IL-4) enhances differentiation and clonal expansion of Th2 cells, perpetuating the allergic response. IFN-γ, interferon-γ; TGF-β, transforming growth factor-β. (From Akdis M, Palomares O, van de Veen W, van Splunter M, Akdis CA. TH17 and TH22 cells: a confusion of antimicrobial response with tissue inflammation versus protection, J Allergy Clin Immunol 129:1438–1449, 2012.)
The acute allergic response depends on IgE and its ability to bind selectively to the α chain of the high-affinity FcεRI or the low-affinity FcεRII (CD23). Cross-linking of receptor-bound IgE molecules by allergen initiates a complex intracellular signaling cascade followed by the release of various mediators of allergic inflammation from mast cells and basophils. The FcεRI molecule is also found on the surface of antigen-presenting DCs (e.g., Langerhans cells), but differs from the structure found on mast cells/basophils in that the FcεRI molecule found on DCs lacks the β chain. CD23 is found on B cells, eosinophils, platelets, and DCs. Cross-linking and FcεRII aggregation on mast cells and basophils can also lead to anaphylaxis (see Chapter 149). Differential expression of tyrosine kinases responsible for positive and negative regulation of mast cell/basophil degranulation are thought to be responsible for this aberrant allergic response.

The induction of IgE synthesis requires 2 major signals. The first signal (signal 1) initiates IL-4 or IL-13 activation of germline transcription at the ε Ig locus, which dictates isotype specificity. The second signal (signal 2) involves the engagement of CD40 on B cells by CD40 ligand expressed on T cells. This engagement results in activation of the recombination machinery, resulting in DNA switch recombination. Interactions between several costimulatory molecule pairs (CD28 and B7; lymphocyte function–associated antigen-1 and intercellular adhesion molecule-1; CD2 and CD58) can further amplify signal 1 and signal 2 to enhance IgE synthesis. Factors that inhibit IgE synthesis include Th1-type cytokines (IL-12, IFN-α, IFN-γ) and microbial DNA containing CpG (cytosine-phosphate-guanine) repeats.

**Eosinophils**

Allergic diseases are characterized by peripheral blood and tissue eosinophilia. Eosinophils participate in both innate and adaptive immune responses and, like mast cells, contain dense intracellular granules that are sources of inflammatory proteins. These granule proteins include major basic protein, eosinophil-derived neurotoxin, peroxidase, and cationic protein. Eosinophil granule proteins damage epithelial cells, induce airway hyperresponsiveness, and cause degranulation of basophils and mast cells. Major basic protein released from eosinophils can bind to an acidic moiety on the M2 muscarinic receptor and block its function, thereby leading to increased acetylcholine levels and the development of increased airway hyperreactivity. Eosinophils are also a rich source of prostaglandins and leukotrienes; in particular, cysteinyl leukotriene C4 contracts airway smooth muscle and increases vascular permeability. Other secretory products of eosinophils include cytokines (IL-4, IL-5, TNF-α), proteolytic enzymes, and reactive oxygen intermediates, all of which significantly enhance allergic tissue inflammation.

Several cytokines regulate the function of eosinophils in allergic disease. Eosinophils develop and mature in the bone marrow from myeloid precursor cells activated by IL-3, IL-5, and granulocyte-macrophage colony-stimulating factor (GM-CSF). Allergen exposure of allergic patients causes resident hematopoietic CD34 cells to express the IL-5 receptor. The IL-5 receptor activation induces eosinophil maturation, causing eosinophils to synthesize granule proteins, prolonging their survival, potentiating degranulation of eosinophils, and stimulating release of eosinophils from the bone marrow. GM-CSF also enhances proliferation, cell survival, cytokine production, and degranulation of eosinophils. Certain chemokines, such as RANTES (regulated upon activation, normal T-cell expressed and secreted),
macrophage inflammatory protein-1α (MIP-1α), and eotaxins, are important for recruiting eosinophils into local allergic tissue inflammatory reactions. Eotaxins mobilize IL-5-dependent eosinophil colony–forming progenitor cells from the bone marrow. These progenitors are rapidly cleared from the blood and either return to the bone marrow or are recruited to inflamed tissue sites.

**Mast Cells**

Mast cells are derived from CD34 hematopoietic progenitor cells that arise in bone marrow. Upon entering the circulation, they travel to peripheral tissue, where they undergo tissue-specific maturation. Mast cell development and survival relies on interactions between the tyrosine kinase receptor c-kit expressed on the surface of mast cells and the fibroblast-derived c-kit ligand stem cell factor. Unlike mature basophils, mature mast cells do not typically circulate in the blood. They are, instead, widely distributed throughout connective tissues, where they often lie adjacent to blood vessels and beneath epithelial surfaces that are exposed to the external environment, such as the respiratory tract, gastrointestinal tract, and skin. So placed, mast cells are positioned anatomically to participate in allergic reactions. At least 2 subpopulations of human mast cells are recognized: mast cells with tryptase and mast cells with both tryptase and chymase. Mast cells with tryptase are the predominant type found in the lung and small intestinal mucosa, whereas mast cells with both tryptase and chymase are the predominant type found in skin, the gastrointestinal submucosa, and blood vessels.

Mast cells contain, or produce on appropriate stimulation, a diverse array of mediators that have different effects on allergic inflammation and organ function. They include preformed granule-associated mediators (histamine, serine proteases, proteoglycans) and membrane-derived lipid, cytokine, and chemokine mediators arising from de novo synthesis and release. The most important mast cell-derived lipid mediators are the cyclooxygenase and lipoxygenase metabolites of arachidonic acid, which have potent inflammatory activities. The major cyclooxygenase product of mast cells is prostaglandin D2, and the major lipoxygenase products are the sulfidopeptide leukotrienes (LTs): LTC4 and its peptidolytic derivatives LTD4 and LTE4. Mast cells also can produce cytokines that promote Th2-type responses (IL-4, IL-13, GM-CSF) and inflammation (TNF-α IL-6), and regulate tissue remodeling (TGFβ vascular endothelial cell growth factor). Immunologic activation of mast cells and basophils typically begins with cross-linkage of IgE bound to the FcεRI with multivalent allergen. Mast cell surface FcεRI is increased by IL-4 and IgE. Surface levels of FcεRI decrease in subjects receiving treatment with anti-IgE antibody that lowers serum IgE, which is of potential therapeutic interest.

**MECHANISMS OF ALLERGIC TISSUE INFLAMMATION**

IgE-mediated immune responses can be classified chronologically according to 3 reaction patterns. The early-phase response is the immediate response after allergen is introduced into target organs. This response is characterized by mast cell degranulation and release of preformed mediators, occurring within an immediate time frame of between 1 and 30 min after allergen exposure and resolving within 1-3 hr. Acute reactions are associated with increased local vascular permeability, which leads to leakage of plasma proteins, tissue swelling, and increased blood flow, as well as itching, sneezing, wheezing, and acute abdominal cramps in the skin, nose, lung, and gastrointestinal tract, respectively, depending on the targeted organ.

A second, late-phase response can occur within hours of allergen exposure, reaching a maximum at 6-12 hr and resolving by 24 hr. Late-phase responses are characterized in the skin by edema, redness, and induration; in the nose by sustained nasal blockage; and in the lung by airway obstruction and persistent wheezing. In general, late-phase responses are associated with early infiltration of neutrophils and eosinophils followed by basophils, monocytes, macrophages, and Th2-type cells. Recruitment of inflammatory cells from the circulation requires increased expression of adhesion molecules on their cell surfaces and expression of their ligand on endothelial cells, which are under the control of cytokines. Several hours after allergen exposure, TNF-α released by activated mast cells induces the vascular endothelial expression of cell adhesion molecules, and this change leads to transendothelial migration of various inflammatory cells. Preferential accumulation of eosinophils occurs through interactions between selective adhesion molecules on the eosinophil cell surface (e.g., α4β7, integrin or very late antigen-4); vascular cell adhesion molecule-1 surface expression can be enhanced by IL-4 and IL-13 on endothelial cells.

Chemokines are chemotactic cytokines that play a central role in tissue-directed migration of inflammatory cells. RANTES, MIP-1α, monocyte chemotactic protein (MCP)-3, and MCP-4 are chemotactants for eosinophils and mononuclear cells, whereas eotaxins are relatively selective for eosinophils. These chemotactants have been detected in epithelium, macrophages, lymphocytes, and eosinophils at sites of late-phase responses and allergic tissue inflammation. Blockade of these chemokines leads to significant reduction in tissue-directed migration of allergic effector cells.

In the third reaction pattern, chronic allergic disease, tissue inflammation can persist for days to years. Several factors contribute to persistent tissue inflammation, including recurrent exposure to allergens and microbial agents. The repeated stimulation of allergic effector cells such as mast cells, basophils, eosinophils, and Th2 cells contributes to unresolved inflammatory conditions. Additionally, Th2-type cytokines (IL-3, IL-5, GM-CSF) secreted during allergic reactions can prolong survival of allergic effector cells by delaying apoptosis. Local differentiation of tissue-infiltrating eosinophil precursors induced by IL-5 results in self-generation of eosinophils, further sustaining damage of local tissue. Tissue remodeling leading to irreversible changes in target organs is also a feature of chronic allergic disease. In asthma, remodeling involves thickening of the airway walls and submucosal tissue, as well as smooth muscle hypertrophy and hyperplasia, which are associated with a decline in lung function. This is an unexpected role for eosinophils in airway remodeling as well as chronic inflammation. In atopic dermatitis, lichenification is an obvious manifestation of skin remodeling.

Th2 cytokines can not only maintain allergic inflammation but also influence tissue remodeling by activating resident cells in target organs; IL-4, IL-9, and IL-13 induce mucus hypersecretion and metaplasia of mucus cells; IL-4 and IL-13 stimulate fibroblast growth and synthesis of extracellular matrix proteins; and IL-5 and IL-9 increase subepithelial fibrosis. TGFβ produced by eosinophils and fibroblasts can enhance subepithelial fibrosis. IL-11 expressed by eosinophils and epithelial cells also contributes to subepithelial fibrosis, in addition to enhancing deposition of collagen and the accumulation of fibroblasts. Additional interleukins released from epithelial cells and DCs, such as IL-25, IL-31, and IL-33, also contribute to the Th2 and eosinophilic inflammation in the affected tissues. The resulting tissue injury amplifies further epithelial injury through proinflammatory cytokine release, extracellular matrix deposition in target organs, and angiogenesis. Genetic predisposition to aberrant injury-repair responses may contribute to chronicity of illness. Once the allergic immune response is established, it can be self-perpetuating and can lead to chronic disease in genetically predisposed individuals. The subsequent infiltration of Th1 cells and Th17 cells enhances the inflammatory potential of allergic effector cells and contributes to chronic tissue inflammatory responses through the release of proinflammatory cytokines and chemokines. In addition, an autoimmune response might be playing a causative role in allergic inflammation resulting from possible mechanisms through IgE autoantibodies, IgG autoantibodies, and Th1 and Th17 cell autoreactivity.

**GENETIC BASIS OF ATOPY**

Allergic diseases are complex genetic conditions susceptible to environmental triggers. Several major groups of genes are associated with allergic diseases: genes that regulate systemic expression of atopy (increased IgE synthesis, eosinophilia, mast cell responses) that are commonly expressed among various allergic diseases, genes that control barrier function in specific target organs (e.g., the skin in atopic
dermatitis, the lung in asthma, the gastrointestinal tract in food allergy), and genes encoding pattern-recognition receptors of the innate immune system that engage microbial pathogens and influence adaptive immune responses. Once allergic responses have been initiated, a genetic predisposition to chronic allergic inflammation and aberrant injury-repair responses contribute to tissue remodeling and persistent disease.

Atopic diseases have a strong familial predisposition, with approximately 60% heritability found in twin studies of asthma and atopic dermatitis. The 5q23−35 region comprises several genes implicated in allergic disease pathogenesis, including genes coding for Th2 cytokines (IL-3, IL-4, IL-5, IL-9, IL-13, GM-CSF). Among these, IL4 is a well-studied potential candidate gene. A nucleotide change at position 589 of the IL4 promoter region is associated with the formation of a unique binding site for NF-AT (nuclear factor for activated T cells) transcription factor, increased IL-4 gene transcription, higher NF-AT binding affinity, and increased IgE production. Similarly, IL13 coding region variants have been associated with asthma and atopic dermatitis. An association between atopy and a gain-of-function polymorphism on chromosome 16, which codes for the α subunit of the IL-4R, has been found. This finding is consistent with the important role of IL-4, IL-13, and their receptors in the immunopathogenesis of allergic diseases.

Genome-wide searches have also linked atopy to chromosome region 11q13. The gene encoding the β subunit of FcεRI-β has been proposed to be the candidate gene in this region. The β subunit gene modifies the FcεRI activity on mast cells, and several genetic variants of FcεRI-β are associated with asthma and atopic dermatitis. Chromosome 6 contains genes coding for human leukocyte antigen class I and class II molecules, which regulate the specificity and intensity of the immune responses to specific allergens. IgE responses to specific allergens, such as ragweed antigen Amb a V and mite allergen Der p 1, have been linked to specific MHC class II loci. TNF-α, a key cytokine that contributes to the influx of inflammatory cells, is also located on chromosome 6. TNF-α polymorphisms are associated with asthma.

Barrier dysfunction has a key role in the pathogenesis of allergic diseases. Genetic linkage studies of atopic dermatitis have demonstrated the importance of chromosome 1q21, which contains a cluster of genes involved in epidermal differentiation. Filaggrin is a protein that is essential in the formation of the stratum corneum. Null mutations of the filaggrin gene are strongly associated with early onset and severe atopic dermatitis. Mutations in the gene encoding the serine protease inhibitor SPINK5 has been shown to cause Netherton disease, a single-gene disorder associated with erythroderma, food allergy, and high serum IgE levels. A common polymorphism in SPINK5 (in particular, Glu420Lys) increases the risk of developing atopic dermatitis and asthma. SPINK5 is expressed in the outer epidermis and is thought to be critical for neutralizing the proteolytic activity of Staphylococcus aureus and common allergens such as Der p 1, which use these proteases to penetrate the skin to induce allergic responses. Barrier dysfunction is involved in other allergic diseases, such as asthma and rhinosinusitis, but likely involves other barrier genes, such as those encoding gap junctions.

Candidate genes associated with asthma susceptibility have been identified by positional cloning: GPRA (G-protein coupled receptor for asthma susceptibility on chromosome 7p14), ADAM-33 (a disintegrin and metalloproteinase 33 on chromosome 20p), and DPP10 (dipeptidyl peptidase 10 on chromosome 2q14). The functions of these genes do not fit into classical pathways of atopy and therefore provide new insights into asthma pathogenesis. GPRA encodes a G-protein coupled receptor, with isoforms expressed in bronchial epithelial cells and smooth muscle in asthmatic persons, suggesting an important role for these tissues in asthma. ADAM-33 is expressed in bronchial smooth muscle and has been linked to bronchial hyperresponsiveness. DPP10 encodes a dipeptidyl dipeptidase that can remove the terminal 2 peptides from certain proinflammatory chemokines, a change that may modulate allergic inflammation.

Pattern-recognition receptors of the innate immune system, which are expressed by epithelial cells and DCs, are associated with disease susceptibility. These receptors recognize specific microbial compo-

Bibliography is available at Expert Consult.
Bibliography


ALLERGY HISTORY

Obtaining a complete history from the allergic patient involves eliciting a description of all symptoms along with their timing and duration, exposure to common allergens, and responses to previous therapies. Because patients often suffer from more than 1 allergic disease, the presence or absence of other allergic diseases, including allergic rhinoconjunctivitis, asthma, food allergy, eosinophilic esophagitis, atopic dermatitis, and drug allergy should be determined. A family history of allergic disease is common and is one of the most important factors predisposing a child to the development of allergies. The risk of allergic disease in a child approaches 50% when 1 parent is allergic and 66% when both parents are allergic, with maternal history of atopy having a greater effect than paternal history.

Several characteristic behaviors are often seen in allergic children. Because of nasal pruritus and rhinorrhea, children with allergic rhinitis often perform the allergic salute by rubbing their nose upward with the palm of their hand. This repeated maneuver may give rise to the nasal crease, a horizontal wrinkle over the bridge of the nose. Characteristic vigorous grinding of the eyes with the thumb and side of the fist is frequently observed in children with allergic conjunctivitis. The allergic cluck is produced when the tongue is placed against the roof of the mouth to form a seal and withdrawn rapidly in an effort to scratch the palate. The presence of other symptoms, such as fever, unilateral nasal obstruction, and purulent nasal discharge, suggests other diagnoses.

The timing of onset and the progression of symptoms are relevant. The onset of recurrent or persistent nasal symptoms coinciding with placement in a daycare center might suggest recurrent infection rather than allergy. When patients present with a history of episodic acute symptoms, it is important to review the setting in which symptoms occur as well as the activities and exposures that immediately precede their onset. Symptoms associated with lawn mowing suggest allergy to grass pollen or fungi, whereas if symptoms occur in homes with pets, animal dander sensitivity is an obvious consideration. Reproducible reactions after ingestion of a specific food raise the possibility of food allergy. When symptoms wax and wane but evolve gradually and are more chronic in duration, a closer look at whether the timing and progression of symptoms correlate with exposure to a seasonal aeroallergen is warranted.

Aeroallergens, such as pollens and fungal spores, the concentrations of which in outdoor air fluctuate seasonally, are prominent causes of allergic disease. Correlating symptoms with seasonal pollination patterns of geographically relevant plants and trees along with information provided by local pollen counts can aid in identifying the allergen. Throughout most of the United States, trees pollinate in the early spring, grasses pollinate in the late spring and early summer, and...
weeds pollinate in late summer through the fall. The presence of fungal spores in the atmosphere follows a seasonal pattern in the northern United States with spore counts rising with the onset of warmer weather and peaking in late summer months, only to recede again with the first frost through the winter. In warmer regions of the southern United States, fungal spores and grass pollen may cause symptoms on a perennial basis.

Rather than experiencing seasonal symptoms, some patients suffer allergic symptoms year-round. In these patients, sensitization to perennial allergens usually found indoors, such as dust mites, animal dander, cockroaches, and fungi, warrants consideration. Species of certain fungi, such as Aspergillus and Penicillium, are found indoors whereas Alternaria is found in both indoor and outdoor environments. Cockroach allergens are often problematic in inner city environments. Patients sensitive to perennial allergens often also become sensitized to seasonal allergens and experience baseline symptoms year-round with worsening during the pollen seasons.

The age of the patient is an important consideration in identifying potential allergens. Infants and young children are first sensitized to allergens that are in their environment on a continuous basis, such as dust mites, animal dander, and fungi. Sensitization to seasonal allergens usually takes several seasons of exposure to develop and is thus unlikely to be a significant trigger of symptoms in infants and toddlers.

Food allergies are more common in infants and young children, resulting primarily in cutaneous, gastrointestinal, and, less frequently, respiratory symptoms. Symptoms of immediate or immunoglobulin (Ig) E-mediated hypersensitivity food reactions develop within minutes to 2 hr after ingestion of the offending food. Symptoms of non-IgE-mediated food allergies are often delayed or chronic (see Chapter 151). Complete information from previous evaluations and prior treatments for allergic disease should be reviewed, including impact of changes in local environment (e.g., home vs. school), response to medications, elimination diets, and duration and impact of allergen immunotherapy (if applicable). Improvement in symptoms with medications or avoidance strategies used to treat allergic disease provides additional evidence for an allergic process.

A thorough environmental survey should be performed, focusing on potential sources of allergens and/or irritant exposure, particularly when respiratory symptoms (upper and/or lower) are reported. The age and type of the dwelling, how it is heated and cooled, the use of humidifiers or air filtration units, and any history of water damage should be noted. Forced air heating may stir up dust mite, fungi, and animal allergens. The irritant effects of wood-burning stoves, fireplaces, and kerosene heaters may provoke respiratory symptoms. Increased humidity or water damage in the home is often associated with greater exposure to dust mites and fungi. Carpeting serves as a reservoir for dust mites, fungi, and animal dander. The number of domestic pets and their movements about the house should be ascertained. Special attention should be focused on the bedroom, where a child spends a significant proportion of time. The age and type of bedding, the number of stuffed animals, type of window treatments, and the accessibility of pets to the room should be reviewed. The number of smokers in the home and where they smoke is useful information. Activities that might result in exposure to allergens or respiratory irritants such as paint fumes, cleansers, sawdust, or glues should be identified. Similar information should be obtained in regard to other environments where the child spends large portions of time, such as a relative’s home or school setting.

**PHYSICAL EXAMINATION**

In patients with asthma, spirometry should be performed. If respiratory distress is observed, pulse oximetry should be performed. The child presenting with a chief complaint of rhinitis or rhinoconjunctivitis should be observed for mouth breathing, paroxysms of sneezing, sniffing/snorting, throat clearing, and rubbing of the nose and eyes (representing pruritus). Infants should be observed during feeding for nasal obstruction severe enough to interfere with feeding or for more obvious signs of aspiration or gastroesophageal reflux. The frequency and nature of coughing that occurs during the interview and any positional increase in coughing or wheezing should be noted. Children with asthma should be observed for congested or wet cough, tachypnea at rest, retractions, and audible wheezes, which may worsen with crying. Patients with atopic dermatitis should be monitored for repetitive scratching and the extent of skin involvement.

Because children with severe asthma as well as those receiving chronic or frequent oral corticosteroids may suffer growth suppression, an accurate height should be plotted at regular intervals. However, long-term follow-up studies suggest that use of inhaled glucocorticoids in prepubertal children is associated with a small initial decrease in attained height (~1 cm) that may persist as a reduction in adult height that is not progressive or cumulative. Poor weight gain in a child with chronic chest symptoms should prompt consideration of cystic fibrosis. Anthropometric measures are also important to monitor in those on restricted diets because of multiple food allergies or eosinophilic esophagitis. Blood pressure should be measured to evaluate for steroid-induced hypertension. The patient with acute asthma may present with **pulsus paradoxus**, defined as a drop in systolic blood pressure during inspiration >10 mm Hg. Moderate to severe airways obstruction is indicated by a decrease of >20 mm Hg. An increased heart rate may be the result of an asthma flare or the use of a β-agonist or decongestant. Fever is not caused by allergy alone and should prompt consideration of an infectious process, which may exacerbate asthma.

Parents are often concerned about blue-gray to purple discolorations beneath their child’s lower eyelids, which can be attributed to venous stasis and are referred to as **allergic shiners**. They are found in up to 60% of allergic patients and almost 40% of patients without allergic disease. Thus, “shiners” may suggest, but are not diagnostic of, allergic disease. In contrast, the **Dennie-Morgan folds** (Dennie lines) are a feature of atop dermatitis. These are prominent infrabrow skin folds that extend in an arc from the inner canthus beneath and parallel to the lower lid margin.

In patients with **allergic conjunctivitis**, involvement of the eyes is bilateral. Examination of the conjunctiva reveals varying degrees of lacrimation, conjunctival injection, and edema. In severe cases, periorbital edema involving primarily the lower eyelids or **chemosis** (conjunctival edema that is gelatinous in appearance) may be observed. The classic discharge associated with allergic conjunctivitis is usually described as “stringy” or “ropy.” In children with vernal conjunctivitis, a more severe, chronic phenotype, examination of the tarsal conjunctiva may reveal cobblestoning. **Keratoconus**, or protrusion of the cornea, may occur in patients with vernal conjunctivitis or periorbital atop dermatitis as a result of repeated trauma produced by persistent rubbing of the eyes. Children treated with high-dose or chronic corticosteroids are at risk for development of posterior subcapsular cataracts.

The external ear should be examined for eczematous changes in patients with atop dermatitis, including the postauricular area and base of the earlobe. Because otitis media with effusion is common in children with allergic rhinitis, pneumatic otoscopy should be performed to evaluate for the presence of fluid in the middle ear and to exclude infection.

Examination of the nose in allergic patients may reveal the presence of a nasal crease. Nasal patency should be assessed, and the nose examined for structural abnormalities affecting nasal airflow, such as septal deviation, turbinate hypertrophy, and nasal polyps. Decrease or absence of the sense of smell should raise concern about chronic sinusitis or nasal polyposis. Nasal polypos in children should raise concerns of cystic fibrosis. The nasal mucosa in allergic rhinitis is classically described as pale to purple in comparison with the beefy red mucosa of patients with nonallergic rhinitis. Allergic nasal secretions are typically thin and clear. Purulent secretions suggest another cause of rhinitis. The frontal and maxillary sinuses should be palpated to identify tenderness to pressure that might be associated with acute sinusitis.

Examination of the lips may reveal cheilitis caused by drying of the lips from continuous mouth breathing or repeated licking of the lips in an attempt to replenish moisture and relieve discomfort (lip locker’s dermatitis). Tonsillar and adenoidal hypertrophy along with a history of impressive snoring raises the possibility of obstructive
sleep apnea. The posterior pharynx should be examined for the presence of postnasal drip and posterior pharyngeal lymphoid hyperplasia ("cobblestoning").

Chest findings in asthmatic children vary significantly and may depend on disease duration, severity, and activity. In a child with well-controlled asthma, the chest should appear entirely normal on examination between asthma exacerbations. Examination of the same child during an acute episode of asthma may reveal hyperinflation, tachypnea, use of accessory muscles, wheezing, and decreased air exchange with a prolonged expiratory time. Tachycardia may be caused by the asthma exacerbation or accompanied by jitteriness after treatment with β-agonists. Decreased airflow or rhonchi and wheezes over the right chest may be noted in children with mucus plugging and right middle lobe atelectasis. The presence of cyanosis indicates severe respiratory compromise. Unilateral wheezing after an episode of coughing and choking in a small child without a history of previous respiratory illness suggests aspiration of a foreign body. Wheezing limited to the larynx in association with inspiratory stridor may be seen in older children and adolescents with vocal cord dysfunction. Digital clubbing is rarely seen in patients with uncomplicated asthma and should prompt further evaluation to rule out other potential chronic diagnoses, such as cystic fibrosis.

The skin of the allergic patient should be examined for evidence of urticaria/angioedema or atopic dermatitis. Xerosis, or dry skin, is the most common skin abnormality of allergic children. Keratosis pilaris, often found on facial cheeks and extensor surfaces of the upper arms and thighs, is a benign condition characterized by skin-colored or slightly pink papules caused by keratin plugs lodged in the openings of hair follicles. Examination of the skin of the palms and soles may reveal thickened skin and exaggerated palmar and plantar creases (hyperlinear- earity) in children with moderate-to-severe atopic dermatitis.

**DIAGNOSTIC TESTING**

**In Vitro Tests**

Allergic diseases are often associated with increased numbers of eosinophils circulating in the peripheral blood and invading the tissues and secretions of target organs. Eosinophilia, defined as the presence of >500 eosinophils/µL in peripheral blood, is the most common hematologic abnormality of allergic patients. Seasonal increases in the number of circulating eosinophils may be observed in sensitized patients after exposure to allergens such as tree, grass, and weed pollens. The number of circulating eosinophils can be suppressed by certain infections and systemic corticosteroids. In certain pathologic conditions, such as drug reactions, eosinophilic pneumonias, and eosinophilic esophagitis, significantly increased numbers of eosinophils may be present in the target organ in the absence of peripheral blood eosinophilia. Increased numbers of eosinophils are observed in a wide variety of disorders in addition to allergy (Table 141-1; see Chapter 129). Eosinophil counts >1500 without an identifiable etiology should suggest 1 of the 2 hypereosinophilic syndromes (Table 141-1; see Chapter 129).

Nasal and bronchial secretions may be examined for the presence of eosinophils. The presence of eosinophils in the sputum of asthmatic patients is classic. An increased number of eosinophils in a smear of nasal mucus with Hansel stain is a more sensitive indicator of nasal allergies than peripheral blood eosinophilia and can aid in distinguishing allergic rhinitis from other causes of rhinitis. An elevated IgE value is often found in the serum of allergic patients, because IgE is the primary antibody associated with immediate hypersensitivity reactions. IgE values are measured in international units (IU), with 1 IU equal to 2.4 ng of IgE. Maternal IgE (unlike IgG) does not cross the placenta. Serum IgE levels gradually rise over the first years of life to peak in the teen years and decrease steadily thereafter. Additional factors, such as genetic influences, race, gender, certain diseases, and exposure to cigarette smoke and allergens, also affect serum IgE levels. Total serum IgE levels may increase 2- to 4-fold during and immediately after the pollen season and then gradually decline until the next pollen season. Comparison of total IgE levels among patients with allergic diseases reveals that those with atopic dermatitis tend to have the highest levels while patients with allergic asthma generally have higher levels than those with allergic rhinitis. Although average total IgE levels are higher in populations of allergic patients than in comparable populations without allergic disease, the overlap in levels is such
that the diagnostic value of a total IgE level is poor. Approximately one-half of patients with allergic disease have total IgE levels in the normal range. However, measurement of total IgE is indicated when the diagnosis of allergic bronchopulmonary aspergillosis is suspected because total serum IgE concentration >1,000 ng/mL is a criterion for diagnosis of this disorder (see Chapter 237.1). Total serum IgE may also be elevated in several nonallergic diseases (Table 141-2; see Chapter 126).

The presence of IgE specific for a particular allergen can be documented in vivo by skin testing or in vitro by the measurement of allergen-specific IgE (sIgE) levels in the serum (Table 141-3). The first test for documenting the presence of sIgE was called the radioallergosorbent test because it used a radiolabeled anti-IgE antibody. The radioallergosorbent test has been replaced by an improved generation of automated enzymatic sIgE immunoassays. These assays use solid-phase supports to which allergens of an individual allergen extract are bound. A small amount of the patient’s serum is incubated with the allergen-coated support. The allergen-coated support bound to the patient’s sIgE is then incubated with enzyme-conjugated antihuman IgE. Incubation of this sIgE-antihuman IgE complex with a fluorescent substrate of the conjugated enzyme results in the generation of fluorescence that is proportional to the amount of sIgE in the serum sample. The amount of sIgE in the serum sample is calculated by interpolation from a standard calibration curve and reported in arbitrary mass units (kilo-IU of allergen-specific antibody per unit volume of sample [kU/L]). Laboratory reports may specify classes, counts, or units, but quantification of results in kU/L is most useful. There are 3 commercial detection systems approved by the U.S. Food and Drug Administration that have excellent performance characteristics, but the individual systems do not measure sIgE antibodies with comparable efficiencies and thus are not interchangeable. Component testing refers to emerging diagnostic tests where sIgE is measured to specific proteins that comprise allergens (e.g., Ara h 2 from peanut or Bet v 1 from birch pollen), rather than to a mixture of the allergens extracted from the source. Testing sIgE to component allergens may add additional diagnostic value by differentiating immune responses that are directed toward clinically relevant allergenic proteins.

### Table 141-2 Nonallergic Diseases Associated with Increased Serum IgE Concentrations

| PARASITIC INFESTATIONS | | |
|------------------------|--------------------------------------------------|
| Ascariasis             | Capillariais                                     |
| Echinococcus           | Fasciolasis                                      |
| Filariasis             | Hookworm                                         |
| Onchocerciasis         | Malaria                                          |
| Paragonimiasis         | Schistosomias                                    |
| Strongyloidiasis       | Trichinosis                                      |
| Visceral larva migrans |                                                  |

| INFECTIONS | | |
|------------|--------------------------------------------------|
| Allergic bronchopulmonary aspergilosis | Candidiasis, systemic |
| Coccidioidomycosis                     | Cytomegalovirus mononucleosis                     |
| Human immunodeficiency virus type 1 infections | Infectious mononucleosis (Epstein-Barr virus) |
| Leprosy | Pertussis |
| Viral respiratory infections | |

| IMMUNODEFICIENCY | | |
|------------------|--------------------------------------------------|
| Autosomal dominant hyperimmunoglobulin E syndrome (STAT3 mutations) | Autosomal recessive hyperimmunoglobulin E syndrome (DOCK8, TYK2 mutations) |
| IgA deficiency, selective | Nezefol syndrome (cellular immunodeficiency with immunoglobulins) |
| Thymic hypoplasia (DiGeorge anomaly) | Wiskott-Aldrich syndrome |

| NEOPLASTIC DISEASES | | |
|---------------------|--------------------------------------------------|
| Hodgkin disease     | IgE myeloma                                      |
| Bronchial carcinoma |                                                  |

| OTHER DISEASES AND DISORDERS | | |
|------------------------------|--------------------------------------------------|
| Alopecia areata              | Bone marrow transplantation                       |
| Burns                        | Cystic fibrosis                                  |
| Dermatitis, chronic acral    | Erythema nodosum, streptococcal infection        |
| Guillain-Barré syndrome      | Kawasaki disease                                |
| Liver disease                | Medications                                      |
| Nephritis, drug-induced interstitial | Nephrotic syndrome |
| Pemphigus, bullous           | Polyarteritis nodosa, infantile                  |
| Primary pulmonary hemosiderosis | Rheumatoid arthritis |

### Table 141-3 Determination of Specific IgE by Skin Testing Versus In Vitro Testing

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>SKIN TEST*</th>
<th>sIgE ASSAY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk of allergic reaction</td>
<td>Yes (especially ID)</td>
<td>No</td>
</tr>
<tr>
<td>Relative sensitivity</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>Affected by antihistamines</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Affected by corticosteroids</td>
<td>Usually not</td>
<td>No</td>
</tr>
<tr>
<td>Affected by extensive dermatitis or dermographism</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Broad selection of antigens</td>
<td>Fewer</td>
<td>Yes</td>
</tr>
<tr>
<td>Immediate results</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Expensive</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Lability of allergens</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Results evident to patient</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

*Skin testing may be the prick test or intradermal (ID) injection.
from the proximal and distal esophagus must show eosinophil-
predominant inflammation. With few exceptions, 15 eosinophils/hpf
(high power field) (peak value) is considered a minimum threshold for
the diagnosis.

Bibliography is available at Expert Consult.
Bibliography
The basic principles of the treatment of allergic disease include the avoidance of exposure to allergens and irritants that trigger symptoms and the pharmacologic management of symptoms caused by unavoidable acute and chronic allergen exposures. In selected patients, allergen immunotherapy may be considered.

ENVIRONMENTAL CONTROL MEASURES

Children spend the majority of their time in indoor environments, including the home. In an effort to save energy, houses and buildings have been built more tightly and with more insulation with limited air exchange. These factors have led to an increase in indoor humidity and higher concentrations of allergens and irritants. Examination of indoor environments suggests that house dust mite, cat, and cockroach allergens are the most common significant triggers of allergic disease in these settings; exposures to allergens from other pets, pests, mold, and respiratory irritants such as cigarette smoke are also a problem.

More than 30,000 species of mites have been identified, but the term dust mites usually refers to the pyroglyphid mites *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, and *Euroglyphus maynei*, which are the major sources of allergen in house dust. Respiration and water vapor exchange occur through the skin of dust mites, rendering them sensitive to humidity and temperature extremes. The regular use of humidifiers promotes dust mite survival. Mites do not survive with relative humidity <50%. They feed on animal and human skin scales and other debris, which is why they exist in large numbers in mattresses and bedding, carpet, and upholstered furniture. They may also be found in flour and mixes for baked goods. Anaphylaxis has been reported following the ingestion of baked goods, such as waffles and pancakes, prepared with flour infested with dust mites (“pancake syndrome”). Dust mite fecal pellets are a major source of allergens. They consist of partially digested food combined with digestive enzymes encased in a permeable membrane, which keeps the fecal pellets intact. These fecal pellets have been likened to pollen grains, given their similarities in size (10-40 µm), the amount of allergen they contain, and their ability to release allergens rapidly on contact with moist mucous membranes. Mites can persist in imported furnishings for at least 2 yr; mite allergens have been shown to remain stable under domestic conditions for periods of at least 4 yr. Dust mite allergens become airborne during normal household activities; a vigorous disturbance, such as vacuuming without a vacuum bag, shaking a bed sheet, or a pillow fight, can launch significant amounts of dust mite allergens into the air. Once airborne, dust mite allergen particles settle out of the air relatively rapidly because of their size and weight. Nonetheless, dust mite allergen exposure likely occurs during sleep on mite-infested pillows and mattresses and during normal household activities when dust mite concentrations in the home are high. Levels of dust mite allergens as
low as 2 µg/g of house dust can lead to sensitization, whereas levels of 10 µg/g of house dust are associated with symptoms.

Appropriate environmental control measures can significantly reduce exposure to dust mite allergens (Table 142-1). Major emphasis should be placed on reducing exposure to dust mite allergens in the bedroom and living areas in which the child spends a large amount of time. Encasements impermeable to dust mite allergens should be placed on all pillows, the mattress, and the box spring. Dust should be removed from the surfaces of these covers and the bed frame by vacuuming weekly. The sheets and mattress pad should be washed weekly. The sheets and mattress pad should be washed weekly with an efficient double-thickness-bagged vacuum cleaner is also encouraged. Similar measures for dust mite allergen control include maintaining the indoor relative humidity at <50% and keeping the air conditioning set at the lowest level during the warmer months.

In many countries, more than half of the households have pets, the most common of which are cats and dogs. The major sources of allergens from cats, dogs, and horses are hair, dander, and saliva, whereas the major source of allergens from rodents is urine. Studies of airborne cat allergen have shown that a significant portion is found on small particles. As much as 30% of airborne cat allergen may reside on particles <5 µm. Particles this small may not be adequately filtered by the nose and could potentially be deposited in the airways. Their small size enables these particles to remain airborne for longer periods and to be suspended repeatedly by air currents from heating and ventilation systems or just by walking across the carpet or sitting in an upholstered chair. Fel d 1, the major cat allergen, is a highly charged protein that readily sticks to a variety of surfaces, including walls, carpeting, and upholstered furniture. Owing to this adhesiveness, cat allergens bind to the cat owner's clothing and are routinely transported to public buildings, including schools, where they have been measured in moderately high amounts. From these sites, significant amounts of cat allergen can subsequently be carried into homes without cats. Analysis of house dust from homes with cats reveals levels of Fel d 1 ranging from 8 µg to 1.5 mg/g of house dust. Levels of Fel d 1 in homes without cats vary from 0.2 to 80 µg/g of house dust. Sensitization to cat allergen is associated with levels ranging from 1 to 8 µg/g of house dust. Carpets, upholstered furniture, and bedding serve as reservoirs of cat allergens, resulting in the persistence of significant amounts in the home for months after a cat has been removed. Complete avoidance of cat allergen is virtually impossible, although significant reduction in exposure to cat allergens is achievable.

Removing the pet from the home is obviously the most effective means of reducing exposure to animal allergens, although it has been demonstrated that without other interventions, such as removing carpeting and upholstered furniture and wiping down walls, it takes 6 mo or more for the levels of cat allergen to drop to a level found in houses without a cat. As a result, cat owners who remove their pets from their homes should be informed not to expect immediate results. Unfortunately, advice to remove a pet from the home or keep it outdoors is often ignored. In contrast to dust mite allergens, cat allergen is light and remains suspended in the air for long periods. As a result, air cleaners with high-efficiency particulate air (HEPA) filters are helpful in reducing the amount of airborne cat allergen. Other suggested methods include washing the cat regularly and maintaining a cat allergen–free bedroom from which the cat is excluded and where mattress covers and air-filtering devices are used. The cat should also be restricted from other living areas where the sensitized child spends large amounts of time, such as the family room and other play areas (see Table 142-1). Regular vacuuming with a HEPA-filtered and double-thickness bag vacuum cleaner is also encouraged. Similar measures are suggested for the control of exposure to other animal allergens, although whether these measures reduce exposure to levels resulting in clinical improvement as demonstrated by decreased symptoms, improved peak flows, or decreases in bronchial hyperreactivity remains to be documented by appropriately controlled studies.

Infestation of the home by insects and other pests, such as mice and rats, is another potential source of significant indoor allergen exposure. Studies have identified exposure to cockroach allergens as a major risk factor for the development of asthma in inner-city children. Once sensitized, inner-city cockroach-sensitive asthmatic children with continued exposure to high levels of cockroach allergens in their bedrooms are at higher risk for urgent care visits and hospitalization than are inner-city asthmatic children who are not allergic to cockroaches. Recommended methods to decrease cockroach allergen exposure include reducing cockroaches’ access to the home by sealing cracks in the flooring and walls and removing sources of food and water by repairing leaky pipes, putting away food in sealed containers, and frequent cleaning (see Table 142-1). Regular extermination using baits or chemical treatment of infested areas is also advised.

Efforts to improve indoor air quality should also encompass reducing exposure to respiratory irritants. Passive exposure to environmental tobacco smoke worsens asthma and increases nasal symptoms in patients with allergic nasal disease. Smoking cessation should be repeatedly encouraged, and smoking indoors should never be permitted. The use of wood-burning stoves, fireplaces, and kerosene heaters should also be discouraged.

Although exposure to pollens and molds occurs primarily outdoors, these allergens are detectable indoors during the warmer months,
when their indoor levels often reflect their prevalence in the outdoor environment. During the winter, when the outdoor levels of other molds are lowest, the indoor molds Aspergillus and Penicillium are the most prevalent. Molds are often found in damp basements and thrive in conditions associated with increased moisture in the home, such as water leaks, flooding, and increased humidity promoted by the excessive use of humidifiers or swamp coolers. Exposure to indoor mold allergens can be reduced by maintaining the indoor relative humidity at <50%, removing contaminated carpets, and wiping down washable surfaces prone to fungal growth, such as shower stalls, shower curtains, sinks, drip trays, and garbage pails, with the use of solutions of detergent and 5% bleach (see Table 142-1). Dehumidifiers should be placed in damp basements. Standing water at any site in the home should be eliminated, and the cause addressed. Removing all items from the home that are prone to mold contamination is also encouraged. Keeping the windows and doors closed and using air conditioning to filter outdoor air can keep both indoor pollen and mold levels to a minimum during the warmer months, when outdoor levels of these allergens are at their peak. The use of window or attic fans is to be avoided. Laundry should be dried in a dryer rather than on a clothesline. Measures to avoid pollens and mold spores when out of the house include closing the windows and using the air conditioner when traveling in the car, avoiding moldy vegetation, and wearing a mask when these materials cannot be avoided. Outdoor activities during periods of high pollen counts should be kept to a minimum. Pollen travels best on warm, dry, breezy days but counts are lowest during chilly, wet periods. Someone other than the sensitized patient should mow the lawn and rake leaves. Hand washing after outdoor play is suggested to avoid transferring pollens from the hands to the eyes and nose. At the end of the day, showering and shampooing are suggested to avoid contamination of the bed with allergens.

PHARMACOLOGIC THERAPY

Adrenergic Agents

Adrenergic agents exert their effects through the stimulation of cell surface α- and β-adrenergic receptors in a variety of target tissues. In general, α-adrenergic receptor stimulation results in excitatory responses such as vasoconstriction, whereas β-adrenergic stimulation leads to inhibitory responses such as bronchodilation. The α-adrenergic receptors have been classified into α1- and α2-adrenergic receptors. There are 3 subtypes of α1-adrenergic receptors and 3 subtypes of α2-adrenergic receptors. The β-adrenergic receptors are further divided into 3 subtypes: β1, β2, and β3. Each of these adrenergic receptors exhibits a distinctive tissue distribution. The physiologic response in a given tissue to the administration of an adrenergic agent depends on the specific receptor-binding characteristics of the drug as well as the numbers and distribution of the various types of adrenergic receptors in the tissue. Epinephrine remains the drug of choice for the treatment of anaphylaxis because of its combined α- and β-adrenergic effects. Epinephrine autoinjectors are prescribed for ease of administration and are available in 2 dosages: 0.15 mg for children who weigh <30 kg, and 0.30 mg for children who weigh ≥30 kg, according to manufacturer recommendations. Consider prescribing the 0.15 mg dose for children who weigh ≥25 kg to avoid under-dosing.

The α-adrenergic agents are effective in the treatment of allergic nasal disease because of their decongestant effects (see Tables 143-4 and 143-5). In the nose, stimulation of α1-adrenergic receptors on postcapillary venules and of α2-adrenergic receptors on precapillary arterioles leads to vasoconstriction, resulting in a reduction in nasal congestion. The oral decongestants currently in clinical use include pseudoephedrine and phenylephrine. These medications are available individually or in combination with antihistamines in liquid and tablet forms, including sustained-release preparations. Pseudoephedrine is rapidly and thoroughly absorbed, whereas phenylephrine, the less effective of the 2 drugs, is incompletely absorbed, resulting in a significantly lower bioavailability of ~38%. Peak plasma concentrations of these drugs are reached between 30 min and 2 hr of administration, but the decongestant effect has not been directly correlated to the plasma concentration. Pseudoephedrine is excreted essentially unchanged by the kidney. The use of oral decongestants should be avoided in patients <6 yr of age and in patients with hypertension, coronary artery disease, glaucoma, or metabolic disorders, such as diabetes and hyperthyroidism. Reported adverse effects of oral decongestants include excitability, headache, nervousness, palpitations, tachycardia, arrhythmias, hypertension, nausea, vomiting, and urinary retention. Decongestants available as topical nasal sprays include phenylephrine, oxymetazoline, naphazoline, tetrahydrozoline, and xylometazoline. Given their efficacy and rapid onset of action, the potential for excessive use of topical nasal decongestants resulting in rebound nasal congestion (rhinitis medicamentosa) is high and patients should be carefully counseled to prevent dependency on the product. Thus, limiting the use of these sprays to 2-3 days is generally recommended.

Drugs that stimulate β-adrenergic receptors have been used for years in the treatment of asthma because of their potent bronchodilator effects (see Table 144-16). The subclassification of β-adrenergic receptors into β1, and β2 subtypes led to the development of drugs selective for the β1, adrenergic receptor, such as albuterol, levalbuterol, and pirbuterol, that have the advantage of producing significant bronchodilation with less cardiac stimulation. The long-acting inhaled β2-adrenergic agonists (LABAs) salmeterol and formoterol, with a 12-hr duration of action, are approved for use in children ≥4 yr of age. LABAs are not recommended for the treatment of acute asthma exacerbations because of their relatively slow onset of action. Concern about an increased risk of asthma-related adverse events is why LABAs are not recommended as monotherapy for the long-term control of persistent asthma, but are promoted as best used in conjunction with an inhaled steroid. Dry powder inhaled and metered-dose inhaler preparations combining a LABA with an inhaled corticosteroid have had significant impact on treatment of moderate persistent asthma. In addition to their bronchodilating effects, β1-adrenergic agonists have been reported to improve mucociliary clearance, decrease microvascular permeability, inhibit cholinergic nerve transmission, and reduce mediator release in mast cells, basophils, and eosinophils. Although β2-adrenergic agonists can be delivered orally, by inhalation, or by injection, the inhaled route is preferred because of the rapid onset of action and fewer adverse effects. Reported adverse effects of β-adrenergic agents include tremor, palpitations, tachycardia, arrhythmias, central nervous system stimulation, hyperglycemia, hypokalemia, hypomagnesemia, and a transient increase in hypoxia, which is attributed to an increase in perfusion to inadequately ventilated areas of the asthmatic lung.

Anticholinergic Agents

Anticholinergic drugs inhibit vagally mediated reflexes by antagonizing the action of acetylcholine at muscarinic receptors. Of the available anticholinergic agents, ipratropium bromide is the most commonly used. It is a quaternary amine that is poorly absorbed across mucosal surfaces and does not readily cross the blood–brain barrier. As a bronchodilator, it has a slower onset of action than short-acting inhaled β2-agonist and takes longer to reach maximal effect, making it less effective as a rescue medication. There is increasing support, particularly in children, for combination therapy using ipratropium bromide and β2-agonist therapy in more severe asthma exacerbations. Multiple doses of combined therapy can decrease risk of hospitalization in children by 25%. Ipratropium is available by prescription as a metered-dose inhaler delivering 17 µg/spray and as a 0.02% nebulized solution (500 µg/2.5 mL).

Ipratropium given as a nasal spray (0.03-0.06%) is effective in the reduction of rhinorrhea resulting from perennial nonallergic rhinitis, the common cold, and vasomotor rhinitis. The use of ipratropium is suboptimal in the treatment of moderate to severe allergic rhinitis because it does not alter other common allergic nasal symptoms, such as sneezing, nasal congestion, and pruritus. Nasal dryness and epistaxis are occasionally encountered with use of the nasal spray.

Antihistamines

The release of histamine and its effects on surrounding tissues is central to the development of symptoms classically associated with the allergic response. Histamine exerts its effects through binding with 1 of its 4
receptors, as H₁-, H₂-, H₃-, or H₄-receptor. Histamine effects triggered through H₁-receptor binding are those most relevant to allergic inflammation, and include pain, pruritus, vasodilation, increased vascular permeability, smooth muscle contraction, mucus production, and the stimulation of parasympathetic nerve endings and reflexes. The antimuscarinic effect of some of the early H₁-type antihistamines may be explained by the reported 45% homology of the H₁-receptor with the human muscarinic receptor. The H₁-type antihistamines prevent the effects of H₁-receptor activation through reversible, competitive inhibition of histamine by binding to the H₁-receptor. Antihistamines work best in preventing rather than reversing the actions of histamine and are most effective when given at doses and dosing intervals resulting in the persistent saturation of target organ tissue histamine receptors.

The H₁-type antihistamines are traditionally divided into 6 classes on the basis of differences in their chemical structures (Tables 142-2 and 143-3). These antihistamines are further divided into first-generation antihistamines, which, because of their lipophilicity, cross the blood–brain barrier to exert effects on the central nervous system, and second-generation antihistamines, which exert minimal, if any, central nervous system effects because of their inability to cross the blood–brain barrier owing to their size, charge, and lipophilicity. The sedative effects and cognitive impairment associated with the use of first-generation antihistamines are well documented. Thus, a primary advantage of second-generation antihistamines is that they are nonsedating or much less sedating than first-generation antihistamines. Although fexofenadine is considered the least sedating of the available nonprescription antihistamines (0% occupation of central nervous system H₁-receptors), cetirizine has the most potential for sedation (26–30%). Both first- and second-generation antihistamines are available in oral preparations. Many first-generation and second-generation antihistamines are available in nonprescription form, including diphenhydramine, loratadine, fexofenadine, and cetirizine. Other antihistamines require a prescription, such as hydroxyzine and cyproheptadine, loratadine, fexofenadine, and cetirizine. Other antihistamines are available in nonprescription form, including ethanamines, piperidines, and alkylamines.

### Table 142-2 Classification of Antihistamines (H₁-Antagonists)

<table>
<thead>
<tr>
<th>CLASS</th>
<th>EXAMPLES</th>
</tr>
</thead>
<tbody>
<tr>
<td>ETHANEDIAMINES</td>
<td>Antazoline, pyrilamine, tripelemamine</td>
</tr>
<tr>
<td>TYPE II ETHANOLAMINES</td>
<td>First-generation: Carbinoxamine, clemastine, diphenhydramine</td>
</tr>
<tr>
<td></td>
<td>Second-generation: Brompheniramine, chlorpheniramine, triprolidine</td>
</tr>
<tr>
<td></td>
<td>Activastine</td>
</tr>
<tr>
<td>TYPE IV PIPERAZINES</td>
<td>First-generation: Cyclizine, hydroxyzine, meclizine</td>
</tr>
<tr>
<td></td>
<td>Second-generation: Cetirizine, levocetirizine</td>
</tr>
<tr>
<td>TYPE V PIPERIDINES</td>
<td>First-generation: Azatadine, cyproheptadine, ketotifen</td>
</tr>
<tr>
<td></td>
<td>Second-generation: Fexofenadine, loratadine, desloratadine</td>
</tr>
<tr>
<td>TYPE VI PHENOTHIAZINES</td>
<td>First-generation: Methdilazine, promethazine</td>
</tr>
</tbody>
</table>

Orally administered antihistamines are well absorbed and reach peak serum concentrations within ~2 hr. High tissue concentrations of antihistamines are usually achieved, likely accounting for the sustained suppression of wheal and flare reactions even after serum levels have significantly declined. Most antihistamines are metabolized by the hepatic cytochrome P450 enzyme system. Elimination of antihistamines may be reduced in patients with hepatic impairment or by the simultaneous ingestion of inhibitors of this pathway, such as erythromycin and other macrolide antibiotics, ciprofloxacin, ketoconazole, itraconazole, and certain antidepressants, such as nefazodone and fluvoxamine. Some antihistamines, such as hydroxyzine and loratadine, are converted to clinically active metabolites. Clearance of fexofenadine and cetirizine is reduced in patients with impaired renal function. Cetirizine clearance is also reduced in patients with hepatic dysfunction. Fruit juices (apple, orange, grapefruit) are organic anion transporter inhibitors and interfere with the absorption of fexofenadine: juices should be avoided 4 hr before or 1-2 hr after taking fexofenadine.

The efficacy of antihistamines in the treatment of seasonal and perennial allergic rhinoconjunctivitis is well documented (see Chapter 143). Compared with other medications in regard to the relief of allergic nasal symptoms, antihistamines are more effective than cromolyn sodium, but significantly less effective than intranasal corticosteroids. Improvement in symptom relief in patients with allergic rhinitis has been reported when an antihistamine is given in combination with a decongestant or with an intranasal steroid. Numerous formulations combining antihistamines and decongestants are available. Antihistamines have also been shown to be beneficial in the treatment of acute and chronic urticaria/angioedema. With regard to asthma, a significant clinical effect of antihistamines at conventional doses is difficult to document, other than the possible improvement offered by better control of allergic nasal symptoms.

Second-generation antihistamines are preferable over first-generation antihistamines for the treatment of allergic disease in children because of negligible sedative and anticholinergic effects without a sacrifice in efficacy. Most second-generation antihistamines are effective with convenient once-daily dosing, which may improve therapy adherence. The widespread availability of first-generation antihistamines and their lower cost account for their continued use. The adverse effects most often encountered with second-generation agents include the performance impairment and anticholinergic effects noted with first-generation antihistamines although generally to a lesser degree. The anticholinergic adverse effects encountered may include drying of the mouth and eyes, urinary retention, constipation, excitement, nervousness, palpitations, and tachycardia. Prolongation of the QT interval and ventricular tachycardia (torsades de pointes) has been noted in older, no longer available second-generation antihistamines; current antihistamines are not associated with concerning cardiac effects.

### Chromones

Cromolyn sodium and nedocromil sodium are the 2 chromones used to treat allergic disorders. Neither cromolyn nor nedocromil is absorbed well orally, with only 1% of the swallowed dose absorbed. These drugs must be applied topically to the mucosal surface of the target organ to be effective. Both drugs inhibit mast cell degranulation and mediator release. They suppress the activation of a variety of cells, such as eosinophils, neutrophils, macrophages, and epithelial cells. They also suppress the activity of afferent C-type sensory nerve fibers of the nonadrenergic, noncholinergic nervous system. Both drugs inhibit the intracellular increase in free calcium after mast cell activation and phosphorylate a mast cell protein resembling moesin, which is thought to be involved in terminating mediator release.

Cromolyn and nedocromil prevent early- and late-phase allergic responses when administered before allergen exposure. They block allergen-induced increases in bronchial hyperresponsiveness, as well as seasonal increases in nonspecific bronchial hyperresponsiveness. With prolonged use, both drugs are capable of reducing bronchial hyperresponsiveness. These drugs have no bronchodilator properties but can inhibit the bronchoconstrictive effects of a variety of stimuli, such as allergen challenge, exercise, hyperventilation with cold air,
Cromolyn and nedocromil are used as alternative, but not preferred, therapy for the treatment of mild persistent asthma. Because of their lack of bronchodilator properties, neither drug is useful for the treatment of acute asthma, although both may be used as preventive therapy before vigorous exercise or unavoidable known allergen exposure. Nedocromil is the more potent of the two, but no formulation of nedocromil is currently available for asthma in the United States. Cromolyn is available for the treatment of asthma by prescription as a 1% solution (20 mg/2 mL) for nebulization. The suggested dose for the treatment of asthma is 20 mg of cromolyn 2-4 times/24 hr by nebulization. In numerous studies, cromolyn has been found useful in the treatment of allergic rhinitis and allergic conjunctivitis. Preparations for the nasal and ocular administration of cromolyn are available without a prescription. The suggested dose for the treatment of allergic rhinitis is one spray in each nostril 3 to 4 times daily of a nasal spray containing 5.2 mg of cromolyn per spray (see Table 143-5). For the treatment of allergic conjunctivitis, the suggested dose is 1 drop in each eye 4-6 times a day of a 4% ophthalmic solution. A 2% solution of nedocromil is available by prescription for the treatment of allergic conjunctivitis at a suggested dose of 1-2 drops in each eye twice daily.

The safety of these drugs, even with prolonged administration, is well documented. Because of their favorable safety profile, the monomers are often chosen for use during pregnancy.

**Glucocorticoids**

Glucocorticoids are widely used in the treatment of allergic disorders because of their potent antiinflammatory properties. The diverse antiinflammatory actions of glucocorticoids are mediated via the glucocorticoid receptor, which is present in all inflammatory effector cells, as well as by direct inhibition of cytokines and mediators. Glucocorticoids are administered topically in ophthalmic preparations, nasal sprays, creams and ointments, metered-dose inhalers, and as a solution for nebulization. Systemic administration is accomplished orally or parenterally. The proper use and efficacy of glucocorticoids in the treatment of allergic disease along with the adverse effects associated with their use are presented in discussions of individual allergic diseases (see Chapters 142-152).

**Leukotriene-Modifying Agents**

Drugs that alter the leukotriene pathway exert their clinical effects either by inhibiting leukotriene production or by blocking receptor binding. These agents possess mild antiinflammatory properties and exhibit bronchodilator effects. In addition to inhibiting the early- and late-phase allergic responses to inhaled allergen, they diminish bronchoconstriction induced by exercise and exposure to aspirin, cold air. Leukotriene-modifying agents have some use in the treatment of asthma (see Chapter 144) and are modestly effective in the treatment of allergic rhinitis (see Chapter 143).

**Theophylline**

Because of its bronchodilating effects, theophylline (3,7-dimethylxanthine) had been used for yr for the treatment of acute and chronic asthma. The bronchodilator effect of theophylline is likely caused by its action as a phosphodiesterase inhibitor, whereas its ability to antagonize adenosine receptors may play a role in other effects, such as the attenuation of diaphragmatic muscle fatigue and diminishing adenosine-enhanced mast cell mediator release. Theophylline inhibits the immediate- and late-phase pulmonary responses to allergen challenge and exhibits modest protective effects. The therapeutic and toxic effects of theophylline are related to the serum concentration, with the incidence of toxic effects significantly increasing as the serum levels approach and exceed 20 µg/mL. A variety of conditions and medications are capable of increasing or decreasing theophylline metabolism. The toxic effects of theophylline, ranging from mild nausea, insomnia, irritability, tremors, and headache to cardiac arrhythmias, seizures, and death, necessitate the routine monitoring of theophylline serum levels. Because of the introduction of other effective therapies for the treatment of acute and chronic asthma, the need to monitor drug serum levels routinely, and the potential for significant toxicity, the role of theophylline in the treatment of asthma has contracted significantly (see Chapter 144).

**Lodoxamide Tromethamine**

A mast cell stabilizer, lodoxamide tromethamine is more effective than topical cromolyn sodium in alleviating signs and symptoms of allergic ocular disease (see Chapter 147). It is used in children >2 yr of age for vernal keratoconjunctivitis, vernal conjunctivitis, and vernal keratitis. Occasional adverse effects have included transient burning or stinging after instillation.

**Combination Mast Cell Stabilizer and Antihistamine**

Olopatadine, epinastine, and ketotifen are examples of combination mast cell stabilizers and H<sub>1</sub>-receptor antagonists effective in relieving signs and symptoms of allergic conjunctivitis after topical instillation, although all H<sub>1</sub>-antihistamines likely have some mast cell stabilizing activity. Dosing is typically twice per day, except of olopatadine, which is dosed once daily.

**Antiimmunoglobulin E**

Monoclonal antiimmunoglobulin E antibodies (anti-IgE) bind to circulating IgE at a site that prevents its subsequent attachment to the high-affinity receptors for IgE on the mast cell surface. The parental administration of anti-IgE reduces free serum IgE concentrations, inhibits skin test responses in allergic patients, suppresses early- and late-phase responses to allergens, and decreases sputum eosinophilia in asthmatic persons. Anti-IgE has a beneficial effect in the treatment of patients with asthma, allergic rhinitis, and urticaria. An anti-IgE preparation (omalizumab) is available for the treatment of children ≥12 yr of age with documented allergen-induced asthma that is inadequately controlled by inhaled corticosteroids. Although this agent is usually well tolerated, local reactions at the injection site and rare episodes of anaphylaxis have been reported. Anti-IgE may also be beneficial in the treatment of other allergic disorders, such as anaphylaxis and food allergy, but more studies are needed. One monoclonal antibody preparation of anti-IgE used in the treatment of adults with peanut allergy resulted in a significant increase in the symptom threshold dose of peanuts. The cost of anti-IgE therapy and need for regular injections requires careful patient selection, special consideration being given to those patients with persistent symptoms despite aggressive pharmacotherapy, significant adverse effects of current therapy, and more than 1 allergic disorder.

**Nasal Saline Irrigation**

Irrigation with nasal saline can improve symptoms for those with mild allergic rhinitis. Nasal saline irrigation can be used alone or before topical medication. Squeeze bottle kits for this purpose are available over the counter, and typically about 200 mL are irrigated through the nares. Patients may make their own irrigation solutions or buy commercially-prepared solutions. Patients should use boiled or distilled water, as cases of sinus infection with amoebas found in tap water have been reported.

**New Therapies**

Recombinant soluble interleukin (IL)-4 receptor antagonists exert their effects by binding to and inactivating IL-4 before it can attach to its cell surface receptor. Although initial studies of an inhaled soluble IL-4 receptor in patients with moderate asthma requiring inhaled corticosteroids suggested a beneficial clinical effect, subsequent clinical studies of the effects of anti–IL-4 drugs in the treatment of asthma revealed these therapies to be safe, but clinical efficacy was lacking. Clinical trials of humanized monoclonal anti–IL-5 antibodies administered by injection to asthmatic patients revealed a decrease in circulating eosinophils and sputum eosinophilia, but a lesser reduction of eosinophils from the bronchial submucosa, and this effect was
unaccompanied by a reduction in methacholine reactivity or a suppression of the early- or late-phase response to allergen.

The use of cytokines with antiinflammatory effects in the treatment of allergic disorders is under investigation. Unfortunately, initial studies have not demonstrated a beneficial effect of IL-10 or interferons in the treatment of asthma. Although studies have documented that IL-12 administration is associated with a decrease in eosinophil accumulation in response to allergen challenge, inhibition of early- and late-phase responses to allergen and decreases in bronchial hyperreactivity have not been observed. In addition, the high incidence of significant adverse effects encountered with IL-12 administration limits its potential as a viable therapeutic option.

**ALLERGEN IMMUNOTHERAPY**

Allergen immunotherapy involves administering gradually increasing doses of allergens to a person with allergic disease for the purpose of reducing or eliminating the patient’s adverse clinical response to subsequent natural exposure to those allergens. When properly administered, to an appropriate candidate, allergen immunotherapy is a safe, effective form of therapy capable not only of reducing or preventing symptoms but also of potentially altering the natural history of the disease by minimizing disease duration and preventing disease progression. Conventional allergen immunotherapy is given subcutaneously under the direction of an experienced allergist. Sublingual immunotherapy (SLIT) is widely used in Europe for Aeroallergens but is not yet FDA-approved in the United States. Sublingual and oral immunotherapy (OIT) for foods are being investigated and are also not FDA-approved.

**Indications and Contraindications**

Allergen immunotherapy is reserved for patients with an allergic disease demonstrated to respond to this form of therapy, such as seasonal or perennial allergic rhinoconjunctivitis, asthma triggered by allergen exposures, and insect venom sensitivity. Proof of the efficacy of conventional allergen immunotherapy for the treatment of food allergy, atopic dermatitis, latex allergy, and acute or chronic urticaria is lacking; consequently, conventional allergen immunotherapy is not recommended for the treatment of these disorders. Before allergen immunotherapy is considered, sensitivity of the patient to the allergens to be administered should be documented by a positive skin test result or an in vitro test revealing an increased serum level of allergen-specific IgE. The clinical relevance of these allergens should be supported by a history of symptoms upon known exposure or a timing of symptoms that correlates well with suspected allergen exposure, such as the presence of allergic nasal and ocular symptoms throughout the late summer and fall in a child with a positive ragweed skin test response. The duration and severity of the patient’s symptoms, as well as the patient’s preferences, should warrant the expense, effort, and risk associated with the administration of allergen immunotherapy. The presence of disabling symptoms in spite of a trial of allergen avoidance and appropriate medications at a suitable dose should be documented.

Venom immunotherapy (VIT) is indicated in children <16 yr of age who have experienced respiratory or cardiovascular symptoms following a sting. For those ≥16 yr, VIT is indicated for any systemic reaction, including those limited to skin but not contiguous from the site of the sting (see Chapter 146).

Other factors that may affect the decision to institute allergen immunotherapy include quality-of-life issues, such as the amount of school missed or medical resource utilization, the age of the patient, and other logistical factors. With the exception of VIT, few data for the efficacy of allergen immunotherapy in children <5 yr of age are available. Allergen immunotherapy is not recommended for children <5 yr of age because of their increased risk of systemic reactions, the special expertise required to treat anaphylaxis in this age group, their potential inability to communicate clearly with the physician in the event of an allergic reaction, and their age-related potential for emotional distress with frequent injections. Other important logistic factors include the willingness of the patient to comply with a schedule of frequent injections over the course of several yr, cost considerations, and the availability of an appropriate medically supervised setting for administering allergen immunotherapy.

Allergen immunotherapy is contraindicated in children undergoing β-blocker therapy as well as those with certain immunologic or autoimmune disorders, allergic bronchopulmonary aspergillosis, hypersensitivity pneumonitis, severe psychiatric disturbance, or a medical condition that would impair the ability to survive an allergic reaction. Pregnancy is a contraindication to the initiation of allergen immunotherapy or dosing increases, although a pregnant adolescent can continue to receive her usual maintenance dose. Patients with unstable asthma should not be started on allergen immunotherapy because of their increased risk for anaphylaxis. Allergen immunotherapy is not used for the treatment of allergic bronchopulmonary aspergillosis or hypersensitivity pneumonitis because it has no benefit. Children receiving β-blockers and angiotensin-converting enzyme inhibitors are not ideal candidates for allergen immunotherapy because of an increased intensity of allergic reactions and a poor response of conventional therapy to these reactions with β-blocker therapy. Allergen immunotherapy is usually avoided in patients with autoimmune disorders because of the theoretical concern for stimulation of the immune system (formation of antigen–antibody complexes), which might result in disease activation.

**Allergen Extracts**

The potency of the aqueous extracts used in allergen immunotherapy is affected by numerous factors. Allergens from weed and grass pollens are more easily extracted in aqueous solutions and, as a result, are more potent than extracts obtained from other sources, such as molds, tree pollens, and dust mites. Owing to their complexity, allergen extracts from mold allergens are more variable than extracts from pollen allergens. Refrigeration and appropriate handling of allergen extracts used in allergen immunotherapy are important because degradation of many allergen extracts, such as those from tree, grass, weed pollens, and dust mites, may occur at higher temperatures. Dilute extracts are more susceptible to loss of potency resulting from adherence of allergen to the glass vial than are more concentrated extracts. To combat this effect, preservatives such as 0.03% human serum albumin or 10-50% glycerin may be added to dilute allergen extracts. Some allergen extracts, such as those from cockroaches, dust mites, and molds, contain proteases capable of degrading other allergens in the extract. It is often recommended that these allergens not be mixed with those from tree, grass, and weed pollens. Insect venoms are never mixed with other allergens. When available, the use of standardized allergen extracts is preferred to ensure consistency in dosing and to avoid the variability in allergen content encountered with nonstandardized allergen extracts.

**Allergen Extract Administration**

The goal of allergen immunotherapy is to increase gradually the dose of allergen extract administered until the injection of an “optimal” maintenance dose containing 4-12 µg of each major allergen in the extract is reached. The mixture of allergen extracts administered during the course of allergen immunotherapy is individually formulated for each patient on the basis of the patient’s documented sensitivities. Although various dosing schedules are used, initial injections are most often given at 5-10-day intervals year-round. Schedules of allergen administration are selected according to the sensitivity of the patient to the allergens in the extract. The most sensitive patients are advanced to a maintenance dose more gradually. Doses of allergen immunotherapy are increased according to a set schedule, although the reaction to the previous injection is also taken into account. A systemic reaction to the previous dose would result in a significant reduction in the next dose, whereas reducing the dose solely on the basis of a large local reaction does not reduce the rate of systemic reactions. Usually 5-6 mo of weekly injections is required to reach the maintenance dose, although it may take longer in highly sensitive patients. Unique schedules for the administration of insect venoms, which differ from those for the administration of other allergens (see Chapter 146), are used. Once the maintenance dose is reached and well tolerated, the interval between injections is increased to a few weeks.
or a month. Because allergen extracts gradually lose potency, the first dose from a fresh replacement vial of maintenance allergen extract is reduced by 25-75% and is then increased in increments weekly until the usual maintenance dose is reached. The recommended length for a course of allergen immunotherapy is 3-5 yr. Insect VIT may be continued indefinitely in patients with a history of life-threatening anaphylaxis. Patients who have not shown improvement after 1 year of receiving maintenance doses of an appropriate allergen extract are unlikely to benefit, and allergen immunotherapy should be discontinued. Most patients enjoy a sustained improvement after allergen immunotherapy whereas others experience a gradual return of symptoms. Those who experience a relapse would be expected to respond upon resuming immunotherapy.

**Rush immunotherapy** is the administration of multiple injections either in a single day or over several days in an attempt to reach maintenance dose more rapidly. The risk of adverse reactions, including systemic reactions, is higher than with traditional allergen immunotherapy schedules. Patients to undergo rush immunotherapy are often pretreated with antihistamines and corticosteroids. Children are at even greater risk for adverse reactions with rush immunotherapy; thus the benefits and risks should be fully considered. Preadministration of omalizumab (anti-IgE therapy) reduces the incidence of systemic reactions associated with the use of this form of immunotherapy.

Although allergen immunotherapy is regarded as safe, the potential for anaphylaxis always exists when patients are injected with extracts containing allergens to which they are sensitized. Allergen immunotherapy should be offered in only medical settings where a physician with access to emergency equipment and medications required for the treatment of anaphylaxis is available (see Chapter 149). Allergen injections should never be given at home or by untrained personnel. The patient should remain in the office for 30 min after the injection because most reactions to allergen immunotherapy begin within this time frame. Fatal anaphylaxis triggered by allergen immunotherapy, although rare, is estimated to occur at an incidence of 1 per 2 million injections. The risk of an adverse reaction is increased by dosage errors and the use of rush immunotherapy schedules. Particular caution is warranted when injections from a new vial are given. Patients with exquisite sensitivity or unstable asthma and those experiencing exacerbations of allergic rhinitis or asthma are also at increased risk for adverse reactions to allergen immunotherapy. Precautions to reduce significant adverse reactions include using standardized extracts, having extract vials personalized for each patient, allowing only trained personnel to administer injections, paying careful attention to detail when giving injections, ensuring beforehand that the patient is medically stable, having appropriate medications and equipment available, and requiring the patient to remain in the office for 30 min after each injection. Checking peak flow or spirometry before an injection is advisable for some asthmatic patients. It is also prudent to advise patients to carry self-injectable epinephrine for 24 hr following each injection. While uncommon, delayed systemic reactions have been reported following immunotherapy injections.

Other approaches to immunotherapy are under investigation; they include chemical or genetic manipulation of the allergen and linking of the principle allergenic moiety of a relevant allergen to a highly active adjuvant, such as an immunostimulatory sequence mimicking patterns of bacterial DNA.

Local nasal immunotherapy is administered by having the patient spray allergen solutions into the nose at scheduled intervals. Although symptom improvement has been noted, a lack of a significant systemic immunologic response has decreased interest in pursuing this form of therapy. SLIT involves the sublingual administration of high-dose allergen, which is then swallowed. SLIT is now FDA-approved for a limited number of pollens, and its use is expected to increase given its favorable safety profile and convenience of administration.

**Efficacy**

The positive impact of allergen immunotherapy on seasonal or perennial allergic rhinitis or rhinoconjunctivitis is well documented. In regard to the treatment of allergic rhinitis, birch, mountain cedar, grass, ragweed, and *Cladosporium* are allergens for which allergen immunotherapy has been effective. Effectiveness of allergen immunotherapy with other allergens commonly used for the treatment of allergic rhinitis is inconclusive. Most of the controlled trials examining the effects of allergen immunotherapy on seasonal or perennial allergic asthma also report favorable results. A meta-analysis of 20 trials examining the effects of allergen immunotherapy on allergic asthma revealed a significant increase in the odds for improvement after treatment along with fewer symptoms, improved pulmonary functions, less need for medication, and a reduction in bronchial hyperreactivity. The most convincing data for the benefit of allergen immunotherapy in the treatment of allergic asthma are available for birch, mountain cedar, grass, ragweed, and dust mite with less conclusive but suggestive data available for *Cladosporium*, *Alternaria*, and cat allergens. Studies examining the effects of allergen immunotherapy in the treatment of patients with allergic rhinitis and allergic asthma have documented increases in circulating allergen-specific IgG and decreases in allergen-specific IgE after treatment. Reductions in sensitivity to administrered allergens have been demonstrated in nasal and bronchial challenges. These studies have often shown that the late-phase response after allergen challenge is ablated or significantly reduced. The protective benefit as well as the safety of VIT in patients with sensitivity to *Hymenoptera* venoms has also been well documented in several large studies. The efficacy of allergen immunotherapy for the treatment of urticaria and latex allergy has not been documented. Dust mite allergen immunotherapy may be helpful in patients with atopic dermatitis. Studies using OIT, involving the oral administration of gradually increasing doses of a food allergen under close medical observation followed by a prolonged maintenance phase of daily fixed-dose food allergen administration at home, has been shown to desensitize patients but has not yet proven to induce tolerance. Although still under investigation, OIT and perhaps SLIT are promising therapeutic approaches to the treatment of food allergy in the future.

Bibliography is available at Expert Consult.
Bibliography
The Medical Letter: Fexofenadine (Allegra) and fruit juice, Med Lett Drugs Ther 53:41, 2011.
Allergic rhinitis (AR) is an inflammatory disorder of the nasal mucosa marked by nasal congestion, rhinorrhea, and itching, often accompanied by sneezing and conjunctival inflammation. Its recognition as a major chronic respiratory disease of children rests largely on its high prevalence, detrimental effects on quality of life and school performance, and comorbidities. Children with AR often have related conjunctivitis, sinusitis, otitis media, serous otitis, hypertrophic tonsils and adenoids, and eczema. Childhood AR is associated with a 3-fold increase in risk for asthma at an older age. Over the past 50 yr an upsurge in AR has been observed throughout the world, particularly in areas where its prevalence previously had been low. In prosperous societies, 20-40% of children suffer from AR. The symptoms may appear in infancy; with the diagnosis generally established by the time the child reaches age 6 yr. The prevalence peaks late in childhood.

Risk factors include family history of atopy and serum immunoglobulin (Ig) E higher than 100 IU/mL before age 6 yr. Early life exposures and/or their absence have a profound influence on the development of the allergic phenotype. The risk increases in children whose mothers smoke heavily, even before delivery and especially before the infants are 1 yr old, and those with heavy exposure to indoor allergens. A critical period exists early in infancy when the genetically susceptible individual is at greatest risk of sensitization. Delivery by
ETIOLOGY AND CLASSIFICATION

Two factors necessary for expression of AR are sensitivity to an allergen and the presence of the allergen in the environment. AR classification as **seasonal** or **perennial** is giving way to the designations **intermittent** and **persistent**. The 2 sets of terms are based on different suppositions, but inhalant allergens are the main cause of all forms of AR irrespective of terminology. AR may also be categorized as **mild-intermittent**, **moderate-severe intermittent**, **mild-persistent**, and **moderate-severe persistent** (Fig. 143-1). The symptoms of intermittent AR occur on <4 days per week or for <4 consecutive weeks. In persistent AR symptoms occur on >4 days per week and/or for >4 consecutive weeks. The symptoms are considered mild when they are not troublesome, the sleep is normal, there is no impairment in daily activities, and no incapacity at work or school. Severe symptoms result in sleep disturbance, and impairment in daily activities and school (Fig. 143-1).

In temperate climates, airborne pollen responsible for exacerbation of intermittent AR appear in distinct phases: trees pollinate in the spring, grasses in the early summer, and weeds in the late summer. In temperate climates, mold spores persist outdoors only in the summer, but in warm climates throughout the year. Symptoms of intermittent AR typically cease with the appearance of frost. Knowledge of the time of occurrence of symptoms, of the regional patterns of pollination and mold sporulation, and of the patient's specific IgE is necessary for the recognition of the cause of intermittent AR. Persistent AR is most often associated with the indoor allergens: house dust mites, animal danders, mold, cockroaches, and the ubiquitous major cat allergen Fel d 1, may be carried on cat owners' clothing into such "cat-free" settings as schools and hospitals.

**PATHOGENESIS**

The exposure of an atopic host to an allergen leads to specific IgE production. The clinical reactions on reexposure to the allergen have been designated as early-phase and late-phase allergic responses. Bridging of the IgE molecules on the surface of mast cells by allergen initiates early-phase allergic response, characterized by degranulation of mast cells and release of preformed and newly generated inflammatory mediators including histamine, prostaglandin 2, and the cysteinyl leukotrienes. Late-phase allergic response appears 4-8 hr following allergen exposure. Inflammatory cells, including basophils, eosinophils, neutrophils, mast cells, and mononuclear cells, infiltrate the nasal mucosa. Eosinophils release proinflammatory mediators, including cysteinyl leukotrienes, cationic proteins, eosinophil peroxidase, and major basic protein, and serve as a source of interleukin (IL)-3, IL-5, granulocyte-macrophage colony-stimulating factor, and IL-13. Repeated intranasal introduction of allergens causes "priming"—a more brisk response even with a lesser provocation. Over the course of an allergy season a multifold increase in submucosal mast cells takes place. These cells, once thought to have a role exclusively in the early-phase allergic response, have an important function in sustaining chronic allergic disease. Allergens, autoantigens, and components of superimposed infectious agents activate the immune system.

**CLINICAL MANIFESTATIONS**

Symptoms of AR may be ignored or mistakenly attributed to a respiratory infection. Older children blow their noses, but younger children tend to sniff and snort. Nasal itching brings on grimacing, twitching, and picking of the nose that may result in epistaxis. Children with AR often perform the allergic salute, an upward rubbing of the nose with an open palm or extended index finger. This maneuver relieves itching and briefly unblocks the nasal airway. It also gives rise to the nasal crease, a horizontal skin fold over the bridge of the nose. The diagnosis of AR is based on symptoms in the absence of an upper respiratory tract infection and structural abnormalities. Typical complaints include intermittent nasal congestion, itching, sneezing, clear rhinorrhea, and conjunctival irritation. Symptoms increase with greater exposure to the responsible allergen. The patients may lose their sense of smell and taste. Some experience headaches, wheezing, and coughing. Nasal congestion is often more severe at night, causing mouth breathing and snoring, interfering with sleep, and arousing irritability.

Signs on physical exam include abnormalities of facial development, dental malocclusion, and the "allergic gape" or continuous open-mouth breathing, chapped lips, "allergic shiners" (dark circles under the eyes), and the transverse nasal crease. Conjunctival edema, itching, tearing, and hyperemia are frequent findings. A nasal exam performed with a source of light and a speculum may reveal clear nasal secretions; edematous, boggy, and bluish mucus membranes with little or no erythema; and swollen turbinates that may block the nasal airway. It may be necessary to use a topical decongestant to perform an adequate examination. Thick, purulent nasal secretions indicate the presence of infection.

**DIFFERENTIAL DIAGNOSIS**

Evaluation of AR calls for a thorough history, including details of the patient's environment and diet and family history of allergic conditions such as eczema, asthma, and AR, physical examination, and laboratory evaluation. The history and laboratory findings provide clues to the provoking factors. Symptoms that include sneezing, rhinorrhea, nasal itching, and congestion and the laboratory findings of elevated IgE, specific IgE antibodies, and positive allergy skin test results typify AR. Intermittent AR differs from persistent AR by history and skin test results. Nonallergic rhinitides cause sporadic symptoms. Their causes are often unknown. Nonallergic inflammatory rhinitis with eosinophils imitates AR in presentation and response to treatment, but without elevated IgE antibodies. Vasomotor rhinitis is characterized by excessive responsiveness of the nasal mucosa to physical stimuli. Other nonallergic conditions, such as infectious rhinitis; structural problems, including nasal polyps and septal deviation; rhinitis medicamentosa (caused by the overuse of topical vasoconstrictors); hormonal rhinitis;

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**Figure 143-1** ARIA classification of allergic rhinitis. Every box can be subclassified further into seasonal or perennial on the basis of timing of symptoms or when causative and allergen therapeutic factors are considered. For example, a UK patient with grass pollen allergy might have moderate-to-severe persistent seasonal rhinitis in June and July and be suitable for specific allergen immunotherapy. (From Scadding GK, Durham SR, Mirakian R, et al: BASCl guidelines for the management of allergic and non-allergic rhinitis. Clin Exp Allergy 38:19-42, 2008 [Fig 2, p. 22].)
Causes of Nonallergic Rhinitis

**Structural/mechanical factors:**
- Deviated septum/septal wall anomalies
- Hypertrophic turbinates
- Adenoidal hypertrophy
- Foreign bodies
- Nasal tumors:
  - Benign
  - Malignant
  - Choanal atresia
- Infectious:
  - Acute
  - Chronic

**Inflammatory/immunologic:**
- Granulomatosis with polyangiitis
- Sarcoidosis
- Midline granuloma
- Systemic lupus erythematosus
- Sjögren syndrome
- Nasal polypsis

**Physiologic:**
- Ciliary dyskinesia syndrome
- Atrophic rhinitis

**Hormonally induced:**
- Hypothyroidism
- Pregnancy
- Oral contraceptives
- Menstrual cycle
- Exercise

**Atrophic rhinitis**

**Drug induced:**
- Rhinitis medicamentosa
- Oral contraceptives
- Antihypertensive therapy
- Aspirin
- Nonsteroidal antiinflammatory drugs

**Reflex induced:**
- Gustatory rhinitis
- Chemical or irritant induced
- Posture reflexes
- Nasal cycle
- Environmental factors:
  - Odors
  - Temperature
  - Weather/barometric pressure
  - Occupational
  - Nonallergic rhinitis with eosinophilia syndrome
  - Perennial nonallergic rhinitis (vasomotor rhinitis)
  - Emotional factors


**Complications**

AR is frequently associated with complications and comorbid conditions. Children with AR experience frustration over their appearance. Allergic conjunctivitis, characterized by itching, redness and swelling of the conjunctiva, has been reported in at least 20% of the population and in more the 70% of patients with AR, most frequently in older children and young adults. The 2 conditions share pathophysiologic mechanisms and epidemiologic characteristics (see Chapter 147). Chronic sinusitis is a common complication of AR, sometimes associated with purulent infection, but most patients have negative bacterial cultures despite marked mucosal thickening, and sinus opacification. The inflammatory process is characterized by marked eosinophilia. Allergens, possibly fungal, are the inciting agents. The sinusitis of triad asthma (asthma, sinusitis with nasal polyposis, and aspirin sensitivity) often responds poorly to therapy. Patients who undergo repeated endoscopic surgery derive diminishing benefit with each successive procedure.

Rhinitis that coexists with asthma may be taken too lightly or completely overlooked. Up to 78% of patients with asthma have AR, and 38% of patients with AR have asthma. Aggravation of AR coincides with exacerbation of asthma, and treatment of nasal inflammation reduces bronchospasm, asthma-related emergency department visits, and hospitalizations. Postnasal drip associated with AR commonly causes persistent or recurrent cough. Eustachian tube obstruction and middle ear effusion are frequent complications. Chronic allergic inflammation causes hypertrophy of adenoids and tonsils that may be associated with eustachian tube obstruction, serous effusion, otitis media, and obstructive sleep apnea. AR is linked to snoring in children. The association between rhinitis and sleep abnormalities and subsequent daytime fatigue is well documented.

The Pediatric Rhinoconjunctivitis Quality of Life Questionnaire (PRQLQ) is suitable for children 6-12 yd old, and the Adolescent Rhinoconjunctivitis Quality of Life Questionnaire (ARQLQ) is appropriate for patients 12-17 yr of age. Children with rhinitis have anxiety and physical, social, and emotional issues that affect learning and the ability to integrate with peers. The disorder contributes to headaches and fatigue, limits daily activities, and interferes with sleep. There is evidence of impaired cognitive functioning and learning that may be exacerbated by the adverse effects of sedating medications. Rhinitis is an important cause of lost school attendance, resulting in more than 2 million days of absence in the United States annually.

**Laboratory Findings**

Epicutaneous skin tests provide the best method for detection of allergen-specific IgE (positive predictive value of 48.7% for the epidemiologic diagnosis of AR). They are inexpensive and sensitive, and the risks and discomfort are minimal. Responses to seasonal respiratory allergens are rare before 2 seasons of exposure, and children <1 yr seldom display positive skin test responses to these allergens. To avoid false-negative results, montelukast should be withheld for 1 day, most sedating antihistamine preparations for 3-4 days, and non-sedating antihistamines for 5-7 days. Serum immunoassays for specific IgE to allergens provide a suitable alternative (positive predictive value 43.5%) for patients with dermatographism or extensive dermatitis, those taking medications that interfere with mast cell degranulation, others at high risk for anaphylaxis, and some who cannot cooperate with the procedure. Presence of eosinophils in nasal smear supports the diagnosis of AR, and of neutrophils infectious rhinitis. Eosinophilia and measurements of total serum IgE concentrations have relatively low sensitivity.

**Treatment**

Safe and effective prevention and/or relief of symptoms are the current goals of treatment. Specific measures to limit indoor allergen exposure may reduce the risk of sensitization and symptoms of allergic respiratory disease. Sealing the patient's mattress, pillow, and covers in allergen-proof encasings reduces the exposure to mite allergens. Bed linens and blankets should be washed every week in hot water (>54°F [130°F]). The only effective measure for avoiding animal allergens in the home is the removal of the pet. Avoidance of pollen and outdoor molds can be accomplished by staying in a controlled environment. Air conditioning allows for keeping windows and doors closed, reducing the pollen exposure. High-efficiency particulate air filters lower the counts of airborne mold spores.

Oral antihistamines help reduce sneezing, rhinorrhea and ocular symptoms. Administered as needed they provide acceptable treatment for mild-intermittent disease. Antihistamines have been classified as first generation (relatively sedating) or second generation (relatively non-sedating). Antihistamines usually are administered by mouth, but they are also available for topical ophthalmic and intranasal use. Both first- and second-generation antihistamines are available as nonprescription drugs. Second-generation antihistamines are preferred...
because they cause less sedation. Preparations containing pseudoephedrine, typically in combination with other agents, are used for relief of nasal and sinus congestion and pressure and other symptoms such as rhinorrhea, sneezing, lacrimation, itching eyes, oronasopharyngeal itching, and cough. Pseudoephedrine is available without prescription (generally in fixed combination with other agents such as first-generation antihistamines; brompheniramine, chlorpheniramine, triprolidine; second-generation antihistamines; desloratadine, fexofenadine, loratadine; antipyretics: acetaminophen, ibuprofen; antitussives: codeine, dextromethorphan; anticholinergic: methscopolamine).

Pseudoephedrine is an oral vasoconstrictor disfavored for causing irritability and insomnia and for its association with infant mortality. Because younger children (2-3 yr of age) are at increased risk of overdosage and toxicity, some manufacturers of oral nonprescription cough and cold preparations have voluntarily revised their product labeling to warn against the use of preparations containing pseudoephedrine for children younger than 4 yr. Pseudoephedrine is misused as a starting material for the synthesis of methamphetamine and methcathinone. Oral agents for treatment of AR are shown in Table 143-2, 143-3, and 143-4.

The anticholinergic nasal spray ipratropium bromide is effective for the treatment of serous rhinorrhea (Table 143-5). Intranasal decongestants (oxymetazoline and phenylephrine) should be used for less than 5 days, not to be repeated more than once a month in order to avoid rebound nasal congestion. Sodium cromoglycate (available as nonprescription drug) is effective but requires frequent administration, q4h. Leukotriene-modifying agents have a modest effect on rhinorrhea and nasal blockage (see Chapter 144 for additional indications and side effects). Nasal saline irrigation is a good adjunctive option with all other treatments of AR. Patients with more persistent, severe symptoms require intranasal corticosteroids, the most effective therapy for AR, a treatment that may be beneficial also for concomitant allergic conjunctivitis (Table 143-6). These agents reduce the symptoms of AR with eosinophilic inflammation, but not those of rhinitis associated with neutrophils or free of inflammation. Beclomethasone, triamcinolone, and flunisolide are absorbed from the gastrointestinal tract, as well as from the respiratory tract; budesonide, fluticasone, mometasone, and ciclesonide offer greater topical activity with lower systemic exposure. More severely affected patients may benefit from simultaneous treatment with oral antihistamines and intranasal corticosteroids.

Allergy immunotherapy is an effective treatment for AR and allergic conjunctivitis. In addition to reducing symptoms, it may change the course of allergic disease and induce allergen-specific immune tolerance. Immunotherapy administered by subcutaneous injection should be considered for children in whom IgE-mediated allergic symptoms cannot be adequately controlled by avoidance and medication, especially in the presence of comorbid conditions. Sublingual immunotherapy has been used successfully in Europe and South America. Sublingual immunotherapy is considered investigational in the United States, and there are no extracts for sublingual administration licensed by the FDA. Omalizumab (anti-IgE antibody) given subcutaneously has a dose-dependent effect on seasonal AR; its role compared with standard therapy has yet to be determined.

Typically, treatment of AR with oral antihistamines and inhaled corticosteroids provides sufficient relief for most cases of coexisting allergic conjunctivitis. If it fails, additional therapies directed primarily to allergic conjunctivitis may be added (see Chapter 147). Intranasal corticosteroids are of some value for the treatment of ocular symptoms, but opthalmic corticosteroids remain the most potent pharmacologic agents for ocular allergy. They carry the risk of adverse effects, such as delayed wound healing, secondary infection, elevated intraocular
### Table 143-2 | Oral Allergic Rhinitis Treatments (Prescription, Examples)

#### SECOND-GENERATION ANTIHISTAMINES

<table>
<thead>
<tr>
<th>GENERIC/BRAND</th>
<th>STRENGTH</th>
<th>FORMULATIONS</th>
<th>DOSING</th>
</tr>
</thead>
<tbody>
<tr>
<td>Desloratadine</td>
<td>2.5 mg, 5 mg</td>
<td>Orally disintegrating tablet</td>
<td>Children 6-11 mo of age: 1 mg once daily</td>
</tr>
<tr>
<td>Clarinex RediTabs*</td>
<td>5 mg</td>
<td>Tabs</td>
<td>Children 12 mo-5 yr of age: 1.25 mg once daily</td>
</tr>
<tr>
<td>Clarinex Tablets</td>
<td>0.5 mg/mL</td>
<td>Syrup</td>
<td>Children 6-11 yr of age: 2.5 mg once daily</td>
</tr>
<tr>
<td>Levocetirizine dihydrochloride</td>
<td>0.5 mg/mL</td>
<td>Solution</td>
<td>Adults and adolescents ≥12 yr of age: 5 mg once daily</td>
</tr>
<tr>
<td>Xyzal Oral Solution</td>
<td>0.5 mg/mL</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**SECOND-GENERATION H<sub>1</sub> ANTAGONISTS**

| Montelukast                         | 10 mg            | Tablets                    | 6 mo-5 yr: 4 mg daily                                                |
| Singular                            | 4 mg, 5 mg       | Chewable tablets           | 6-14 yr: 5 mg daily                                                 |
| Singular Oral Granules              | 4 mg/packet      | Oral granules              | >14 yr: 10 mg daily                                                 |

*Contains phenylalanine.


### Table 143-3 | Oral Allergic Rhinitis Treatments (Nonprescription, Examples)

#### FIRST-GENERATION H<sub>1</sub> ANTAGONISTS

<table>
<thead>
<tr>
<th>GENERIC/BRAND</th>
<th>STRENGTH</th>
<th>FORMULATIONS</th>
<th>DOSING</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlorpheniramine maleate</td>
<td>4 mg</td>
<td>Tablets</td>
<td>2-5 yr: 1 mg every 4-6 hr (maximum 6 mg/day)</td>
</tr>
<tr>
<td>Chlor-Trimeton</td>
<td>2 mg/5 mL</td>
<td>Syrup</td>
<td>6-11 yr: 2 mg every 4-6 hr (maximum 12 mg/day)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>&gt;12 yr: 4 mg every 4-6 hr (maximum 24 mg/day)</td>
</tr>
</tbody>
</table>

**SECOND-GENERATION H<sub>1</sub> ANTAGONISTS**

| Cetirizine                          | 1 mg/mL          | Syrup                      | 6-12 mo: 2.5 mg once daily                                           |
|                                    | 5 mg, 10 mg      | Chewable tablets           | 12-23 mo: initial: 2.5 mg once daily; dosage may be increased to 2.5 mg twice daily |
|                                    | 5 mg, 10 mg      | Tablets                    | 2-5 yr: 2.5 mg/day; may be increased to a maximum of 5 mg/day given either as a single dose or divided into 2 doses |
|                                    |                  |                            | >26 yr: 5-10 mg/day as a single dose or divided into 2 doses         |
|                                    |                  |                            |                                                                      |
| Zyrtec Liquid Gels                  | 10 mg            | Liquid-filled gels         |                                                                      |
|                                    |                  |                            |                                                                      |
| Fexofenadine HCl                    | 30 mg            | Tablet                     |                                                                      |
|                                    | 30 mg/5 mL       | Orally disintegrating tablets|                                                                      |
|                                    | 30 mg/5 mL       | Suspension                 |                                                                      |
|                                    | Tabs 30, 60, 180 mg | Tablet                    |                                                                      |
|                                    |                  |                            |                                                                      |
| Loratadine                          | 10 mg            | Orally disintegrating tablets| 2-5 yr: 5 mg once daily                                             |
|                                    | 10 mg            | Tablets                    | >6 yr: 10 mg once daily or 5 mg twice daily                          |
|                                    | 10 mg            | Liquid-filled caps          |                                                                      |
|                                    | 5 mg             | Chewable tablets           |                                                                      |
|                                    | 1 mg/mL          | Syrup                      |                                                                      |

*Contains phenylalanine.


### Table 143-4 | Combined Antihistamine + Sympathomimetic (Examples)

<table>
<thead>
<tr>
<th>GENERIC</th>
<th>STRENGTH</th>
<th>FORMULATIONS</th>
<th>DOSING</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlorpheniramine maleate</td>
<td>4 mg</td>
<td>Tablets</td>
<td>&gt;12 yr: 1 tablet every 4 hr not to exceed 6 tablets per day</td>
</tr>
<tr>
<td>Phenylephrine HCl</td>
<td>10 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sudafed Sinus &amp; Allergy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cetirizine + pseudoephedrine</td>
<td>5 mg cetirizine + 120 mg pseudoephedrine</td>
<td>Extended release tablet</td>
<td>&gt;12 yr: 1 tablet every 12 hr</td>
</tr>
</tbody>
</table>

### Table 143-5  
**Miscellaneous Intranasal Sprays**

<table>
<thead>
<tr>
<th>DRUG</th>
<th>INDICATIONS (I), MECHANISM(s) OF ACTION (M), AND DOSING</th>
<th>COMMENTS, CAUTIONS, ADVERSE EVENTS, AND MONITORING</th>
</tr>
</thead>
</table>
| Ipratropium bromide:        | I: Symptomatic relief of rhinorrhea  
M: Anticholinergic  
Colds (symptomatic relief of rhinorrhea):  
5-12 yr: 2 sprays in each nostril 3 times/day  
≥12 yr and adults: 2 sprays in each nostril 3-4 times/day                                                   | Atrovent inhalation aerosol is contraindicated in patients with hypersensitivity to soy lecithin  
Safety and efficacy of use beyond 4 days in patients with the common cold have not been established  
Adverse effects: Epistaxis, nasal dryness, nausea                                                             |
| Atrovent nasal spray (0.06%)|                                                                                                                        |                                                                                                              |
| Azelastine:                 | I: Treatment of rhinorrhea, sneezing, and nasal pruritus  
M: Antagonism of histamine H₁-receptor  
6-12 yr: 1 spray bid  
>12 yr: 1-2 sprays bid                                                                                         | May cause drowsiness  
Adverse effects: Headache, somnolence, bitter taste                                                              |
| Astelin                     |                                                                                                                        |                                                                                                              |
| Cromolyn sodium:           | I: AR  
M: Inhibition of mast cell degranulation  
>2 yr: 1 spray tid-qid, max x6/day                                                                               | Not effective immediately; requires frequent administration                                                      |
| NasalCrom                  |                                                                                                                        |                                                                                                              |
| Oxymetazoline:             | I: Symptomatic relief of nasal mucosal congestion  
M: Adrenergic agonist, vasoconstricting agent  
0.05% solution: instill 2-3 sprays into each nostril twice daily; therapy should not exceed 3 days          | Excessive dosage may cause profound central nervous system (CNS) depression  
Use in excess of 3 days may result in severe rebound nasal congestion  
Do not repeat more than once a month  
Use with caution in patients with hyperthyroidism, heart disease, hypertension, and diabetes  
Adverse effects: Hypertension, palpitations, reflex bradydcardia, nervousness, dizziness, insomnia, headache, CNS depression, convulsions, hallucinations, nausea, vomiting, mydriasis, elevated intraocular pressure, blurred vision |
| Afrin, Nostrilla            |                                                                                                                        |                                                                                                              |
| Phenylephrine:             | I: Symptomatic relief of nasal mucosal congestion  
M: Adrenergic, vasoconstricting agent  
0.05% solution: instill every 2-4 hr of 0.125% solution as needed. Note: Therapy should not exceed 3 continuous days  
6-12 yr: 1-2 sprays or 1-2 drops every 4 hr of 0.25% solution as needed. Note: Therapy should not exceed 3 continuous days  
>12 yr: 1-2 sprays or 1-2 drops every 4 hr of 0.25% to 0.5% solution as needed; 1% solution may be used in adults with extreme nasal congestion. Note: Therapy should not exceed 3 continuous days | Use in excess of 3 days may result in severe rebound nasal congestion  
Do not repeat more than once a month  
0.16% and 0.125% solutions are not commercially available  
Adverse effects: Reflex bradycardia, excitability, headache, anxiety, and dizziness |
| Neo-Synephrine              |                                                                                                                        |                                                                                                              |

### Table 143-6  
**Intranasal Inhaled Corticosteroids**

<table>
<thead>
<tr>
<th>DRUG</th>
<th>INDICATIONS (I), MECHANISM(s) OF ACTION (M), AND DOSING</th>
<th>COMMENTS, CAUTIONS, ADVERSE EVENTS, AND MONITORING</th>
</tr>
</thead>
</table>
| Beclomethasone:             | I: AR  
M: Antiinflammatory, immune modulator  
6-12 yr: 1 spray in each nostril bid; may increase if needed to 2 sprays in each nostril bid  
>12 yr: 1 or 2 sprays in each nostril bid                                                                           | Shake container before use; blow nose; occlude 1 nostril, administer dose to the other nostril  
Adverse effects: Burning and irritation of nasal mucosa, epistaxis  
Monitor growth                                                                                                        |
| Beconase AQ (42 µg/spray)   |                                                                                                                        |                                                                                                              |
| Qnasl (80 µg/spray)         |                                                                                                                        |                                                                                                              |
| Flunisolide                 | 6-14 yr: 1 spray each nostril 3 times daily or 2 sprays in each nostril twice daily; not to exceed 4 sprays/day in each nostril  
≥15 yr: 2 sprays each nostril twice daily (morning and evening); may increase to 2 sprays 3 times daily; maximum dose: 8 sprays/day in each nostril (400 µg/day) | Shake container before use; blow nose; occlude 1 nostril, administer dose to the other nostril  
Adverse effects: Burning and irritation of nasal mucosa, epistaxis  
Monitor growth                                                                                                        |

Continued
<table>
<thead>
<tr>
<th>DRUG</th>
<th>INDICATIONS (I), MECHANISM(S) OF ACTION (M), AND DOSING</th>
<th>COMMENTS, CAUTIONS, ADVERSE EVENTS, AND MONITORING</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triamcinolone</td>
<td>I: AR M: Antiinflammatory, immune modulator</td>
<td>Shake container before use; blow nose; occlude 1 nostril, administer dose to the other nostril. Adverse effects: Burning and irritation of nasal mucosa, epistaxis. Monitor growth.</td>
</tr>
<tr>
<td>Nasacort AQ (55 µg/spray)</td>
<td>2-6 yr: 1 spray in each nostril qd 6-12 yr: 1-2 sprays in each nostril qd ≥12 yr: 2 sprays in each nostril qd</td>
<td></td>
</tr>
<tr>
<td>Fluticasone furoate: Veramyst (27.5 µg/spray)</td>
<td>2-12 yr: Initial dose: 1 spray (27.5 µg/spray) per nostril once daily (55 µg/day) Patients who do not show adequate response may use 2 sprays per nostril once daily (110 µg/day) Once symptoms are controlled, dosage may be reduced to 55 µg once daily Total daily dosage should not exceed 2 sprays in each nostril (110 µg/day) ≥12 yr and adolescents: Initial dose: 2 sprays (27.5 µg/spray) per nostril once daily (110 µg/day) Once symptoms are controlled, dosage may be reduced to 1 spray per nostril once daily (55 µg/day) Total daily dosage should not exceed 2 sprays in each nostril (110 µg/day)</td>
<td></td>
</tr>
<tr>
<td>Flonase (50 µg/spray)</td>
<td>≥4 yr: 1-2 sprays in each nostril qd</td>
<td></td>
</tr>
<tr>
<td>Mometasone: Nasonex (50 µg/spray)</td>
<td>I: AR M: Antiinflammatory, immune modulator</td>
<td>Mometasone and its major metabolites are undetectable in plasma after nasal administration of recommended doses. Preventive treatment of seasonal AR should begin 2-4 wk prior to pollen season. Shake container before use; blow nose; occlude 1 nostril, administer dose to the other nostril. Adverse effects: Burning and irritation of nasal mucosa, epistaxis. Monitor growth.</td>
</tr>
<tr>
<td>Budesonide: Rhinocort Aqua (32 µg/spray)</td>
<td>I: AR M: Antiinflammatory, immune modulator</td>
<td>Shake container before use; blow nose; occlude 1 nostril, administer dose to the other nostril. Adverse effects: Burning and irritation of nasal mucosa, epistaxis. Monitor growth.</td>
</tr>
<tr>
<td>Ciclesonide: Omnaris Zetonna (50 µg/spray)</td>
<td>I: AR M: Antiinflammatory, immune modulator</td>
<td>Prior to initial use, gently shake, then prime the pump by actuating 8 times. If the product is not used for 4 consecutive days, gently shake and reprime with 1 spray or until a fine mist appears.</td>
</tr>
<tr>
<td>Azelastine/fluticasone (137 µg azelastine/50 µg fluticasone) Dymista</td>
<td>&gt;12 yr: 1 spray in each nostril bid</td>
<td>Shake bottle gently before using. Blow nose to clear nostrils. Keep head tilted downward when spraying. Insert applicator tip 1/4 to 1/2 inch into nostril, keeping bottle upright, and close off the other nostril. Breathe in through nose. While inhaling, press pump to release spray.</td>
</tr>
</tbody>
</table>
pressure, and formation of cataracts. These agents are only suited for the treatment of allergic conjunctivitis that does not respond to the medications discussed above. Sound practice calls for the assistance of an ophthalmologist.

**PROGNOSIS**

Therapy with nonsedating antihistamines and topical corticosteroids, when taken faithfully, significantly improves health-related quality-of-life measures in patients. The reported rates of remission among children are between 10% and 23%. Pharmacotherapy that will target cells and cytokines involved in inflammation and treat allergy as a systemic process is on the horizon, and more selective targeting of drugs based on the development of specific biomarkers and genetic profiling may soon be realized.

_Bibliography is available at Expert Consult._
Bibliography


Asthma is a chronic inflammatory condition of the lung airways resulting in episodic airflow obstruction. This chronic inflammation heightens the twitchiness of the airways—airways hyperresponsiveness (AHR)—to provocative exposures. Asthma management is aimed at reducing airways inflammation by minimizing proinflammatory environmental exposures, using daily controller antiinflammatory medications, and controlling comorbid conditions that can worsen asthma. Less inflammation typically leads to better asthma control, with fewer exacerbations and decreased need for quick-reliever asthma medications. Nevertheless, exacerbations can still occur. Early intervention with systemic corticosteroids greatly reduces the severity of such episodes. Advances in asthma management and, especially, pharmacotherapy enable all but the uncommon child with difficult asthma to live normally.

**ETIOLOGY**

Although the cause of childhood asthma has not been determined, a combination of environmental exposures and inherent biologic and genetic susceptibilities has been implicated (Fig. 144-1). In the susceptible host, immune responses to common airways exposures (e.g., respiratory viruses, allergens, tobacco smoke, air pollutants) can stimulate prolonged, pathogenic inflammation and aberrant repair of injured airways tissues. Lung dysfunction (AHR, reduced airflow) and airway remodeling develop. These pathogenic processes in the growing lung during early life adversely affect airways growth and differentiation, leading to altered airways at mature ages. Once asthma has developed, ongoing inflammatory exposures appear to worsen it, driving disease persistence and increasing the risk of severe exacerbations.

**Genetics**

To date, more than 100 genetic loci have been linked to asthma, although relatively few have consistently been linked to asthma in different study cohorts. Replicating variants include genetic loci containing proallergenic, proinflammatory genes. Because epigenetic marks are heritable, they are responsive to environmental exposures, and can result in rapid and persistent changes in gene expression it is conceivable that epigenetic modification of genes play a role in the transmission of asthma.

**Environment**

Recurrent wheezing episodes in early childhood are associated with common respiratory viruses, especially common cold rhinoviruses, and also respiratory syncytial virus, influenza virus, adenovirus, parainfluenza virus, and human metapneumovirus. This association implies that host features affecting immunologic host defense, inflammation, and the extent of airways injury from ubiquitous viral pathogens underlie susceptibility to recurrent wheezing in early childhood. Other airway exposures can also exacerbate ongoing airways inflammation, increase disease severity, and drive asthma persistence. Home allergen exposures in sensitized individuals can initiate airways inflammation and hypersensitivity to other irritant exposures, and are strongly linked to disease severity and persistence. Consequently, eliminating the offending allergen(s) can lead to resolution of asthma symptoms and can sometimes cure asthma. Environmental tobacco smoke and common air pollutants can aggravate airways inflammation and increase asthma severity. Cold, dry air, hyperventilation from physical play or exercise, and strong odors can trigger bronchoconstriction. Although many exposures that trigger and aggravate asthma are well recognized, the causal environmental factors underlying the development of host susceptibilities to the various common airway exposures are not well defined.

**EPIDEMIOLOGY**

Asthma is a common chronic disease, causing considerable morbidity. In 2011, more than 10 million children (14% of U.S. children) had ever been diagnosed with asthma, with 70% of this group reporting current asthma. Male gender and living in poverty are demographic risk factors for having childhood asthma in the U.S. Fifteen percent of boys...
compared to 13% of girls who have had asthma; and 18% of all children living in poor families (incomes less than $25,000 per year), compared to 12% of children in families not classified as poor, have had asthma. Childhood asthma is among the most common causes of childhood emergency department visits, hospitalizations, and missed school days. In the United States in 2006, childhood asthma accounted for 593,000 emergency department visits, 155,000 hospitalizations, and 167 deaths. A disparity in asthma outcomes links high rates of asthma hospitalization and death with poverty, ethnic minorities, and urban living. In the past 2 decades, black children have had 2-7 times more emergency department visits, hospitalizations, and deaths as a result of asthma than nonblack children. Although current asthma prevalence is higher in black than in nonblack U.S. children (in 2011, 16.5% vs 8.1% for white and 9.8% for Latino children), prevalence differences cannot fully account for this disparity in asthma outcomes.

Worldwide, childhood asthma appears to be increasing in prevalence, despite considerable improvements in our management and pharmacopoeia to treat asthma. Numerous studies conducted in different countries have reported an increase in asthma prevalence of approximately 50% per decade. Globally, childhood asthma prevalence varies widely in different locales. A study of childhood asthma prevalence in 233 centers in 97 countries (International Study of Asthma and Allergies in Childhood, Phase 3) found a wide range in the prevalence of current wheeze in 6-7 yr (2.4-37.6%) and 13-14 yr old children (0.8-32.6%). Asthma prevalence correlated well with reported allergic rhinoconjunctivitis and atopic eczema prevalence. Childhood asthma seems more prevalent in modern metropolitan locales and more affluent nations, and is strongly linked with other allergic conditions. In contrast, children living in rural areas of developing countries and farming communities with domestic animals are less likely to experience asthma and allergy.

Approximately 80% of all asthmatic patients report disease onset prior to 6 yr of age. However, of all young children who experience recurrent wheezing, only a minority go on to have persistent asthma in later childhood. Early childhood risk factors for persistent asthma have been identified (Table 144-1) and have been described as major (parent asthma, eczema, infantile atopy, and allergen sensitization) and minor (allergic rhinitis, wheezing apart from colds, ≥4% peripheral blood eosinophils, food allergen sensitization) risk factors. Allergy in young children with recurrent cough and/or wheeze is the strongest identifiable factor for the persistence of childhood asthma.

Types of Childhood Asthma
There are 2 common types of childhood asthma based on different natural courses: (1) recurrent wheezing in early childhood, primarily triggered by common viral respiratory infections, usually resolves during the preschool/lower school years; and (2) chronic asthma associated with allergy that persists into later childhood and often adulthood (Table 144-2). School-age children with mild-moderate persistent asthma generally improve as teenagers, with some (~40%) developing intermittent disease. Milder disease is more likely to remit. Inhaled corticosteroid controller therapy for children with persistent asthma does not alter the likelihood of outgrowing asthma in later childhood; however, because children with asthma generally improve with age, their need for controller therapy subsequently lessens and often resolves. Progressive decline in lung function can be a feature of severe, persistent disease.

Asthma is also classified by disease severity (e.g., intermittent or persistent [mild, moderate, or severe]) or control (e.g., well, not well, or very poorly controlled), especially for asthma management purposes. Because most children with asthma can be well controlled with conventional management guidelines, children with asthma can also be characterized according to treatment response and medication requirements as being: (1) easy-to-treat: well controlled with low dose as-needed controller therapy, (2) difficult-to-treat: severe asthma requiring high level of daily controller therapy, or (3) refractory: despite being well controlled, continue to have severe exacerbations.

### Table 144-1 | Early Childhood Risk Factors for Persistent Asthma

<table>
<thead>
<tr>
<th>Risk Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parental asthma</td>
</tr>
<tr>
<td>Atopic dermatitis (eczema)</td>
</tr>
<tr>
<td>Allergic rhinitis</td>
</tr>
<tr>
<td>Food allergy</td>
</tr>
<tr>
<td>Infantile atopy</td>
</tr>
<tr>
<td>Food allergen sensitization</td>
</tr>
<tr>
<td>Severe lower respiratory tract infection</td>
</tr>
<tr>
<td>Pneumonia</td>
</tr>
<tr>
<td>Bronchiolitis requiring hospitalization</td>
</tr>
<tr>
<td>Wheezing apart from colds</td>
</tr>
<tr>
<td>Male gender</td>
</tr>
<tr>
<td>Low birthweight</td>
</tr>
<tr>
<td>Environmental tobacco smoke exposure</td>
</tr>
<tr>
<td>Reduced lung function at birth</td>
</tr>
</tbody>
</table>

### Table 144-2 | Asthma Patterns in Childhood, Based on Natural History and Asthma Management

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TRANSIENT NONATOPIC WHEEZING</strong></td>
<td>Common in early preschool years</td>
</tr>
<tr>
<td>Recurrent cough/wheeze, primarily triggered by common respiratory viral infections</td>
<td></td>
</tr>
<tr>
<td>Usually resolves during the preschool and lower school years, without increased risk for asthma in later life</td>
<td></td>
</tr>
<tr>
<td>Reduced airflow at birth, suggestive of relatively narrow airways. AHR near birth. Improves by school age</td>
<td></td>
</tr>
<tr>
<td><strong>PERSISTENT ATOPY-ASSOCIATED ASTHMA</strong></td>
<td>Begins in early preschool years</td>
</tr>
<tr>
<td>Associated with atopy in early preschool years:</td>
<td></td>
</tr>
<tr>
<td>• Clinical (e.g., atopogenic dermatitis in infancy, allergic rhinitis, food allergy)</td>
<td></td>
</tr>
<tr>
<td>• Biologic (e.g., early inhalant allergen sensitization, increased serum immunoglobulin E, increased blood eosinophils)</td>
<td></td>
</tr>
<tr>
<td>• Highest risk for persistence into later childhood and adulthood</td>
<td></td>
</tr>
<tr>
<td>Lung function abnormalities:</td>
<td></td>
</tr>
<tr>
<td>• Those with onset before 3 yr of age acquire reduced airflow by school age</td>
<td></td>
</tr>
<tr>
<td>• Those with onset of symptoms, or with later onset of allergen sensitization, are less likely to experience airflow limitation in childhood</td>
<td></td>
</tr>
<tr>
<td><strong>ASTHMA WITH DECLINING LUNG FUNCTION</strong></td>
<td>Children with asthma with progressive increase in airflow limitation</td>
</tr>
<tr>
<td>Associated with hyperinflation in childhood, male gender</td>
<td></td>
</tr>
</tbody>
</table>

### ASHMA MANAGEMENT TYPES
(From national and international asthma management guidelines)

#### SEVERITY CLASSIFICATION*
- Intrinsic disease severity while not on asthma medications

#### Intermittent
- Mild
- Moderate
- Severe

#### CONTROL CLASSIFICATION*
- Clinical assessment while asthma being managed and treated

#### Well controlled
- Not well controlled
- Very poorly controlled

#### MANAGEMENT PATTERNS
- **Easy-to-treat**: well controlled with low levels of daily controller therapy
- **Difficult-to-treat**: well controlled with multiple and/or high levels of controller therapies
- **Exacerbators**: despite being well controlled, continue to have severe exacerbations
- **Refractory**: continue to have poorly controlled asthma despite multiple and high levels of controller therapies

AHR, airflow hyperresponsiveness.
levels of controller therapy; (2) difficult-to-treat: well controlled with multiple and/or high levels of controller therapies; (3) exacerbarers: despite being well controlled, continue to have severe exacerbations; and (4) refractory asthma: continue to have poorly controlled asthma despite multiple and high levels of controller therapies (Table 144-2). Different airways pathologic processes, causing airways inflammation, AHR, and airways congestion and blockage, are believed to underlie these different types of asthma.

**PATHOGENESIS**

Airflow obstruction in asthma is the result of numerous pathologic processes. In the small airways, airflow is regulated by smooth muscle encircling the airway lumen; bronchoconstriction of these bronchiolar muscular bands restricts or blocks airflow. A cellular inflammatory infiltrate and exudates distinguished by eosinophils, but also including other inflammatory cell types (neutrophils, monocytes, lymphocytes, mast cells, basophils), can fill and obstruct the airways and induce epithelial damage and desquamation into the airways lumen. Helper T lymphocytes and other immune cells that produce proallergic, proinflammatory cytokines (interleukin [IL]-4, IL-5, IL-13), and chemokines (eotaxins) mediate this inflammatory process. Pathogenic immune responses and inflammation may also result from a breach in normal immune regulatory processes (such as regulatory T lymphocytes that produce IL-10 and transforming growth factor-β) that dampen effector immunity and inflammation when they are no longer needed. Hypersensitivity or susceptibility to a variety of provocative exposures or triggers (Table 144-3) can lead to airflow obstruction, AHR, edema, basement membrane thickening, subepithelial collagen deposition, smooth muscle and mucous gland hypertrophy, and mucus hypersecretion—all processes that contribute to airflow obstruction.

**CLINICAL MANIFESTATIONS AND DIAGNOSIS**

Intermittent dry coughing and expiratory wheezing are the most common chronic symptoms of asthma. Older children and adults report associated shortness of breath and chest congestion and tightness; younger children are more likely to report intermittent, nonfocal chest pain. Respiratory symptoms can be worse at night, associated with sleep, especially during prolonged exacerbations triggered by respiratory infections or inhalant allergens. Daytime symptoms, often linked with physical activities (exercise-induced) or play, are reported with greatest frequency in children. Other asthma symptoms in children can be subtle and nonspecific, including self-imposed limitation of physical activities, general fatigue (possibly resulting from sleep disturbance), and difficulty keeping up with peers in physical activities. Asking about previous experience with asthma medications (bronchodilators) may provide a history of symptomatic improvement with treatment that supports the diagnosis of asthma. Lack of improvement with bronchodilator and corticosteroid therapy is inconsistent with underlying asthma and should prompt more vigorous consideration of asthma-masquerading conditions.

Asthma symptoms can be triggered by numerous common events or exposures: physical exertion and hyperventilation (laughing), cold or dry air, and airways irritants (see Table 144-3). Exposures that induce airways inflammation, such as infections with common respiratory pathogens (rhinovirus, respiratory syncytial virus, metapneumovirus, parainfluenza virus, influenza virus, adenovirus, *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*), and inhaled allergens in sensitized children, also increase AHR to dry cold air and irritant exposures. An environmental history is essential for optimal asthma management (see Chapter 141).

The presence of risk factors, such as a history of other allergic conditions (allergic rhinitis, allergic conjunctivitis, atopic dermatitis, food allergies), parental asthma, and/or symptoms apart from colds, supports the diagnosis of asthma. During routine clinic visits, children with asthma commonly present without abnormal signs, emphasizing the importance of the medical history in diagnosing asthma. Some may exhibit a dry, persistent cough. The chest findings are often normal. Deeper breaths can sometimes elicit otherwise undetectable wheezing. In clinic, quick resolution (within 10 min) or convincing improvement in symptoms and signs of asthma with administration of a short-acting inhaled β-agonist (SABA; e.g., albuterol) is supportive of the diagnosis of asthma.

During asthma exacerbations, expiratory wheezing and a prolonged exhalation phase can usually be appreciated by auscultation. Decreased breath sounds in some of the lung fields, commonly the right lower posterior lobe, are consistent with regional hypoventilation caused by airways obstruction. Rhonchi and crackles (or rales) can sometimes be heard, resulting from excess mucus production and inflammatory exudate in the airways. The combination of segmental crackles and poor breath sounds can indicate lung segmental atelectasis that is difficult to distinguish from bronchial pneumonia and can complicate acute asthma management. In severe exacerbations, the greater extent of airways obstruction causes labored breathing and respiratory distress, which manifests as inspiratory and expiratory wheezing, increased prolongation of exhalation, poor air entry, suprasternal and intercostal retractions, nasal flaring, and accessory respiratory muscle use. In extremis, airflow may be so limited that wheezing cannot be heard (Table 144-4).

**DIFFERENTIAL DIAGNOSIS**

Many childhood respiratory conditions can present with symptoms and signs similar to those of asthma (Table 144-5). Besides asthma, other common causes of chronic, intermittent coughing include gastroesophageal reflux (GER) and rhinosinusitis. Both GER and chronic sinusitis can be challenging to diagnose in children. Often, GER is clinically silent in children, and children with chronic sinusitis do not report sinusitis-specific symptoms, such as localized sinus pressure and
tenderness. In addition, both GER and rhinosinusitis are often comorbid with childhood asthma and, if not specifically treated, may make asthma difficult to manage.

In early life, chronic coughing and wheezing can indicate recurrent aspiration, tracheobronchomalacia, a congenital anatomic abnormality of the airways, foreign-body aspiration, cystic fibrosis, or bronchopulmonary dysplasia.

In older children and adolescents, vocal cord dysfunction (VCD) can manifest as intermittent daytime wheezing (Table 144-6). In this condition, the vocal cords involuntarily close inappropriately during inspiration and sometimes exhalation, producing shortness of breath, coughing, throat tightness, and often audible laryngeal wheezing and/or stridor. In most cases of VCD, spirometric lung function testing reveals “truncated” and inconsistent inspiratory and expiratory flow-volume loops, a pattern that differs from the reproducible pattern of airflow limitation in asthma that improves with bronchodilators. VCD can coexist with asthma. Flexible rhinolaryngoscopy in the patient with symptomatic VCD can reveal paradoxical vocal cord movements with anatomically normal vocal cords. This condition can be well managed with specialized speech therapy training in the relaxation and control of vocal cord movement. Furthermore, treatment of underlying causes of vocal cord irritability (e.g., high GER/aspiration, allergic rhinitis, rhinosinusitis, asthma) can improve VCD. During acute VCD exacerbations, in addition to relaxation breathing techniques in conjunction with inhalation of heliox (a mixture of 70% helium and 30% oxygen) can relieve vocal cord spasm and VCD symptoms.

Exercise-induced laryngeal obstruction must be considered in children with a presumptive diagnosis of exercise-induced asthma. The diagnosis is confirmed by continuous video laryngoscopy during exercise.

In some locales, hypersensitivity pneumonitis (farming communities, homes of bird owners), pulmonary parasitic infestations (rural areas of developing countries), or tuberculosis may be common causes of chronic coughing and/or wheezing. Rare asthma-masquerading conditions in childhood include bronchiolitis obliterans, interstitial lung diseases, primary ciliary dyskinesias, humoral immune deficiencies, allergic bronchopulmonary mycoses, congestive heart failure, mass lesions in or compressing the larynx, trachea, or bronchi, and coughing and/or wheezing that is an adverse effect of medication. Chronic pulmonary diseases often produce clubbing, but clubbing is a very unusual finding in childhood asthma.

**LABORATORY FINDINGS**

Lung function tests can help to confirm the diagnosis of asthma and to determine disease severity.

**Pulmonary Function Testing**

Forced expiratory airflow measures are helpful in diagnosing and monitoring asthma and in assessing efficacy of therapy. Lung function testing is particularly helpful in children with asthma who are poor perceivers of airflow obstruction or when physical signs of asthma do not occur until airflow obstruction is severe.
Differential Diagnosis of Childhood Asthma

### Table 144-5

**UPPER RESPIRATORY TRACT CONDITIONS**
- Allergic rhinitis*
- Chronic rhinitis*
- Sinusitis*
- Adenoidal or tonsillar hypertrophy
- Nasal foreign body

**MIDDLE RESPIRATORY TRACT CONDITIONS**
- Laryngotracheobronchomalacia*
- Laryngotracheobronchitis (e.g., pertussis)*
- Laryngeal web, cyst, or stenosis
- Exercise-induced laryngeal obstruction
- Vocal cord dysfunction*
- Vocal cord paralysis
- Tracheoesophageal fistula
- Vascular ring, sling, or external mass compressing on the airway (e.g., tumor)
- Foreign body aspiration*
- Chronic bronchitis from environmental tobacco smoke exposure*
- Toxic inhalations

**LOWER RESPIRATORY TRACT CONDITIONS**
- Bronchopulmonary dysplasia (chronic lung disease of preterm infants)
- Viral bronchiolitis*
- Gastroesophageal reflux*
- Causes of bronchiectasis:
  - Cystic fibrosis
  - Immune deficiency
  - Allergic bronchopulmonary mycoses (e.g., aspergillosis)
  - Chronic aspiration
  - Immotile cilia syndrome, primary ciliary dyskinesia
  - Bronchiolitis obliterans
  - Interstitial lung diseases
  - Hypersensitivity pneumonitis
  - Pulmonary eosinophilia, Churg-Strauss vasculitis
  - Pulmonary hemosiderosis
  - Tuberculosis
  - Pneumonia
  - Pulmonary edema (e.g., congestive heart failure)
- Medications associated with chronic cough:
  - Acetylcysteine
  - β-Adrenergic antagonists
  - Angiotensin-converting enzyme inhibitors

*More common asthma masqueraders.

### Table 144-6

**SIMILARITIES AND DIFFERENCES BETWEEN VOCAL CORD DYSFUNCTION AND ASTHMA**

<table>
<thead>
<tr>
<th>VOCAL CORD DYSFUNCTION</th>
<th>ASTHMA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extrathoracic</td>
<td>Intrathoracic</td>
</tr>
<tr>
<td>Rare (?never) hypoxemia</td>
<td>+ Hypoxemia</td>
</tr>
<tr>
<td>No hypercapnia/acidosis</td>
<td>+ Hypercapnia/acidosis</td>
</tr>
<tr>
<td>Normal expiratory spirometry</td>
<td>Reduced expiratory flow</td>
</tr>
<tr>
<td>Abnormal inspiratory loop (in some)</td>
<td>Normal inspiratory loop</td>
</tr>
<tr>
<td>Start/stop abruptly; few symptoms between episodes</td>
<td>Persistent symptoms</td>
</tr>
<tr>
<td>Frequent emergency department/office visits</td>
<td>Frequent emergency department/office visits</td>
</tr>
<tr>
<td>Multiple medications</td>
<td>Multiple medications</td>
</tr>
</tbody>
</table>


### Table 144-7

**LUNG FUNCTION ABNORMALITIES IN ASTHMA**

- Spirometry (in clinic):
  - Airflow limitation:
    - Low FEV1 (relative to percentage of predicted norms)
    - FEV1:FVC ratio <0.80
- Bronchodilator response (to inhaled β-agonist):
  - Improvement in FEV1 ≥12% and ≥200 mL*
- Exercise challenge:
  - Worsening in FEV1 ≥15%*

Daily peak flow or FEV1 monitoring: day to day and/or A.M.-to-P.M. variation ≥20%*

*Main criteria consistent with asthma.

FEV1, forced expiratory volume in 1 sec; FVC, forced vital capacity.

Many asthma guidelines promote spirometric measures of airflow and lung volumes during forced expiratory maneuvers as standard for asthma assessment. Spirometry is a helpful objective measure of airflow limitation (Fig. 144-2). Spirometry is an essential assessment tool in children who are at risk for severe asthma exacerbations and those who have poor perception of asthma symptoms. Knowledgeable personnel are needed to perform and interpret findings of spirometry tests. Valid spirometric measures depend on a patient's ability to properly perform a full, forceful, and prolonged expiratory maneuver, usually feasible in children >6 yr of age (with some younger exceptions). Reproducible spirometric efforts are an indicator of test validity; i.e., the FEV1 (forced expiratory volume in 1 sec) should be reproducible within 5% on 3 measurements, and the highest value taken as the reported measurement of the test is used. This standard utilization of the highest of 3 reproducible efforts is indicative of the effort dependence of reliable spirometric testing.

In asthma, airways blockage results in reduced airflow with forced exhalation (see Fig. 144-2). Because asthmatic patients typically have hyperinflated lungs, FEV1 can be simply adjusted for full expiratory lung volume—the forced vital capacity (FVC)—with an FEV1:FVC ratio. Generally, an FEV1:FVC ratio <0.80 indicates significant airflow obstruction (Table 144-7). Normative values for FEV1 have been determined for children on the basis of height, gender, and ethnicity. Abnormally low FEV1, as a percentage of predicted norms is 1 of 6 criteria used to determine asthma severity and control in asthma management guidelines sponsored by the U.S. National Institutes of Health (NIH) and the Global Initiative for Asthma (GINA).

Such measures of airflow alone are not diagnostic of asthma, because numerous other conditions can cause airflow reduction. Bronchodilator response to an inhaled β-agonist (e.g., albuterol) is greater in asthmatic patients than nonasthmatic persons; an improvement in FEV1 ≥12% or ≥200 mL is consistent with asthma. Bronchoprovocation challenges can be helpful in diagnosing asthma and optimizing asthma management. Asthmatic airways are hyperresponsive and therefore more sensitive to inhaled methacholine, mannitol, and cold or dry air. The degree of AHR to these exposures correlates to some extent with asthma severity and airways inflammation. Although bronchoprovocation challenges are carefully dosed and monitored in an investigational setting, their use is rarely practical in general practice. Exercise challenges (aerobic exertion or “running” for 6-8 min) can help to identify children with exercise-induced bronchospasm. Although the airflow response of nonasthmatic persons to exercise is to increase functional lung volumes and improve FEV1 slightly (5-10%), exercise often provokes airflow obstruction in persons with inadequately treated asthma. Accordingly, in asthmatic patients, FEV1 typically decreases during or after exercise by >15% (see Table 144-7). The onset of exercise-induced bronchospasm is usually within 15 min after a vigorous exercise challenge and can spontaneously resolve within 30-60 min. Studies of exercise challenges in school-age children typically identify an additional 5-10% with exercise-induced bronchospasm and previously unrecognized asthma. There are 2 caveats regarding exercise challenges: first,
treadmill challenges in the clinic are not completely reliable and can miss exertional asthma that can be demonstrated on the playing field; and second, exercise challenges can induce severe exacerbations in at-risk patients. Careful patient selection for exercise challenges and preparedness for severe asthma exacerbations are required.

Measuring **exhaled nitric oxide (FENO)**, a marker of airway inflammation in allergy-associated asthma, may possibly help adjust antiinflammatory management and confirm the diagnosis of asthma.

Pe**ak expiratory flow (PEF) monitoring** devices provide simple and inexpensive home-use tools to measure airflow and can be helpful in a number of circumstances (Fig. 144-3). Similarly to spirometry in clinics, poor perceivers of asthma can benefit by monitoring PEFs at home to assess their airflow as an indicator of asthma control or problems. PEF devices vary in the ability to detect airflow obstruction: they are generally less sensitive and reliable than spirometry to detect airflow obstruction such that, in some patients, PEF values decline only when airflow obstruction is severe. Therefore, PEF monitoring should be started by measuring morning and evening PEFs (best of 3 attempts) for several weeks for patients to practice the technique, to determine diurnal variation and a “personal best,” and to correlate PEF values with symptoms (and ideally spirometry). Diurnal variation in PEF >20% is consistent with asthma (see Fig. 144-3 and Table 144-7).

Radiology

The findings of chest radiographs (posteroanterior and lateral views) in children with asthma often appear to be normal, aside from subtle and nonspecific findings of hyperinflation (e.g., flattening of the diaphragms) and peribronchial thickening (Fig. 144-4). Chest radiographs can help identify abnormalities that are hallmarks of asthma masqueraders (aspiration pneumonitis, hyperlucent lung fields in bronchiolitis obliterans) and complications during asthma exacerbations (atelectasis, pneumomediastinum, pneumothorax). Some lung abnormalities can be better appreciated with high-resolution, thin-section chest CT scans. Bronchiectasis, which is sometimes difficult to appreciate on chest radiograph but is clearly seen on CT scan, implies an asthma masquerader such as cystic fibrosis, allergic bronchopulmonary mycoses (aspergillosis), ciliary dyskinesias, or immune deficiencies.

Other tests, such as allergy testing to assess sensitization to inhalant allergens, help with the management and prognosis of asthma. In a comprehensive U.S. study of 5-12 yr old asthmatic children (Childhood Asthma Management Program [CAMP]), 88% of the subjects had inhalant allergen sensitization according to results of allergy prick skin testing.

**TREATMENT**

The NIH-sponsored National Asthma Education and Prevention Program’s Expert Panel Report 3 (EPR3): Guidelines for the Diagnosis and Management of Asthma 2007 is available online (www.nhlbi.nih.gov/guidelines/asthma/astghdl.htm). Similar guidelines From the Global Strategy for Asthma Management and Prevention, GINA 2012, are also available online (www.ginaasthma.org). The key components to optimal asthma management are specified (Fig. 144-5). Management of asthma should have the following components: (1) assessment and monitoring of disease activity; (2) education to enhance patient and family knowledge and skills for self-management; (3) identification and management of precipitating factors and comorbid conditions that worsen asthma; and (4) appropriate selection of medications to address the patient’s needs. The long-term goal of asthma management is attainment of optimal asthma control.
Classification of asthma severity and control is based on the domains of impairment and risk. These domains may not correlate with each other and may respond differently to treatment. In some children with asthma, day-to-day impairment is well controlled, but the risk of severe exacerbations remains. The NIH guidelines have distinct criteria for 3 childhood age groups—0-4 yr, 5-11 yr, and ≥12 yr—for the evaluation of both severity (Table 144-8) and control (Table 144-9). The level of asthma severity or control is based on the most severe impairment or risk category. In assessing asthma severity, impairment consists of an assessment of the patient's recent symptom frequency (daytime and nighttime, with subtle differences in numeric cutoffs between the 3 age groups), SABA usage for quick relief, ability to engage in normal or desired activities, and airflow compromise evaluated by spirometry in children 5 yr and older. Risk refers to the likelihood of developing severe asthma exacerbations. Of note, in the absence of frequent symptoms, persistent asthma should be considered, and therefore long-term controller therapy should be initiated for infants or children who have risk factors for asthma (see earlier) and 4 or more episodes of wheezing over the past year that lasted longer than 1 day and affected sleep, or 2 or more exacerbations in 6 mo requiring systemic corticosteroids.

Asthma management can be optimized through regular clinic visits every 2-6 wk until good asthma control is achieved. For children already on controller medication therapy, management is tailored to the child's level of control. The NIH guidelines provide tables for evaluating asthma control for the 3 age groups (see Table 144-9). In evaluation of asthma control, as in severity assessment, impairment includes an assessment of the patient's symptom frequency (daytime and nighttime), SABA usage for quick relief, ability to engage in normal or desired activities, and, for older children, airflow measurements. Furthermore, with respect to risk assessment, besides considering severity and frequency of exacerbations requiring systemic corticosteroids, tracking of lung growth in older children and monitoring adverse effects of medications is also warranted. The degree of impairment and presence of risk are used to determine the patient's level of asthma control as well-controlled, not well-controlled, or very poorly controlled. Children with well-controlled asthma have daytime symptoms ≤2 days/wk and need a rescue bronchodilator ≤2 days/wk; an FEV1 of >80% of predicted (and an FEV1/FVC ratio >80% for children 5-11 yr of age); no interference with normal activity; and <2 exacerbations in the past year. The impairment criteria vary slightly depending on age group: there are different thresholds in the frequency of nighttime awakenings; addition of FEV1/FVC ratio criteria for children 5-11 yr old and addition of validated impairment questionnaires (e.g., Asthma Control Test [ACT] for ages ≥12 yr, Childhood ACT for ages 4-11 yr). Children whose status does not meet all of the criteria defining well-controlled asthma are determined to have either not-well-controlled or very poorly controlled asthma, which is determined by the single criterion with the poorest rating.

Two to 4 asthma checkups per year are recommended for reassessing and maintaining good asthma control. Lung function testing (spirometry) is recommended at least annually and more often if asthma is poorly perceived, inadequately controlled and/or lung function is abnormally low. PEF monitoring at home can be helpful in the assessment of asthmatic children with poor symptom perception, other causes of chronic coughing in addition to asthma, moderate to severe asthma, or a history of severe asthma exacerbations. PEF monitoring is feasible in children as young as 4 yr who are able to master this skill. Use of a stoplight zone system tailored to each child's “personal best” PEF values can optimize effectiveness and interest (see Fig 144-3). The green zone (80-100% of personal best) indicates good control; the yellow zone (50-80%) indicates less-than-optimal control and necessitates increased awareness and treatment; the red zone (<50%) indicates poor control and greater likelihood of an exacerbation, requiring immediate intervention. In actuality, these ranges are approximate and may need to be adjusted for many asthmatic children by raising the ranges that indicate inadequate control (in the yellow zone, 70-90%). Once-daily PEF monitoring is preferable in the morning when peak flows are typically lower.

**Component 1: Regular Assessment and Monitoring**

Regular assessment and monitoring are based on the concepts of asthma severity, asthma control, and responsiveness to therapy. Asthma severity is the intrinsic intensity of disease, and assessment is generally most accurate in patients not receiving controller therapy. Hence, assessing asthma severity directs the initial level of therapy. The 2 general categories are intermittent asthma and persistent asthma, the latter being further subdivided into mild, moderate, and severe. In contrast, asthma control refers to the degree to which symptoms, ongoing functional impairments, and risk of adverse events are minimized, and goals of therapy are met. In children receiving controller therapy, assessment of asthma control is important in adjusting therapy and is categorized in 3 levels: well-controlled, not well-controlled, and very poorly controlled. Responsiveness to therapy is the ease or difficulty with which asthma control is attained by treatment.


**Component 2: Patient Education**

Specific educational elements in the clinical care of children with asthma are believed to make an important difference in home management and in adherence of families to an optimal plan of care and eventually impacting patient outcomes (Table 144-10). Every visit presents an important opportunity to educate the child and family, allowing them to become knowledgeable partners in asthma management, because optimal management depends on their daily assessments and implementation of any management plan. Effective communications take into account sociocultural and ethnic factors of children and their families, provide an open forum for concerns about asthma and its treatment to be raised and addressed, and include patients and families as active participants in the development of treatment goals and selection of medications. Self-management skills should be reevaluated regularly (e.g., inhaler medication technique).

During initial patient visits, a basic understanding of the pathogenesis of asthma (chronic inflammation and AHR underlying a clinically intermittent presentation) can help children with asthma and their parents understand the importance of recommendations aimed at reducing airways inflammation to achieve and maintain good asthma control. It is helpful to specify the expectations of good asthma control resulting from optimal asthma management (see Fig. 144-5). Addressing concerns about potential adverse effects of asthma pharmacotherapeutic agents, especially their risks relative to their benefits, is essential in achieving long-term adherence with asthma pharmacotherapy and environmental control measures.

Children with asthma and their families, particularly patients with moderate or severe persistent or poorly controlled asthma and patients who have had severe exacerbations, benefit from a written asthma management plan. This plan has 2 main components: (1) a daily “routine” management plan describing regular asthma medication use and other measures to keep asthma under good control; and (2) an action plan to manage worsening asthma, describing indicators of impending exacerbations, identifying what medications to take, and specifying when and how to contact the regular physician and/or obtain urgent/emergency medical care.

Regular follow-up visits are recommended to help to maintain optimal asthma control. In addition to determining disease control level and revising daily and exacerbation management plans accordingly, follow-up visits are important teaching opportunities to encourage open communication of concerns with asthma management recommendations (e.g., daily administration of controller medications). Reassessing patients’ and parents’ understanding of the role of different medications in asthma management and control, and their technique in using inhaled medications, can be insightful and can help guide teaching to improve adherence to a management plan that might not have been adequately or properly implemented.

**ADHERENCE**

Asthma is a chronic condition that is usually best managed with daily controller medication. However, symptoms wax and wane, severe exacerbations are infrequent, and when asthma is asymptomatic, a natural tendency is to reduce or discontinue daily controller therapies. As such, adherence to a daily controller regimen is commonly suboptimal;
Assessing Asthma Severity and Initiating Treatment for Patients Who Are Not Currently Taking Long-Term Control Medications

**COMPONENTS OF SEVERITY**

**Impairment**

<table>
<thead>
<tr>
<th>Component</th>
<th>Intermittent</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daytime symptoms</td>
<td>≤2 days/wk</td>
<td>&gt;2 days/wk but not daily</td>
<td>Daily</td>
<td>Throughout the day</td>
</tr>
<tr>
<td>Nighttime awakenings:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age 0-4 yr</td>
<td>0</td>
<td>1-2x/mo</td>
<td>3-4x/mo</td>
<td>&gt;1x/wk</td>
</tr>
<tr>
<td>Age ≥5 yr</td>
<td>≤2x/mo</td>
<td>3-4x/mo</td>
<td>&gt;1x/wk but not nightly</td>
<td>Often &gt;1x/wk</td>
</tr>
<tr>
<td>Short-acting β₂-agonist use for symptoms (not for prevention of exercise-induced bronchospasm)</td>
<td>≤2 days/wk</td>
<td>&gt;2 days/wk but not daily, and not more than 1x on any day</td>
<td>Daily</td>
<td>Several times per day</td>
</tr>
<tr>
<td>Interference with normal activity</td>
<td>None</td>
<td>Minor limitation</td>
<td>Some limitation</td>
<td>Extreme limitation</td>
</tr>
</tbody>
</table>

**Risk**

<table>
<thead>
<tr>
<th>Component</th>
<th>Intermittent</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exacerbations requiring systemic corticosteroids:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age 0-4 yr</td>
<td>0-1/y (see notes)</td>
<td>≥2 exacerbations in 6 mo requiring systemic corticosteroids</td>
<td>Step 2</td>
<td>Step 2</td>
</tr>
<tr>
<td>Age ≥ 5 yr</td>
<td>0-1/y (see notes)</td>
<td>≥4 wheezing episodes/yr lasting &gt;1 day and risk factors for persistent asthma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Consider severity and interval since last exacerbation.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frequency and severity may fluctuate over time for patients in any severity category.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relative annual risk of exacerbations may be related to FEV₁.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**RECOMMENDED STEP FOR INITIATING THERAPY**

<table>
<thead>
<tr>
<th>Component</th>
<th>Intermittent</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>All ages</td>
<td>Step 1</td>
<td>Step 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age 0-4 yr</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age 5-11 yr</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age ≥12 yr</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

In 2-6 wk, evaluate level of asthma control that is achieved and adjust therapy accordingly. If no clear benefit is observed within 4-6 wk, consider adjusting therapy or alternative diagnoses.

*Notes:

- The stepwise approach is meant to assist, not replace, the clinical decision-making required to meet individual patient needs.
- Level of severity is determined by both impairment and risk. Assess impairment domain by patient’s/caregiver’s recall of previous 2-4 wk. Symptom assessment for longer periods should reflect a global assessment, such as inquiring whether a patient’s asthma is better or worse since the last visit. Assign severity to the most severe category in which any feature occurs.
- At present, there are inadequate data to correspond frequencies of exacerbations with different levels of asthma severity. For treatment purposes, patients who had ≥2 exacerbations requiring oral systemic corticosteroids in the past 6 mo, or ≥4 wheezing episodes in the past year, and who have risk factors for persistent asthma may be considered the same as patients who have persistent asthma, even in the absence of impairment levels consistent with persistent asthma.
- Normal FEV₁/FVC: 8-19% predicted, age 5-11; 7-17% predicted, age 0-4.
- FEV₁: % predicted, age ≥5 yr Normal FEV₁: between exacerbations ≥80% predicted >80% predicted
- FEV₁:FVC ratio*: Age 5-11 yr >85% Normal Age ≥12 yr Normal
- Risk Exacerbations requiring systemic corticosteroids:
- Age 0-4 yr 0-1/y (see notes) ≥2 exacerbations in 6 mo requiring systemic corticosteroids
- Age ≥ 5 yr 0-1/y (see notes) ≥4 wheezing episodes/yr lasting >1 day and risk factors for persistent asthma

Eliminating and Reducing Problematic Environmental Exposures

The majority of children with asthma have an allergic component to their disease; steps should be taken to investigate and minimize allergen exposures in sensitized asthmatic patients. The medical history should address potential allergen triggers (see below), but often patients have chronic symptoms and cannot identify potential triggers. Therefore, allergy testing should be considered for at least those with persistent asthma. For asthmatic patients who are allergic to allergens in their homes, reducing or eliminating these home allergen exposures can decrease asthma symptoms, medication requirements, AHR, severe exacerbations, and disease persistence. Common home allergen inhaled corticosteroids (ICSs) are underused 60% of the time. In one study, children with asthma who required an oral corticosteroid course for an asthma exacerbation had used their daily controller ICS 15% of the time. Misconceptions about controller medication time to onset, efficacy, and safety often underlie poor adherence and can be addressed by asking about such concerns at each visit.

**Component 3: Control of Factors Contributing to Asthma Severity**

Controllable factors that can worsen asthma can be generally grouped as (1) environmental exposures and (2) comorbid conditions (Table 144.11).
### Table 144-9  Assessing Asthma Control and Adjusting Therapy in Children*

<table>
<thead>
<tr>
<th>COMPONENTS OF CONTROL</th>
<th>CLASSIFICATION OF ASTHMA CONTROL</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Impairment</strong></td>
<td>Well-Controlled</td>
</tr>
<tr>
<td>Impairment</td>
<td>≤2 days/wk but not more than once on each day</td>
</tr>
<tr>
<td>Nighttime awakenings:</td>
<td></td>
</tr>
<tr>
<td>Age 0-4 yr</td>
<td>≤1x/mo</td>
</tr>
<tr>
<td>Age 5-11 yr</td>
<td>≤1x/mo</td>
</tr>
<tr>
<td>Age ≥12 yr</td>
<td>≤2x/mo</td>
</tr>
<tr>
<td>Short-acting β₂-agonist use for symptoms (not for exercise-induced bronchospasm pretreatment)</td>
<td>≤2 days/wk</td>
</tr>
<tr>
<td>Interference with normal activity</td>
<td>None</td>
</tr>
<tr>
<td>Lung function:</td>
<td></td>
</tr>
<tr>
<td>Age 5-11 yr: FEV₁ (% predicted or peak flow)</td>
<td>&gt;80% predicted or personal best</td>
</tr>
<tr>
<td>Age ≥12 yr: FEV₁ (% predicted or peak flow)</td>
<td>&gt;80%</td>
</tr>
<tr>
<td>Validated questionnaires†:</td>
<td></td>
</tr>
<tr>
<td>Age ≥12 yr: ATAQ</td>
<td>≤0.75</td>
</tr>
<tr>
<td>Age ≥12 yr: ACQ</td>
<td>≥20</td>
</tr>
<tr>
<td>Risk:</td>
<td></td>
</tr>
<tr>
<td>Exacerbations requiring systemic corticosteroids:</td>
<td></td>
</tr>
<tr>
<td>Age 0-4 yr</td>
<td>0-1/yr</td>
</tr>
<tr>
<td>Age ≥5 yr</td>
<td>0-1/yr</td>
</tr>
<tr>
<td>Treatment-related adverse effects</td>
<td>Medication side effects can vary in intensity from none to very troublesome and worrisome. The level of intensity does not correlate to specific levels of control but should be considered in the overall assessment of risk.</td>
</tr>
<tr>
<td>Reduction in lung growth or progressive loss of lung function</td>
<td>Maintain current step. Regular follow-up every 1-6 mo to maintain control. Consider step down if well-controlled for at least 3 mo.</td>
</tr>
</tbody>
</table>

---

*Notes:*
- The stepwise approach is meant to assist, not replace, the clinical decision making required to meet individual patient needs.
- The level of control is based on the most severe impairment or risk category. Assess impairment domain by caregiver’s recall of previous 2-4 wk. Symptom assessment for longer periods should reflect a global assessment such as inquiring whether the patient’s asthma is better or worse since the last visit.
- At present, there are inadequate data to correspond frequencies of exacerbations with different levels of asthma control. In general, more frequent and intense exacerbations (e.g., requiring urgent, unscheduled care, hospitalization, or intensive care unit admission) indicate poorer disease control. For treatment purposes, patients who had ≥2 exacerbations requiring oral systemic corticosteroids in the past year may be considered the same as patients who have not-well-controlled asthma, even in the absence of impairment levels consistent with not-well-controlled asthma.
- Validated questionnaires for the impairment domain (the questionnaires do not assess lung function or the risk domain) and definition of minimal important difference (MID) for each:
  - ATAQ, Asthma Therapy Assessment Questionnaire; MID = 1.0
  - ACQ, Asthma Control Questionnaire; MID = 0.5
  - ACT, Asthma Control Test; MID not determined
- ACQ values of 0.76-1.40 are indeterminate regarding well-controlled asthma.
- Before step-up therapy: (a) review adherence to medications, inhaler technique, and environmental control; (b) if alternative treatment option was used in a step, discontinue it and use preferred treatment for that step.
- FEV₁, forced expiratory volume in 1 sec; FVC, forced vital capacity.
Control of Factors Contributing to Asthma Severity

Aspirin-exacerbated respiratory disease, formerly called aspirin-induced asthma, is also associated with chronic eosinophilic rhinitis and nasal polypsis. Inhibition of cyclooxygenase by aspirin and other nonsteroidal antiinflammatory drugs (including cyclooxygenase [COX]-2 inhibiting agents) is thought to be the primary mechanism, which leads to exacerbations of disease, predominantly in patients with moderate to severe persistent asthma. Acetaminophen, a weak COX-1 inhibitor, is safe in low doses, but may produce symptoms if high doses are taken. The incidence is between 5% and 10% of predominantly adolescents with asthma; it is rare in children <10 yr of age. Following ingestion of the drug, symptoms may appear between 30 and 120 min and include profuse rhinorrhea, nasal congestion, and tearing, accompanied by bronchospasm. Vocal cord spasm and an anaphylactic-like reaction are rare complications. Aspirin and related drugs should be avoided in these patients; an alternative approach is aspirin desensitization by an allergist.

Treat Comorbid Conditions
Rhinitis, sinusitis, and GER often accompany asthma and worsen disease severity. They can also mimic asthma symptoms and lead to misclassification of asthma severity and control. Indeed, these conditions with asthma are the most common causes of chronic coughing. Effective management of these comorbid conditions may improve asthma symptoms and disease severity, such that less asthma medication is needed to achieve good asthma control.

GER is observed in 43% of children with persistent asthma. GER may worsen asthma through 2 postulated mechanisms: (1) aspiration of refluxed gastric contents (micro- or macro-aspiration); and (2) vagally mediated reflex bronchospasm. Occult GER should be suspected in individuals with difficult-to-control asthma, especially patients who have prominent asthma symptoms while eating or sleeping (in a horizontal position) or who prop themselves up in bed to reduce nocturnal symptoms. GER can be demonstrated by reflux of barium into the esophagus during a barium swallow procedure or by esophageal probe monitoring. Because radiographic studies lack sufficient sensitivity and specificity, extended esophageal monitoring is the method of choice for diagnosing GER. If significant GER is noted, reflux precautions should be instituted (no food 2 hr before bedtime, head of the bed elevated 6 in, avoidance of caffeinated foods and beverages) and medications such as proton pump inhibitors (omeprazole, lansoprazole) or H₂-receptor antagonists (cimetidine, ranitidine) administered for 8–12 wk. Proton pump inhibition did not improve asthma control in a study of children with persistent, poorly controlled asthma and GER.

Rhinitis is usually comorbid with asthma, detected in ~90% of children with asthma. Rhinitis can be seasonal and/or perennial, with allergic and nonallergic components. Rhinitis complicates and worsens asthma via numerous direct and indirect mechanisms. Nasal breathing may improve asthma and reduce exercise-induced bronchospasm by humidifying and warming inspired air and filtering out allergens and irritants that can trigger asthma and worsen airway inflammation. Reduction of nasal congestion and obstruction can help the nose to perform these humidifying, warming, and filtering functions. In asthmatic patients, improvement in rhinitis is also associated with improvement in AHR, lower airways inflammation, asthma symptoms, and asthma medication use. Optimal rhinitis management in children is similar to asthma management in regard to the importance of interventions to reduce nasal inflammation (see Chapter 143).

Radiographic evidence for sinus disease is common in patients with asthma. There is usually significant improvement in asthma control in patients diagnosed and treated for sinus disease. A coronal, “screening” or “limited” CT scan of the sinuses is the gold standard test for sinus disease and can be helpful if recurrent sinusitis has been suspected and repeatedly treated without such evidence. In comparison, sinus X-rays are inaccurate. If the patient with asthma has clinical and radiographic evidence for sinusitis, topical therapy to include nasal saline irrigations, intranasal corticosteroids, and a 2–3- wk course of antibiotics should be considered.

Exposures include furred or feathered animals as pets (cats, dogs, rodents, birds) or as pests (mice, rats), and occult indoor allergens, such as dust mites, cockroaches, and molds. Although some sensitized children may report an increase in asthma symptoms on exposure to the allergen source, improvement from allergen avoidance may not become apparent without a sustained period of days to weeks away from the offending exposure. Tobacco, wood and coal smoke, dusts, strong odors, and noxious air pollutants can all aggravate asthma. These airway irritants should be eliminated from or reduced in the homes and automobiles used by children with asthma. School classrooms and daycare settings can also be sites of environmental exposures that worsen asthma. Eliminating or minimizing these exposures (e.g., furred or feathered pets in classrooms of sensitized children with asthma) can reduce asthma symptoms, disease severity, and the amount of medication needed to achieve good asthma control. Annual influenza vaccination continues to be recommended for all children with asthma, although influenza is not responsible for the large majority of virus-induced asthma exacerbations experienced by children.

<table>
<thead>
<tr>
<th>Table 144-10</th>
<th>Key Elements of Productive Clinic Visits for Asthma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Specify goals of asthma management</td>
<td>Explain basic facts about asthma:</td>
</tr>
<tr>
<td>Contrast normal vs asthmatic airways</td>
<td>Link airways inflammation, &quot;twitchiness,&quot; and bronchoconstriction</td>
</tr>
<tr>
<td>Long-term-control and quick-relief medications</td>
<td>Address concerns about potential adverse effects of asthma pharmacotherapy</td>
</tr>
<tr>
<td>Teach, demonstrate, and have patient show proper technique for:</td>
<td>Inhaled medication use (spacer use with metered-dose inhaler)</td>
</tr>
<tr>
<td>Peak flow measures</td>
<td>Influenza vaccination continues to be recommended for all children</td>
</tr>
<tr>
<td>Investigate and manage factors that contribute to asthma severity:</td>
<td>Although influenza is not responsible for the large major</td>
</tr>
<tr>
<td>Environmental exposures</td>
<td>ity of virus-induced asthma exacerbations experienced by children.</td>
</tr>
<tr>
<td>Comorbid conditions</td>
<td>The incidence is between 5% and 10% of predominantly</td>
</tr>
<tr>
<td>Create written 2-part asthma management plan:</td>
<td>adolescents with asthma; it is rare in children &lt;10 yr of age. Following</td>
</tr>
<tr>
<td>Daily management</td>
<td>ingestion of the drug, symptoms may appear between 30 and 120 min</td>
</tr>
<tr>
<td>Action plan for asthma exacerbations</td>
<td>and include profuse rhinorrhea, nasal congestion, and tearing, accompanied</td>
</tr>
<tr>
<td>Regular follow-up visits:</td>
<td>by bronchospasm. Vocal cord spasm and an anaphylactic-like reaction are</td>
</tr>
<tr>
<td>Twice yearly (more often if asthma not well-controlled)</td>
<td>rare complications. Aspirin and related drugs should be avoided in these patients; an alternative approach is aspirin desensitization by an allergist.</td>
</tr>
<tr>
<td>Monitor lung function annually</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 144-11</th>
<th>Control of Factors Contributing to Asthma Severity</th>
</tr>
</thead>
<tbody>
<tr>
<td>ELIMINATE OR REDUCE PROBLEMATIC ENVIRONMENTAL EXPOSURES:</td>
<td>Environmental tobacco smoke elimination or reduction in home</td>
</tr>
<tr>
<td>Environmental tobacco smoke elimination or reduction in home and automobiles</td>
<td>and automobiles</td>
</tr>
<tr>
<td>Allergen exposure elimination or reduction in sensitized asthmatic patients:</td>
<td>Animal danders: pets (cats, dogs, rodents, birds)</td>
</tr>
<tr>
<td>Animal danders: pets (cats, dogs, rodents, birds)</td>
<td>Pests (mice, rats)</td>
</tr>
<tr>
<td>Dust mites</td>
<td>Cockroaches</td>
</tr>
<tr>
<td>Cockroaches</td>
<td>Molds</td>
</tr>
<tr>
<td>Molds</td>
<td>Other airway irritants:</td>
</tr>
<tr>
<td>Other airway irritants:</td>
<td>Wood- or coal-burning smoke</td>
</tr>
<tr>
<td>Wood- or coal-burning smoke</td>
<td>Strong chemical odors and perfumes (e.g., household cleaners)</td>
</tr>
<tr>
<td>Strong chemical odors and perfumes (e.g., household cleaners)</td>
<td>Dusts</td>
</tr>
<tr>
<td>Dusts</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>TREAT COMORBID CONDITIONS:</th>
<th>Rhinitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rhinitis</td>
<td></td>
</tr>
<tr>
<td>Sinusitis</td>
<td></td>
</tr>
<tr>
<td>Gastroesophageal reflux</td>
<td></td>
</tr>
</tbody>
</table>
Component 4: Principles of Asthma Pharmacotherapy

The current version of NIH asthma guidelines (2007) provides treatment recommendations that vary by age groups and are based on current evidence (Table 144-12). The goals of therapy are to achieve a well-controlled state by reducing the components of both impairment (e.g., preventing chronic and troublesome symptoms, allowing infrequent need of quick-reliever medications, maintaining “normal” lung function, maintaining normal activity levels including physical activity and school attendance, meeting families’ expectations and satisfaction

### Table 144-12 Stepwise Approach for Managing Asthma in Children

<table>
<thead>
<tr>
<th>Age</th>
<th>Therapy</th>
<th>Intermittent Asthma</th>
<th>Persistent Asthma: Daily Medication</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-4 yr</td>
<td>Preferred</td>
<td>SABA prn</td>
<td>Low-dose ICS</td>
</tr>
<tr>
<td></td>
<td>Alternative</td>
<td>Cromolyn or montelukast</td>
<td>Either low-dose ICS ± LABA, LTRA, or theophylline</td>
</tr>
<tr>
<td>5-11 yr</td>
<td>Preferred</td>
<td>SABA prn</td>
<td>Low-dose ICS + either LABA or LTRA or Theophylline</td>
</tr>
<tr>
<td></td>
<td>Alternative</td>
<td>Cromolyn, LTRA, nedocromil, or theophylline</td>
<td>Medium-dose ICS + either LABA or LTRA or Theophylline</td>
</tr>
<tr>
<td>≥12 yr</td>
<td>Preferred</td>
<td>SABA prn</td>
<td>Low-dose ICS + LABA or Medium-dose ICS</td>
</tr>
<tr>
<td></td>
<td>Alternative</td>
<td>Cromolyn, LTRA, nedocromil, or theophylline</td>
<td>Medium-dose ICS + LTRA, theophylline, or zileuton</td>
</tr>
</tbody>
</table>

Each step: Patient education, environmental control, and management of comorbidities.

Age ≥5 yr: Steps 2-4: Consider subcutaneous allergen immunotherapy for patients who have allergic asthma.

**Quick-Relief Medication for All Patients**

- SABA as needed for symptoms. Intensity of treatment depends on severity of symptoms: up to 3 treatments at 20-min intervals as needed. Short course of oral systemic corticosteroids may be needed.
- Caution: Use of SABA ≥2 days/wk for symptom relief (not prevention of exercise-induced bronchospasm) generally indicates inadequate control and the need to step up treatment.
- For ages 0-4 yr: With viral respiratory infection: SABA q4-6h up to 24 hr (longer with physician consult). Consider short course of systemic corticosteroids if exacerbation is severe or patient has history of previous severe exacerbations.

**Notes:**
- The stepwise approach is meant to assist, not replace, the clinical decision-making required to meet individual patient needs.
- If alternative treatment is used and response is inadequate, discontinue it and use the preferred treatment before stepping up.
- If clear benefit is not observed within 4-6 wk and patient/family medication technique and adherence are satisfactory, consider adjusting therapy or alternative diagnosis.
- Studies on children age 0-4 yr are limited. The stepwise approach is meant to assist, not replace, the clinical decision-making required to meet individual patient needs.
- Clinicians who administer immunotherapy or omalizumab should be prepared and equipped to identify and treat anaphylaxis that may occur.
- Theophylline is a less desirable alternative because of the need to monitor serum concentration levels.
- Zileuton is less desirable alternative because of limited studies as adjunctive therapy and the need to monitor liver function.
- Alphabetical order is used when more than 1 treatment option is listed within either preferred or alternative therapy.

with asthma care) and risk (e.g., preventing recurrent exacerbations, reduced lung growth, and medications’ adverse effects). The recommendations for initial therapy are based on assessment of asthma severity. For patients who are already using controller therapy, modification of treatment is based on assessment of asthma control and responsiveness to therapy. A major objective of this approach is to identify and treat all "persistent" and inadequately controlled asthma with antiinflammatory controller medication. Daily controller therapy is not recommended for children with "intermittent asthma." Management of intermittent asthma is simply the use of a SABA as needed for symptoms and for pretreatment in those with exercise-induced bronchoconstriction (Step 1 therapy; see Table 144-12).

The preferred treatment for all patients with persistent asthma is daily ICS therapy, as monotherapy or in combination with adjunctive therapy. The type(s) and amount(s) of daily controller medications to be used are determined by the asthma severity and control rating. Alternative medications for Step 2 therapy include a leukotriene receptor antagonist (montelukast), nonsteroidal antiinflammatory agents (cromolyn and nedocromil), and theophylline (for youths). For young children (≤5 yr) with moderate or severe persistent asthma, medium-dose ICS monotherapy is recommended (Step 3); combination therapy is recommended only as a Step 4 treatment for uncontrolled asthma.

Along with medium-dose ICSs, combination therapy with an ICS plus any of the following adjunctive therapies (depending on age group) is recommended as Steps 3 and 4 treatment for moderate persistent asthma, or as step-up therapy for uncontrolled persistent asthma: long-acting inhaled β1–agonists (LABAs), leukotriene-modifying agents, chromones, and theophylline. In a study of children with uncontrolled asthma while on low-dose ICS, the addition of LABA provided more improvement than either adding a leukotriene receptor antagonist (LTRA) or increasing ICS dosage. However, some children had a good response to ICS or LTRA, justifying them as step-up controller therapy options.

Children with severe persistent asthma (treatment Steps 5 and 6) should receive high-dose ICS and LABA. Long-term administration of oral corticosteroids as controller therapy can be effective, but is rarely needed with the availability of potent ICS and LABA combination formulations in single devices. In addition, omalizumab can be used in children ≥12 yr old with severe allergic asthma. A rescue course of systemic corticosteroids may be necessary at any step. For children age ≥5 yr with allergic asthma requiring Steps 2-4 care, allergen immunotherapy can be considered.

**"Step-Up, Step-Down" Approach**

The NIH guidelines emphasize initiating higher-level controller therapy at the outset to establish prompt control, with measures to "step down" therapy once good asthma control is achieved. Initially, airflow limitation and the pathology of asthma may limit the delivery and efficacy of ICS such that stepping up to higher doses and/or combination therapy may be needed to gain asthma control. Furthermore, ICS requires weeks to months of daily administration for optimal efficacy. Combination pharmacotherapy can achieve relatively immediate improvement while also providing daily ICS to improve long-term control and reduce exacerbation risk.

Asthma therapy can be stepped down after good asthma control has been achieved and ICS has had time to achieve optimal efficacy. By determining the lowest number or dose of daily controller medications that can maintain good control, the potential for medication adverse effects is reduced. If a child has had well-controlled asthma for at least 3 mo, the guidelines suggest decreasing the dose or number of the child’s controller medication(s) to establish the minimum required medications to maintain well-controlled asthma. Regular follow-up is still emphasized because the variability of asthma’s course is well recognized. In contrast, if a child has not-well-controlled asthma, the therapy level should be increased by 1 step and close monitoring is recommended. For a child with very poorly controlled asthma, the recommendations are that treatment go up 2 steps and/or a short course of oral corticosteroid therapy be given, with evaluation within 2 wk. As step-up therapy is being considered at any point, it is important to check inhaler technique and adherence, implement environmental control measures, and identify and treat comorbid conditions.

**Referral to Asthma Specialist**

Referral to an asthma specialist for consultation or co-management is recommended if there are difficulties in achieving or maintaining control. For children younger than 4 yr, referral is recommended for moderate persistent asthma or if the patient requires at least Step 3 care, and should be considered if the patient requires Step 2 care. For children 5 yr of age and older, consultation with a specialist is recommended if the patient requires Step 4 care or higher, and should be considered if Step 3 is required. Referral is also recommended if allergen immunotherapy or anti–immunoglobulin (Ig) E therapy is being considered.

**Long-Term Controller Medications**

All levels of persistent asthma should be treated with daily medications to improve long-term control (see Table 144-12). Such medications include ICSs, LABAs, leukotriene modifiers, nonsteroidal antiinflammatory agents, and sustained-release theophylline. An anti-IgE preparation, omalizumab (Xolair), is approved by the FDA for use as an add-on therapy in children ≥12 yr who have moderate to severe allergic asthma that is difficult to control. Corticosteroids are the most potent and most effective medications used to treat both the acute (administered systemically) and chronic (administered by inhalation) manifestations of asthma. They are available in inhaled, oral, and parenteral forms (Tables 144-13 and 144-14).

**Inhaled Corticosteroids**

The NIH guidelines recommend daily ICS therapy as the treatment of choice for all patients with persistent asthma (see Table 144-12). ICS therapy improves lung function as well as reduces asthma symptoms, AHR, and use of "rescue" medications; most importantly, it reduces urgent care visits, hospitalizations, and prednisone use for asthma exacerbations by approximately 50%. ICS therapy may lower the risk of death attributable to asthma. It can achieve all of the goals of asthma management and, as a result, is viewed as first-line treatment for persistent asthma.

Six ICSs are approved for use in children by the FDA, and the NIH guidelines provide an equivalence classification (see Table 144-14), although direct comparisons of efficacy and safety outcomes in children are lacking. ICSs are available in metered-dose inhalers (MDIs), in dry powder inhalers (DPIs), or in suspension for nebulization. Fluticasone propionate, mometasone furoate, ciclesonide, and, to a lesser extent, budesonide are considered “second-generation” ICSs, in that they have greater antiinflammatory potency and diminished systemic bioavailability for potential adverse effects, owing to extensive first-pass hepatic metabolism. The selection of the initial ICS dose is based on the determination of disease severity. A fraction of the initial ICS dose is often sufficient to maintain good control after this goal has been achieved.

Although ICS therapy has been widely used in adults with persistent asthma, its application in children has lagged because of concerns about the potential for adverse effects with long-term use. Generally, clinically significant adverse effects that occur with long-term systemic corticosteroid therapy have not been seen or have only very rarely been reported in children receiving ICSs in recommended doses. The risk of adverse effects from ICS therapy is related to the dose and frequency with which ICSs are given (Table 144-15). High doses (≥2,000 μg/day in children) and frequent administration (4 times/day) are more likely to have local and systemic adverse effects. Children who receive maintenance therapy with higher ICS doses are also likely to require systemic corticosteroid courses for asthma exacerbations, further increasing the risk of corticosteroid adverse effects.

The most commonly encountered adverse effects of ICSs are local: oral candidiasis (thrush) and dysphonia (hoarse voice). Thrush results from propellant-induced mucosal irritation and local immunosuppression. Dysphonia occurs from vocal cord myopathy. These effects are
**Table 144-13** Usual Dosages for Long-Term Control Medications

<table>
<thead>
<tr>
<th>Medication</th>
<th>0-4 yr</th>
<th>5-11 yr</th>
<th>≥12 yr</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>INHALED CORTICOSTEROIDS</strong> (see Table 144-13)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methylprednisolone:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2, 4, 8, 16, 32 mg tablets</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prednisolone:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 mg tablets; 5 mg/5 mL, 15 mg/5 mL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prednisone:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1, 2.5, 5, 10, 20, 50 mg tablets; 5 mg/</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mL, 5 mg/5 mL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluticasone/salmeterol:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DPI: 100, 250, or 500 mg/50 mg</td>
<td>NA</td>
<td>1 inhalation bid; dose depends on level of severity or control</td>
<td>1 inhalation bid; dose depends on level of severity or control</td>
</tr>
<tr>
<td>HFA: 45 µg/21 µg, 115 µg/21 µg, 230 µg/21 µg</td>
<td>NA</td>
<td>2 inhalations bid; dose depends on level of severity or control</td>
<td>2 inhalations bid; dose depends on level of severity or control</td>
</tr>
<tr>
<td>Budesonide/formoterol:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HFA: 80 µg/4.5 µg, 160 µg/4.5 µg</td>
<td>NA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mometasone/formoterol:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HFA: 100 µg/5 µg, 200 µg/5 µg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cromolyn: Nebulizer 20 mg/ampule</td>
<td>1 ampule qid; NA &lt;2 yr of age</td>
<td>1 ampule qid</td>
<td>1 ampule qid</td>
</tr>
<tr>
<td>Leukotriene receptor antagonists:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Montelukast:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 or 5 mg chewable tablet</td>
<td>4 mg qhs (1-5 yr of age)</td>
<td>5 mg qhs (6-14 yr)</td>
<td>10 mg qhs</td>
</tr>
<tr>
<td>4 mg granule packets 10 mg tablet</td>
<td>NA</td>
<td>10 mg bid (7-11 yr)</td>
<td>40 mg daily (20 mg tablet bid)</td>
</tr>
<tr>
<td>Zafirlukast: 10- or 20-mg tablet</td>
<td>NA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-Lipoxygenase inhibitor: Zileuton CR: 600-mg tablet</td>
<td>NA</td>
<td>NA</td>
<td>1,200 mg twice daily (give 2 tablets bid)</td>
</tr>
<tr>
<td>Theophylline: Liquids, sustained-release tablets, and capsules</td>
<td>Starting dose 10 mg/kg/day; usual max:</td>
<td>Starting dose 10 mg/kg/day; usual maximum: 16 mg/kg/day</td>
<td>Starting dose 10 mg/kg/day up to 300 mg maximum; usual maximum 800 mg/day</td>
</tr>
<tr>
<td>Starting dose 10 mg/kg/day; usual max: less than 1 yr of age: 0.2 (age in wk) + 5 = mg/kg/day</td>
<td>Starting dose 10 mg/kg/day; usual maximum: 16 mg/kg/day</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immunomodulators: Omalizumab (anti-IgE): Subcutaneous injection, 150 mg/1.2 mL after reconstitution with 1.4 mL sterile water for injection</td>
<td>NA</td>
<td>NA</td>
<td>150-375 mg SC q 2-4 wk, depending on body weight and pretreatment serum IgE level</td>
</tr>
</tbody>
</table>

bid, Twice a day; DPI, dry powder inhaler; HFA, hydrofluoroalkane Ig, immunoglobulin; MDI, metered-dose inhaler; q, every; qhs, every night; qid, 4 times a day; qod, every other day; SC, subcutaneous.

dose-dependent and are most common in individuals receiving high-dose ICS and/or oral corticosteroid therapy. The incidence of these local effects can be greatly minimized by using a spacer with an MDI ICS, because spacers reduce oropharyngeal deposition of the drug and propellant. Mouth rinsing using a “swish and spit” technique after ICS use is also recommended.

The potential for growth suppression and osteoporosis with long-term ICS use has been a concern. In the long-term, prospective NIH-sponsored CAMP study of children with mild to moderate asthma, after 4.3 yr of ICS therapy and 5 yr after the trial, there was a significant 1.7 cm decrease in height in girls, but not in boys. There was also a slight dose-dependent effect of ICS therapy on bone mineral accretion in boys, but not girls. A greater effect on bone mineral accretion was observed with increasing numbers of courses of oral corticosteroid burst therapy for asthma, as well as an increase in risk for osteopenia, again limited to boys. Although this study cannot predict a significant effect of ICS therapy in childhood on osteoporosis in later adulthood, improved asthma control with ICS therapy may result in a need for fewer courses of oral corticosteroid burst therapy over time. These findings were with use of budesonide at doses of about 400 µg/day; higher ICS doses, especially of agents with increased potency, have a greater potential for adverse effects. Hence, corticosteroid adverse effects screening and osteoporosis prevention measures are recommended for patients receiving higher ICS doses, as these patients are also likely to require systemic courses for exacerbations (see Table 144-15).

**Systemic Corticosteroids**

ICS therapy has allowed the large majority of children with asthma to maintain good disease control without maintenance oral corticosteroid therapy. Oral corticosteroids are used primarily to treat asthma exacerbations and, rarely, in patients with severe disease who remain symptomatic despite optimal use of other asthma medications. In these severely asthmatic patients, every attempt should be made to exclude any comorbid conditions and to keep the oral corticosteroid dose at ≤20 mg qod. Doses exceeding this amount are associated with numerous adverse effects (see Chapter 577). To determine the need for continued oral corticosteroid therapy, tapering of the oral corticosteroid...
Table 144-14  Estimated Comparative Inhaled Corticosteroid Doses

<table>
<thead>
<tr>
<th>Drug</th>
<th>LOW DAILY DOSE BY AGE</th>
<th>MEDIUM DAILY DOSE BY AGE</th>
<th>HIGH DAILY DOSE BY AGE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0-4 yr</td>
<td>5-11 yr</td>
<td>≥12 yr</td>
</tr>
<tr>
<td>Beclomethasone HFA, 40 or 80 µg/puff</td>
<td>NA</td>
<td>80-160 µg</td>
<td>80-240 µg</td>
</tr>
<tr>
<td>Budesonide DPI 90, 180, or 200 µg/inhalation</td>
<td>NA</td>
<td>180-400 µg</td>
<td>180-600 µg</td>
</tr>
<tr>
<td>Budesonide inhaled suspension for nebulization, 0.25, 0.5, and 1.0 mg dose</td>
<td>0.25-0.5 mg</td>
<td>0.5 mg</td>
<td>NA</td>
</tr>
<tr>
<td>Flunisolide, 250 µg/puff</td>
<td>NA</td>
<td>500-750 µg</td>
<td>500-1000 µg</td>
</tr>
<tr>
<td>Flunisolide HFA, 80 µg/puff</td>
<td>NA</td>
<td>160 µg</td>
<td>320 µg</td>
</tr>
<tr>
<td>Fluticasone HFA/MDI: 44, 110, or 220 µg/puff</td>
<td>176 µg</td>
<td>88-176 µg</td>
<td>88-264 µg</td>
</tr>
<tr>
<td>Fluticasone DPI, 50, 100, or 250 µg/inhalation</td>
<td>NA</td>
<td>100-200 µg</td>
<td>100-300 µg</td>
</tr>
<tr>
<td>Mometasone DPI, 110 µg and 220 µg/inhalation</td>
<td>NA</td>
<td>NA</td>
<td>220 µg</td>
</tr>
<tr>
<td>Triamcinolone acetonide, 75 µg/puff</td>
<td>NA</td>
<td>300-600 µg</td>
<td>300-750 µg</td>
</tr>
</tbody>
</table>

DPI, dry powder inhaler; HFA, hydrofluoroalkane; MDI, metered-dose inhaler; NA, not approved and no data available for this age group.


Table 144-15  Risk Assessment for Corticosteroid Adverse Effects

<table>
<thead>
<tr>
<th>CONDITIONS</th>
<th>RECOMMENDATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low risk (≤1 risk factor*)</td>
<td>• Monitor blood pressure and weight with each physician visit</td>
</tr>
<tr>
<td>Low- to medium-dose ICS (see Table 144-11)</td>
<td>• Measure height annually (stadiometry); monitor periodically for declining growth rate and pubertal developmental delay</td>
</tr>
<tr>
<td></td>
<td>• Encourage regular physical exercise</td>
</tr>
<tr>
<td></td>
<td>• Ensure adequate dietary calcium and vitamin D with additional supplements for daily calcium if needed</td>
</tr>
<tr>
<td></td>
<td>• Avoid smoking and alcohol</td>
</tr>
<tr>
<td></td>
<td>• Ensure TSH status if patient has history of thyroid abnormality</td>
</tr>
<tr>
<td>Medium risk (If &gt;1 risk factor,* consider evaluating as high risk)</td>
<td>As above, plus:</td>
</tr>
<tr>
<td>High-dose ICS (see Table 144-11)</td>
<td>Yearly ophthalmologic evaluations to monitor for cataracts or glaucoma</td>
</tr>
<tr>
<td>At least 4 courses oral corticosteroid/yr</td>
<td>Baseline bone densitometry (DEXA scan)</td>
</tr>
<tr>
<td></td>
<td>Consider patient at increased risk for adrenal insufficiency, especially with physiologic stressors (e.g., surgery, accident, significant illness)</td>
</tr>
<tr>
<td>High risk</td>
<td>Chronic systemic corticosteroids (&gt;7.5 mg daily or equivalent for &gt;1 mo)</td>
</tr>
<tr>
<td>≥7 oral corticosteroid burst treatments/year</td>
<td>Very-high-dose ICS (e.g., fluticasone propionate ≥800 µg/day)</td>
</tr>
<tr>
<td>As above, plus:</td>
<td></td>
</tr>
<tr>
<td>• DEXA scan: if DEXA Z score ≤1.0, recommend close monitoring (every 12 mo)</td>
<td></td>
</tr>
<tr>
<td>• Consider referral to a bone or endocrine specialist</td>
<td></td>
</tr>
<tr>
<td>• Bone age assessment</td>
<td></td>
</tr>
<tr>
<td>• Complete blood count</td>
<td></td>
</tr>
<tr>
<td>• Serum calcium, phosphorus, alkaline phosphatase determinations</td>
<td></td>
</tr>
<tr>
<td>• Urine calcium and creatinine measurements</td>
<td></td>
</tr>
<tr>
<td>• Measurements of testosterone in males, estradiol in amenorrheic premenopausal women, vitamin D (25-OH and 1,25-OH vitamin D), parathyroid hormone, and osteocalcin</td>
<td></td>
</tr>
<tr>
<td>• Urine telopeptides for those receiving long-term systemic or frequent oral corticosteroid treatment</td>
<td></td>
</tr>
<tr>
<td>• Assume adrenal insufficiency for physiologic stressors (e.g., surgery, accident, significant illness)</td>
<td></td>
</tr>
</tbody>
</table>

*Risk factors for osteoporosis: Presence of other chronic illness(es), medications (corticosteroids, anticonvulsants, heparin, diuretics), low body weight, family history of osteoporosis, significant fracture history disproportionate to trauma, recurrent falls, impaired vision, low dietary calcium and vitamin D intake, and lifestyle factors (decreased physical activity, smoking, and alcohol intake).

DEXA, dual-energy x-ray absorptiometry; ICS, inhaled corticosteroid; TSH, thyroid-stimulating hormone.
dose (over several weeks to months) should be considered, with close monitoring of the patient's symptoms and lung function.

When administered orally, prednisone, prednisolone, and methylprednisolone are rapidly and completely absorbed, with peak plasma concentrations occurring within 1–2 hr. Prednisone is an inactive prodrug that requires biotransformation via first-pass hepatic metabolism to prednisolone, its active form. Corticosteroids are metabolized in the liver into inactive compounds, with the rate of metabolism influenced by drug interactions and disease states. Anticonvulsants (phenytoin, phenobarbital, carbamazepine) increase the metabolism of prednisolone, methylprednisolone, and dexamethasone, with methylprednisolone most significantly affected. Rifampin also enhances the clearance of corticosteroids and can result in diminished therapeutic effect. Other medications (ketonazole, oral contraceptives) can significantly delay corticosteroid metabolism. Macrolide antibiotics (erythromycin, clarithromycin, troleandomycin) delay the clearance of only methylprednisolone.

Children who require long-term oral corticosteroid therapy are at risk for development of associated adverse effects over time. Essentially all major organ systems can be adversely affected by long-term oral corticosteroid therapy (see Chapter 577). Some of these effects occur immediately (metabolic effects). Others can develop insidiously over several months to years (growth suppression, osteoporosis, cataracts). Most adverse effects occur in a cumulative dose- and duration-dependent manner. Children who require routine or frequent short courses of oral corticosteroids, especially with concurrent high-dose ICSs, should receive corticosteroid adverse effects screening (see Table 144-15) and osteoporosis preventive measures (see Chapter 707).

**Long-Acting Inhaled β-Agonists**

LABAs (salmeterol, formoterol) are considered to be daily controller medications, not intended for use as rescue medication for acute asthma symptoms or exacerbations, nor as monotherapy for persistent asthma. Controller formulations that combine an ICS with a LABA (fluticasone/salmeterol, budesonide/formoterol, mometasone/formoterol) are available and recommended, in lieu of separate inhaler delivery devices. Salmeterol has a prolonged onset of action, with maximal bronchodilation approximately 1 hr after administration, whereas formoterol has an onset of action within 5–10 min. Both medications have a prolonged duration of effect, at least 12 hr. Given their long duration of action, they are well suited for patients with nocturnal asthma and for individuals who require frequent SABA use during the day to prevent exercise-induced bronchospasm. Their major role is as an add-on agent in patients whose asthma is suboptimally controlled with ICS therapy alone. For those patients, the addition of a LABA to ICS therapy is superior to doubling the dose of ICS, especially on day and nocturnal symptoms. Of note, the FDA requires all LABA-containing medications to be labeled with a warning of an increase in severe asthma episodes associated with these agents. Some studies have reported a higher number of asthma-related deaths among patients receiving LABA therapy in addition to their usual asthma care than in patients not receiving LABAs. This notice reinforces the appropriate use of LABAs in the management of asthma. Specifically, LABA products should not be initiated as first-line or sole asthma therapy without the concomitant use of an ICS, used with worsening wheezing, or used for acute control of bronchospasm. LABAs should be stopped once asthma control is achieved, and the asthma should be maintained with the use of an asthma controller agent (ICS). Fixed-dose preparations (with an ICS) are recommended to ensure compliance with these guidelines.

**Leukotriene-Modifying Agents**

Leukotrienes are potent proinflammatory mediators that can induce bronchospasm, mucus secretion, and airways edema. Two classes of leukotriene modifiers have been developed: inhibitors of leukotriene synthesis and LTRAs. Zileuton, the only leukotriene synthesis inhibitor, is not approved for use in children <12 yr of age. Because zileuton can result in elevated liver function enzyme values in 2–4% of patients, and interacts with medications metabolized via the cytochrome P450 system, it is rarely prescribed for children with asthma.

LTRAs have bronchodilator and targeted antiinflammatory properties and reduce exercise-, aspirin-, and allergen-induced bronchoconstriction. LTRAs are recommended as alternative treatment for mild persistent asthma and as add-on medication with ICS for moderate persistent asthma. Two LTRAs are FDA-approved for use in children: montelukast and zafirlukast. Both medications improve asthma symptoms, decrease the need for rescue β-agonist use, and improve lung function. Montelukast is FDA-approved for use in children ≥1 yr of age and is administered once daily. Zafirlukast is FDA-approved for use in children ≥5 yr of age and is administered twice daily. Although incompletely studied in children with asthma, LTRAs appear to be less effective than ICSs in patients with mild persistent asthma. In general, ICSs improve lung function by 5–15%, whereas LTRAs improve lung function by 2.75%. LTRAs are not thought to have significant adverse effects, although case reports described a Churg-Strauss–like vasculitis (pulmonary infiltrates, eosinophilia, cardiomyopathy) in adults with corticosteroid-dependent asthma treated with LTRAs. It remains to be determined whether these patients have a primary eosinophilic vasculitis masquerading as asthma, which was “unmasked” as the oral corticosteroid dose was tapered, or whether the disease is a very rare adverse effect of LTRA. Montelukast has rarely been associated with mood changes and suicidality.

**Nonsteroidal Antiinflammatory Agents**

Cromolyn and nedocromil are nonsteroidal antiinflammatory agents that can inhibit allergen-induced asthmatic responses and reduce exercise-induced bronchospasm. Both drugs are considered alternative antiinflammatory drugs for children with mild persistent asthma. Although largely devoid of adverse effects, these medications must be administered frequently (2–4 times/day) and are not nearly as effective daily controller medications as ICSs and leukotriene-modifying agents. Because they inhibit exercise-induced bronchospasm, they can be used in place of SABAs, especially in children who develop unwanted adverse effects with β-agonist therapy (tremor and elevated heart rate). Cromolyn and nedocromil can also be used in addition to a SABA in a combination pretreatment for exercise-induced bronchospasm in patients who continue to experience symptoms with use of SABA pretreatment alone. Nedocromil has been taken off the market and cromolyn is only available in a solution for nebulization.

**Theophylline**

In addition to its bronchodilator effects, theophylline has antiinflammatory properties as a phosphodiesterase inhibitor, although the extent of its clinical relevance has not been clearly established. When used long-term, theophylline can reduce asthma symptoms and the need for rescue SABA use. Although it is considered an alternative onmonotherapy controller agent for older children and adults with mild persistent asthma, it is no longer considered a first-line agent for young children, in whom there is significant variability in the absorption and metabolism of different theophylline preparations, necessitating frequent dose monitoring (drug blood levels) and adjustments. Because theophylline may have some corticosteroid-sparing effects in individuals with oral corticosteroid–dependent asthma, it is still sometimes used in this group of asthmatic children. Theophylline has a narrow therapeutic window; therefore, when it is used, serum theophylline levels need to be routinely monitored, especially if the patient has a viral illness associated with a fever or is started on a medication known to delay theophylline clearance, such as a macrolide antibiotic, cimetidine, an oral antifungal agent, an oral contraceptive, a leukotriene synthesis inhibitor, or ciprofloxacin. Theophylline overdose and elevated theophylline levels have been associated with headaches, vomiting, cardiac arrhythmias, seizures, and death.

**Anti–Immunoglobulin E (Omalizumab)**

Omalizumab is a humanized monoclonal antibody that binds IgE, thereby preventing its binding to the high-affinity IgE receptor and blocking IgE-mediated allergic responses and inflammation. Because it is unable to bind IgE that is already bound to high-affinity IgE
receptors, the risk of anaphylaxis via direct IgE cross linking by the drug is circumvented. It is FDA-approved for patients >12 yr old with moderate to severe asthma, documented hypersensitivity to a perennial aeroallergen, and inadequate disease control with inhaled and/or oral corticosteroids. Omalizumab is given every 2-4 wk subcutaneously, the dosage based on body weight and serum IgE levels. Asthmatic patients receiving omalizumab have fewer asthma exacerbations and symptoms while able to reduce their ICS and/or oral corticosteroid doses. This agent is generally well tolerated, although local injection site reactions can occur. Hypersensitivity reactions (including anaphylaxis) and malignancies have been very rarely associated with omalizumab use. The FDA requires packaging of omalizumab to contain a black box warning of potentially serious and life-threatening anaphylactic reactions with omalizumab treatment. On the basis of reports from approximately 39,500 patients, anaphylaxis following omalizumab treatment occurred in at least 0.1% of treated people. Although most of these reactions occurred within 2 hr of omalizumab injection, there are reports of serious delayed reactions 2-24 hr or even longer after injections. Anaphylaxis occurred after any omalizumab dose (including the first dose). Omalizumab-treated patients should be observed in the facility for an extended period after the drug is given, and medical providers who administer the injection should be prepared to manage life-threatening anaphylactic reactions. Patients who receive omalizumab should be fully informed about the signs and symptoms of anaphylaxis, their chance of development of delayed anaphylaxis following each injection, and how to treat it, including the use of autoinjectable epinephrine.

Mepolizumab, an anti–IL-5 antibody, has been shown to improve asthma control, reduce prednisone dose and lower sputum and blood eosinophil events in adults with prednisone-dependent asthma who also had sputum eosinophils. Dupilumab, an anti–IL-4 receptor antibody and another monoclonal antibody against IL-13, have also shown promise in adult studies.

**Quick-Reliever Medications**
Quick-reliever or “rescue” medications (SABAs, inhaled anticholinergics, and short-course systemic corticosteroids) are used in the management of acute asthma symptoms (Table 144-16).

<table>
<thead>
<tr>
<th>Table 144-16</th>
<th>Management of Asthma Exacerbation (Status Asthmaticus)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RISK ASSESSMENT ON ADMISSION</strong></td>
<td></td>
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<tr>
<td><strong>Focused history</strong></td>
<td></td>
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<tr>
<td>Onset of current exacerbation</td>
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<tr>
<td>Frequency and severity of daytime and nighttime symptoms and activity limitation</td>
<td></td>
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<tr>
<td>Frequency of rescue bronchodilator use</td>
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<tr>
<td>Current medications and allergies</td>
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<tr>
<td>Potential triggers</td>
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<tr>
<td>History of systemic steroid courses, emergency department visits, hospitalization, intubation, or life-threatening episodes</td>
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<tr>
<td><strong>Clinical assessment</strong></td>
<td></td>
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<tr>
<td>Physical examination findings: vital signs, breathlessness, air movement, use of accessory muscles, retractions, anxiety level, alteration in mental status</td>
<td></td>
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<tr>
<td>Pulse oximetry</td>
<td></td>
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<tr>
<td>Lung function (defer in patients with moderate to severe distress or history of labile disease)</td>
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<tr>
<td><strong>TREATMENT</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Drug and Trade Name</strong></td>
<td><strong>Mechanisms of Action and Dosing</strong></td>
</tr>
<tr>
<td>Oxygen (mask or nasal cannula)</td>
<td>Treats hypoxia</td>
</tr>
<tr>
<td>Inhaled short-acting β-agonists:</td>
<td>Bronchodilator</td>
</tr>
<tr>
<td>Albuterol nebulizer solution (5 mg/mL concentrate; 2.5 mg/3 mL, 1.25 mg/3 mL, 0.63 mg/3 mL)</td>
<td>Nebulizer: 0.15 mg/kg (minimum: 2.5 mg) as often as every 20 min for 3 doses as needed, then 0.15-0.3 mg/kg up to 10 mg every 1-4 hr as needed, or up to 0.5 mg/kg/hr by continuous nebulization</td>
</tr>
<tr>
<td>Albuterol MDI (90 µg/puff)</td>
<td>2-8 puffs up to every 20 min for 3 doses as needed, then every 1-4 hr as needed</td>
</tr>
<tr>
<td>Levalbuterol (Xopenex) nebulizer solution (1.25 mg/0.5 mL concentrate; 0.31 mg/3 mL, 0.63 mg/3 mL, 1.25 mg/3 mL)</td>
<td>0.075 mg/kg (minimum: 1.25 mg) every 20 min for 3 doses, then 0.075-0.15 mg/kg up to 5 mg every 1-4 hr as needed, or 0.25 mg/kg/hr by continuous nebulization</td>
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<tr>
<td>Systemic corticosteroids:</td>
<td>Antiinflammatory</td>
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</table>
Part XV

Management of Asthma Exacerbation (Status Asthmaticus)—cont’d

Continuous IV infusion (terbutaline only):
- Short-course “burst” for exacerbation: 1-2 mg/kg/day qd or bid for 3-7 days
- Should not be used as first-line therapy; added to β₂-agonist therapy
- Nebulizer: 0.5 mg q6-8h (tid-qid) as needed
- MDI: 2 puffs qid
- Nebulizer: may mix ipratropium with albuterol
- For extreme circumstances (e.g., impending respiratory failure despite high-dose inhaled SABA, respiratory failure)
- Terbutaline is β₂-agonist-selective relative to epinephrine
- Monitoring with continuous infusion: cardiorespiratory monitor, pulse oximetry, blood pressure, serum potassium
- Adverse effects: tremor, tachycardia, palpitations, arrhythmia, hypertension, headaches, nervousness, nausea, vomiting, hypoxemia

Anticholinergic Agents

As bronchodilators, the anticholinergic agents (ipratropium bromide) are less potent than the β₂-agonists. Inhaled ipratropium is used primarily in the treatment of acute severe asthma. When used in combination with albuterol, ipratropium can improve lung function and reduce the rate of hospitalization in children who present to the emergency department with acute asthma. Ipratropium is the anticholinergic formulation of choice for children because it has few central nervous system adverse effects and it is available in both MDI and nebulizer formulations. Although widely used in children with asthma exacerbations of all ages, it is approved by the FDA for use in children >12 yr of age. A long-acting inhaled anticholinergic agent, tiotropium, is gaining interest as a potential add-on controller therapy (i.e., in addition to ICS with or without LABA) for adults with asthma.

Delivery Devices and Inhalation Technique

Inhaled medications are delivered in aerosolized form in a MDI, as a DPI formulation, or in a suspension or solution form delivered via a nebulizer.
nebulizer. In the past, MDIs, which require coordination and use of a spacer device, have dominated the market. MDIs are now using hydrofluoralkane propellant for its ozone-friendly properties, rather than chlorofluorocarbon. Spacer devices, recommended for the administration of all MDI medications, are simple and inexpensive tools that: (1) decrease the coordination required to use MDIs, especially in young children; (2) improve the delivery of inhaled drug to the lower airways; and (3) minimize the risk of propellant-mediated adverse effects (thrust). Optimal inhalation technique for each puff of MDI-delivered medication is a slow (5 sec) inhalation, then a 5-10 sec breathhold. No waiting time between puffs of medication is needed. Young, preschool-age children cannot perform this inhalation technique. MDI medications can also be delivered with a spacer and mask, using a different technique: Each puff is administered with regular breathing for about 30 sec or 5-10 breaths, a tight seal must be maintained, and talking, coughing, or crying will blow the medication out of the spacer. This technique will not deliver as much medication per puff as the optimal MDI technique used by older children and adults.

DPI devices (e.g., Diskus, Flexhaler Autohaler, Twistrhaler, Aerolizer) are popular because of their simplicity of use, albeit adequate inspiratory flow is needed. They are breath-actuated (the drug comes out only as it is breathed in) and spacers are not needed. Mouth rinsing is recommended after ICS use to rinse out ICS deposited on the oral mucosa and reduce the swallowed ICS and the risk of thrust.

Nebulizers have been the mainstay of aerosol treatment for infants and young children. An advantage of using nebulizers is the simple technique required of relaxed breathing. The preferential nasal breathing, small airways, low tidal volume, and high respiratory rate of infants markedly increase the difficulty of inhaled drug therapy targeting the lung airways. Disadvantages of nebulizers include need for a power source, inconvenience in that treatments take about 5 min, expense, and potential for bacterial contamination.

Asthma Exacerbations and Their Management

Asthma exacerbations are acute or subacute episodes of progressively worsening symptoms and airflow obstruction. Airflow obstruction during exacerbations can become extensive, resulting in life-threatening respiratory insufficiency. Often, asthma exacerbations worsen during sleep (between midnight and 8 A.M.), when airways inflammation and hyperresponsiveness are at their peak. Importantly, SABAs, which are first-line therapy for asthma symptoms and exacerbations, increase pulmonary blood flow through obstructed, unoxygenated areas of the lungs with increasing dosage and frequency. When airflow obstruction is not resolved with SABA use, ventilation–perfusion mismatching can cause significant hypoxemia, which can perpetuate bronchoconstriction and further worsen the condition. Severe, progressive asthma exacerbations need to be managed in a medical setting, with administration of supplemental oxygen as first-line therapy and close monitoring for potential worsening. Complications that can occur during severe exacerbations include atelectasis and air leaks in the chest (pneumomediastinum, pneumothorax).

A severe exacerbation of asthma that does not improve with standard therapy is termed status asthmaticus. Immediate management of an asthma exacerbation involves a rapid evaluation of the severity of obstruction and assessment of risk for further clinical deterioration (see Tables 144-15 and 144-16). For most patients, exacerbations improve with frequent bronchodilator treatments and a course of systemic (oral or intravenous) corticosteroid. However, the optimal management of a child with an asthma exacerbation should include a more comprehensive assessment of the events leading up to the exacerbation and the underlying disease severity. Indeed, the frequency and severity of asthma exacerbations help define the severity of a patient’s asthma. Whereas most children who experience life-threatening asthma episodes have moderate to severe asthma by other criteria, some children with asthma appear to have mild disease except when they suffer severe, even near-fatal exacerbations. The biologic, environmental, economic, and psychosocial risk factors associated with asthma morbidity and death can further guide this assessment (Table 144-17).

### Table 144-17 Risk Factors for Asthma Morbidity and Mortality

<table>
<thead>
<tr>
<th>Category</th>
<th>Risk Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BIOLOGIC</strong></td>
<td>Previous severe asthma exacerbation (intensive care unit admission, intubation for asthma)</td>
</tr>
<tr>
<td></td>
<td>Sudden asphyxia episodes (respiratory failure, arrest)</td>
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<tr>
<td></td>
<td>Two or more hospitalizations for asthma in past year</td>
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<tr>
<td></td>
<td>Three or more emergency department visits for asthma in past year</td>
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<tr>
<td></td>
<td>Increasing and large diurnal variation in peak flows</td>
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<tr>
<td></td>
<td>Use of &gt;2 canisters of short-acting β-agonists per month</td>
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<tr>
<td></td>
<td>Poor response to systemic corticosteroid therapy</td>
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<td></td>
<td>Male gender</td>
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<td></td>
<td>Low birthweight</td>
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<tr>
<td></td>
<td>Nonwhite (especially black) ethnicity</td>
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<td></td>
<td>Sensitivity to Alternaria</td>
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<tr>
<td><strong>ENVIRONMENTAL</strong></td>
<td>Allergen exposure</td>
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<tr>
<td></td>
<td>Environmental tobacco smoke exposure</td>
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<tr>
<td></td>
<td>Air pollution exposure</td>
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<tr>
<td></td>
<td>Urban environment</td>
</tr>
<tr>
<td><strong>ECONOMIC AND PSYCHOSOCIAL</strong></td>
<td>Poverty</td>
</tr>
<tr>
<td></td>
<td>Crowding</td>
</tr>
<tr>
<td></td>
<td>Mother &lt;20 yr old</td>
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<tr>
<td></td>
<td>Mother with less than high school education</td>
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<tr>
<td></td>
<td>Inadequate medical care</td>
</tr>
<tr>
<td></td>
<td>Inaccessible</td>
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<tr>
<td></td>
<td>Unaffordable</td>
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<tr>
<td></td>
<td>No regular medical care (only emergency)</td>
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<tr>
<td></td>
<td>Lack of written asthma action plan</td>
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<tr>
<td></td>
<td>No care sought for chronic asthma symptoms</td>
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<tr>
<td></td>
<td>Delay in care of asthma exacerbations</td>
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<tr>
<td></td>
<td>Inadequate hospital care for asthma exacerbation</td>
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<tr>
<td></td>
<td>Psychopathology in the parent or child</td>
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<tr>
<td></td>
<td>Poor perception of asthma symptoms or severity</td>
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<tr>
<td></td>
<td>Alcohol or substance abuse</td>
</tr>
</tbody>
</table>

Asthma exacerbations characteristically vary among individuals but tend to be similar in the same patient. Severe asthma exacerbations, resulting in respiratory distress, hypoxia, hospitalization, and/or respiratory failure, are the best predictors of future life-threatening exacerbations or a fatal asthma episode. In addition to distinguishing such high-risk children, some experience exacerbations that come on over days, with airflow obstruction resulting from progressive inflammation, epithelial sloughing, and cast impaction of small airways. When such a process is extreme, respiratory failure as a result of fatique can ensue, necessitating mechanical ventilation for numerous days. In contrast, some children experience abrupt-onset exacerbations that may result from extreme AHR and physiologic susceptibility to airways closure. Such exacerbations, when extreme, are asphyxial in nature, often occur outside medical settings, are initially associated with very high arterial partial pressure of carbon dioxide (Paco₂) levels, and tend to require only brief periods of supportive ventilation. Recognizing the characteristic differences in asthma exacerbations is important for optimizing their early management.

### Home Management of Asthma Exacerbations

Families of all children with asthma should have a written action plan to guide their recognition and management of exacerbations, along with the necessary medications and tools to manage them. Early recognition of asthma exacerbations in order to intensify treatment early can often prevent further worsening and keep exacerbations from becoming severe. A written home action plan can reduce the risk of asthma death by 70%. The NIH guidelines recommend immediate treatment with “rescue” medication (inhaled SABA, up to 3 treatments in 1 hr). A good response is characterized by resolution of symptoms within 1 hr, no further symptoms over the next 4 hr, and improvement in PEF value to at least 80% of personal best. The child’s physician
should be contacted for follow-up, especially if bronchodilators are required repeatedly over the next 24-48 hr. If the child has an incomplete response to initial treatment with rescue medication (persistent symptoms and/or a PEF value <80% of personal best), a short course of oral corticosteroid therapy (prednisone 1-2 mg/kg/day [not to exceed 60 mg/day] for 4 days), in addition to inhaled β-agonist therapy, should be instituted. The physician should also be contacted for further instructions. Immediate medical attention should be sought for severe exacerbations, persistent signs of respiratory distress, lack of expected response or sustained improvement after initial treatment, further deterioration, or high-risk factors for asthma morbidity or mortality (previous history of severe exacerbations). For patients with severe asthma and/or a history of life-threatening episodes, especially if (previous history of severe exacerbations). Patients requiring frequent or continuous nebulized β-agonist therapy should have ongoing cardiac monitoring. Because frequent β-agonist therapy can cause ventilation-perfusion mismatch and hypoxemia, oximetry is also indicated. Inhaled ipratropium bromide is often added to albuterol every 6 hr if patients do not show a remarkable improvement, although there is little evidence to support its use in hospitalized children receiving aggressive inhaled β-agonist therapy and systemic corticosteroids. In addition to its potential to provide a synergistic effect with a β-agonist agent in relieving severe bronchospasm, ipratropium bromide may be beneficial in patients who have mucous hypersecretion or are receiving β-blockers.

Short-course systemic corticosteroid therapy is recommended for use in moderate to severe asthma exacerbations to hasten recovery and prevent recurrence of symptoms. Corticosteroids are effective as single doses administered in the emergency department, short courses in the clinic setting, and both oral and intravenous formulations in hospitalized children. Studies in children hospitalized with acute asthma have found corticosteroids administered orally to be as effective as intravenous corticosteroids. Accordingly, oral corticosteroid therapy can often be used, although children with sustained respiratory distress who are unable to tolerate oral preparations or liquids are obvious candidates for intravenous corticosteroid therapy.

 Patients with persistent severe dyspnea and high-flow oxygen requirements require additional evaluations, such as complete blood cell counts, measurements of arterial blood gases and serum electrolytes, and chest radiograph, to monitor for respiratory insufficiency, comorbidities, infection, and/or dehydration. Hydration status monitoring is especially important in infants and young children, whose increased respiratory rate (insensible losses) and decreased oral intake put them at higher risk for dehydration. Further complicating this situation is the association of increased anti-diuretic hormone secretion with status asthmaticus. Administration of fluids at or slightly below maintenance fluid requirements is recommended. Chest physical therapy, incentive spirometry, and mucolytics are not recommended during the early acute period of asthma exacerbations as they can trigger severe bronchoconstriction.

 Despite intensive therapy, some asthmatic children remain critically ill and at risk for respiratory failure, intubation, and mechanical ventilation. Complications (air leaks) related to asthma exacerbations increase with intubation and assisted ventilation; every effort should be made to relieve bronchospasm and prevent respiratory failure. Several therapies, including inhaled corticosteroids, methyloxanthines, magnesium sulfate (25-75 mg/kg, maximum dose 2.5 g, given intravenously over 20 min), and inhaled heliox (helium and oxygen mixture) have demonstrated some benefit as adjunctive therapies in patients with severe status asthmaticus. Administration of either methyloxanthine or magnesium sulfate requires monitoring of serum levels and cardiovascular status. Parenteral (subcutaneous, intramuscular, or intravenous) epinephrine or terbutaline sulfate may be effective in patients with life-threatening obstruction that is not responding to high doses of inhaled β-agonists, because in such patients, inhaled medication may not reach the lower airway.

 Rarely, a severe asthma exacerbation in a child results in respiratory failure, and intubation and mechanical ventilation become necessary. Mechanical ventilation in severe asthma exacerbations requires the careful balance of enough pressure to overcome airways obstruction while reducing hyperinflation, air trapping, and the likelihood of barotrauma (pneumothorax, pneumomediastinum) (see Chapter 411). To minimize the likelihood of such complications, mechanical ventilation should be anticipated, and asthmatic children at risk for the development of respiratory failure should be managed in a pediatric ICU. Elective tracheal intubation with rapid-induction sedatives and paralytic agents is safer than emergency intubation. Mechanical ventilation aims to achieve adequate oxygenation while tolerating mild to

**Emergency Department Management of Asthma Exacerbations**

In the emergency department, the primary goals of asthma management include correction of hypoxemia, rapid improvement of airflow obstruction, and prevention of progression or recurrence of symptoms. Interventions are based on clinical severity on arrival, response to initial therapy, and presence of risk factors that are associated with asthma morbidity and mortality (see Table 144-17). Indications of a severe exacerbation include breathlessness, dyspnea, retractions, accessory muscle use, tachypnea or labored breathing, cyanosis, mental status changes, a silent chest with poor air exchange, and severe airflow limitation (PEF or FEV<sub>1</sub>, value <50% of personal best or predicted values). Initial treatment includes supplemental oxygen, inhaled β-agonist therapy every 20 min for 1 hr, and, if necessary, systemic corticosteroids given either orally or intravenously (see Table 144-16). Inhaled ipratropium may be added to the β-agonist treatment if no significant response is seen with the first inhaled β-agonist treatment. An intramuscular injection of epinephrine or other β-agonist may be administered in severe cases. Oxygen should be administered and continued for at least 20 min after SABA administration to compensate for possible ventilation-perfusion abnormalities caused by SABAs.

Close monitoring of clinical status, hydration, and oxygenation are essential elements of immediate management. A poor response to intensified treatment in the 1st hr suggests that the exacerbation will not remit quickly. The patient may be discharged to home if there is sustained improvement in symptoms, normal physical findings, PEF >70% of predicted or personal best, an oxygen saturation >92% while the patient is breathing room air for 4 hr. Discharge medications include administration of an inhaled β-agonist up to every 3-4 hr plus a 3-7 day course of an oral corticosteroid. Optimizing controller therapy before discharge is also recommended. The addition of ICS to a course of oral corticosteroid in the emergency department setting reduces the risk of exacerbation recurrence over the subsequent month.

**Hospital Management of Asthma Exacerbations**

For patients with moderate to severe exacerbations that do not adequately improve within 1-2 hr of intensive treatment, observation and/ or admission to the hospital, at least overnight, is likely to be needed. Other indications for hospital admission include high-risk features for asthma morbidity or death (see Table 144-17). Admission to an intensive care unit is indicated for patients with severe respiratory distress, poor response to therapy, and concern for potential respiratory failure and arrest.

Supplemental oxygen, frequent or continuous administration of an inhaled bronchodilator, and systemic corticosteroid therapy are the conventional interventions for children admitted to the hospital for status asthmaticus (see Table 144-16). Supplemental oxygen is administered because many children hospitalized with acute asthma have or eventually have hypoxemia, especially at night and with increasing SABA administration. SABAs can be delivered frequently (every 20 min to 1 hr) or continuously (at 5-15 mg/hr). When administered continuously, significant systemic absorption of β-agonist occurs and, as a result, continuous nebulization can obviate the need for intravenous β-agonist therapy. Adverse effects of frequently administered β-agonist therapy include tremor, irritability, tachycardia, and hypokalemia. Patients requiring frequent or continuous nebulized β-agonist therapy should have ongoing cardiac monitoring. Because frequent β-agonist therapy can cause ventilation-perfusion mismatch and hypoxemia, oximetry is also indicated. Inhaled ipratropium bromide is often added to albuterol every 6 hr if patients do not show a remarkable improvement, although there is little evidence to support its use in hospitalized children receiving aggressive inhaled β-agonist therapy and systemic corticosteroids. In addition to its potential to provide a synergistic effect with a β-agonist agent in relieving severe bronchospasm, ipratropium bromide may be beneficial in patients who have mucous hypersecretion or are receiving β-blockers.

Short-course systemic corticosteroid therapy is recommended for use in moderate to severe asthma exacerbations to hasten recovery and prevent recurrence of symptoms. Corticosteroids are effective as single doses administered in the emergency department, short courses in the clinic setting, and both oral and intravenous formulations in hospitalized children. Studies in children hospitalized with acute asthma have found corticosteroids administered orally to be as effective as intravenous corticosteroids. Accordingly, oral corticosteroid therapy can often be used, although children with sustained respiratory distress who are unable to tolerate oral preparations or liquids are obvious candidates for intravenous corticosteroid therapy.

Patients with persistent severe dyspnea and high-flow oxygen requirements require additional evaluations, such as complete blood cell counts, measurements of arterial blood gases and serum electrolytes, and chest radiograph, to monitor for respiratory insufficiency, comorbidities, infection, and/or dehydration. Hydration status monitoring is especially important in infants and young children, whose increased respiratory rate (insensible losses) and decreased oral intake put them at higher risk for dehydration. Further complicating this situation is the association of increased anti-diuretic hormone secretion with status asthmaticus. Administration of fluids at or slightly below maintenance fluid requirements is recommended. Chest physical therapy, incentive spirometry, and mucolytics are not recommended during the early acute period of asthma exacerbations as they can trigger severe bronchoconstriction.

Despite intensive therapy, some asthmatic children remain critically ill and at risk for respiratory failure, intubation, and mechanical ventilation. Complications (air leaks) related to asthma exacerbations increase with intubation and assisted ventilation; every effort should be made to relieve bronchospasm and prevent respiratory failure. Several therapies, including inhaled corticosteroids, methyloxanthines, magnesium sulfate (25-75 mg/kg, maximum dose 2.5 g, given intravenously over 20 min), and inhaled heliox (helium and oxygen mixture) have demonstrated some benefit as adjunctive therapies in patients with severe status asthmaticus. Administration of either methyloxanthine or magnesium sulfate requires monitoring of serum levels and cardiovascular status. Parenteral (subcutaneous, intramuscular, or intravenous) epinephrine or terbutaline sulfate may be effective in patients with life-threatening obstruction that is not responding to high doses of inhaled β-agonists, because in such patients, inhaled medication may not reach the lower airway.

Rarely, a severe asthma exacerbation in a child results in respiratory failure, and intubation and mechanical ventilation become necessary. Mechanical ventilation in severe asthma exacerbations requires the careful balance of enough pressure to overcome airways obstruction while reducing hyperinflation, air trapping, and the likelihood of barotrauma (pneumothorax, pneumomediastinum) (see Chapter 411). To minimize the likelihood of such complications, mechanical ventilation should be anticipated, and asthmatic children at risk for the development of respiratory failure should be managed in a pediatric ICU. Elective tracheal intubation with rapid-induction sedatives and paralytic agents is safer than emergency intubation. Mechanical ventilation aims to achieve adequate oxygenation while tolerating mild to
moderate hypercapnia (PCO2, 50-70 mm Hg) to minimize barotrauma. Volume-cycled ventilators, using short inspiratory and long expiratory times, 10-15 mL/kg tidal volume, 8-15 breaths/min, peak pressures <60 cm H2O, and without positive end-expiratory pressure are starting mechanical ventilation parameters that can achieve these goals. As measures to relieve mucous plugs, chest percussion and airways lavage are not recommended because they can induce further bronchospasm. One must consider the nature of asthma exacerbations leading to respiratory failure; those of rapid or abrupt onset tend to resolve quickly (hours to 2 days), whereas those that progress gradually to respiratory failure can require days to weeks of mechanical ventilation. Such prolonged cases are further complicated by muscle atrophy and, when combined with corticosteroid-induced myopathy, can lead to severe muscle weakness requiring prolonged rehabilitation. This myopathy should not be confused with the rare occurrence of an asthma-associated flaccid paralysis (Hopkins syndrome), which is of unknown etiology but prolongs the intensive care stay.

In children, management of severe exacerbations in medical centers is usually successful, even when extreme measures are required. Consequently, asthma deaths in children rarely occur in medical centers; most occur at home or in community settings before lifesaving medical care can be administered. This point highlights the importance of home and community management of asthma exacerbations, early intervention measures to keep exacerbations from becoming severe, and steps to reduce asthma severity. A follow-up appointment within 1-2 wk of a child’s discharge from the hospital after resolution of an asthma exacerbation should be used to monitor clinical improvement and to reinforce key educational elements, including action plans and controller medications.

**Special Management Circumstances**

**Management of Infants and Young Children.** Recurrent wheezing episodes in preschool-age children are very common, occurring in as much as one-third of this population. Of them, most improve and even become asymptomatic during the presubpneumonic school-age years, whereas others have lifelong persistent asthma. All require management of their recurrent wheezing problems (see Tables 144-5, 144-7, and 144-12). The updated NIH guidelines recommend risk assessment to identify preschool-age children who are likely to have persistent asthma. One implication of this recommendation is that these at-risk children may be candidates for conventional asthma management, including daily controller therapy and early intervention with exacerbations (see Tables 144-8, 144-9, and 144-12). Nebulized budesonide and montelukast appear to be more effective than cromolyn. For young children with a history of moderate to severe exacerbations, nebulized budesonide is FDA approved, and its use as a controller medication could prevent subsequent exacerbations.

Using aerosol therapy in infants and young children with asthma presents unique challenges. There are 2 delivery systems for inhaled medications for this age group, the nebulizer and the MDI with spacer/holding chamber and face mask. Multiple studies demonstrate the effectiveness of both nebulized albuterol in acute episodes and nebulized budesonide in the treatment of recurrent wheezing in infants and young children. In such young children, inhaled medications administered via MDI with spacer and face mask may be acceptable, although perhaps not preferred owing to limited published information and lack of FDA approval for children <4 yr of age.

**Asthma Management in Pregnancy.** The goals of asthma management during pregnancy should include prevention of exacerbations and control of chronic symptoms through the use of medications that pose minimal risk to the mother and fetus because most drugs cross the placenta. It is considered safer for pregnant asthmatic women to be treated with controller medications than it is to have uncontrolled symptoms and severe exacerbations. Albuterol is the preferred SABA for use during pregnancy. There is reassuring efficacy and safety data from prospective cohort studies supporting ICS use in pregnant women with asthma. Budesonide is currently the preferred ICS for pregnant women, attaining an FDA Pregnancy Category B rating because of substantial reassuring safety data. Nonmedication approaches to improve asthma control are encouraged. A multidisciplinary approach with monthly evaluations (including pulmonary function tests when not contraindicated) and ongoing consultation with the obstetrician and asthma specialist is recommended. Frequent fetal and maternal surveillance is especially important for adolescents with suboptimal asthma control, those with moderate to severe asthma, and those with a recent exacerbation.

**Asthma Management During Surgery.** Patients with asthma are at risk from disease-related complications from surgery, such as bronchoconstriction and asthma exacerbation, atelectasis, impaired coughing, respiratory infection, and latex exposure, that may induce asthma complications in patients with latex allergy. All patients with asthma should be evaluated before surgery, and those who are inadequately controlled should allow time for intensified treatment in order to improve asthma stability before surgery if possible. A systemic corticosteroid course may be indicated for the patient who is having symptoms and/or FEV1 or PEF values <80% of the patient’s personal best. In addition, patients who have received >2 wk of systemic corticosteroid and/or moderate- to high-dose ICS therapy may be at risk for intraoperative adrenal insufficiency. For these patients, anesthesia services should be alerted to provide “stress” replacement doses of systemic corticosteroid for the surgical procedure and possibly the postoperative period if needed.

**PROGNOSIS**

Recurrent coughing and wheezing occurs in 35% of preschool-age children. Of these, approximately one-third continue to have persistent asthma into later childhood, and approximately two-thirds improve on their own through their teen years. Asthma severity by the ages of 7-10 yr is predictive of asthma persistence in adulthood. Children with moderate to severe asthma and with lower lung function measures are likely to have persistent asthma as adults. Children with milder asthma and normal lung function are likely to improve over time, with some becoming periodically asthmatic (disease-free for months to years); however, complete remission for 5 yr in childhood is uncommon.

**PREVENTION**

Although chronic airways inflammation may result in pathologic remodeling of lung airways, conventional anti-inflammatory interventions—the cornerstone of asthma control—do not help children outgrow their asthma. Although controller medications reduce asthma morbidities, most children with moderate to severe asthma continue to have symptoms into young adulthood. Investigations into the environmental and lifestyle factors responsible for the prevalence of childhood asthma in rural areas and farming communities suggest that early immunomodulatory intervention might prevent asthma development. A *hygiene hypothesis* purports that naturally occurring microbial exposures in early life might drive early immune development away from allergic sensitization, persistent airways inflammation, and remodeling. If these natural microbial exposures truly have an asthma-protective effect, without significant adverse health consequences, then these findings may foster new strategies for asthma prevention.

Several nonpharmacotherapeutic measures with numerous positive health attributes—avoidance of environmental tobacco smoke (beginning prenatally), prolonged breastfeeding (>4 mo), an active lifestyle, and a healthy diet—might reduce the likelihood of asthma development. Immunizations are currently not considered to increase the likelihood of development of asthma; therefore, all standard childhood immunizations are recommended for children with asthma, including varicella and annual influenza vaccines.

Bibliography is available at Expert Consult.
Bibliography


Chapter 145
Atopic Dermatitis
(Atopic Eczema)
Donald Y.M. Leung and Scott H. Sicherer

Atopic dermatitis (AD), or eczema, is the most common chronic relapsing skin disease seen in infancy and childhood. It affects 10–30% of children worldwide and frequently occurs in families with other atopic diseases, such as asthma, allergic rhinitis, and food allergy. Infants with AD are predisposed to development of allergic rhinitis and/or asthma later in childhood, a process called “the atopic march.”

**ETIOLOGY**
AD is a complex genetic disorder that results in a defective skin barrier, reduced skin innate immune responses, and exaggerated T-cell responses to environmental allergens and microbes that lead to chronic skin inflammation.

**PATHOLOGY**
Acute AD skin lesions are characterized by spongiosis, or marked intercellular edema, of the epidermis. In AD, dendritic antigen-presenting cells in the epidermis, such as Langerhans cells, exhibit surface-bound immunoglobulin (Ig) E molecules. These antigen-presenting cells play an important role in cutaneous allergen presentation to T-helper type 2 (Th2) cells (see Chapter 140). There is a marked perivascular T-cell infiltrate with occasional monocyte-macrophages in acute AD lesions. Mast cells are found in normal numbers but in different stages of degranulation. Chronic, lichenified AD is characterized by a hyperplastic epidermis with hyperkeratosis, and minimal spongiosis. There are predominantly IgE-bearing Langerhans cells in the epidermis, and macrophages in the dermal mononuclear cell infiltrate. Mast cell and eosinophil numbers are increased, contributing to skin inflammation.

**PATHOGENESIS**
Two forms of AD have been identified. **Atopic eczema** is associated with IgE-mediated sensitization (at onset or during the course of eczema) and occurs in 70–80% of patients with AD. **Nonatopic eczema** is not associated with IgE-mediated sensitization and is seen in 20–30% of patients with AD. Both forms of AD are associated with eosinophilia. In atopic eczema, circulating T cells expressing the skin homing receptor cutaneous lymphocyte-associated antigen produce increased levels of Th2 cytokines, including interleukin (IL)-4 and IL-13, which induce isotype switching to IgE synthesis. Another cytokine, IL-5, plays an important role in eosinophil development and survival. Nonatopic eczema is associated with lower IL-4 and IL-13 production than is atopic eczema.

Compared with the skin of healthy subjects, both unaffected skin and acute skin lesions of patients with AD have an increased number of cells expressing IL-4 and IL-13. Chronic AD skin lesions, by contrast, have significantly fewer cells that express IL-4 and IL-13, but increased numbers of cells that express IL-5, granulocyte-macrophage colony-stimulating factor, IL-12, and interferon (IFN)-γ than acute AD lesions. Chronic AD is characterized by a shift from a Th2-dominant to a Th1-dominant profile. The infiltration of IL-22–expressing T cells correlates with severity of AD, blocks keratinocyte differentiation, and induces epidermal hyperplasia.

The development of AD skin lesions is orchestrated by local tissue expression of proinflammatory cytokines and chemokines, which play a central role in defining the nature of the inflammatory infiltrate in AD. The chemotactic protein, CCL27, is highly upregulated in AD and preferentially attracts cutaneous lymphocyte-associated antigen-positive T cells to the skin. Other C-C chemokines, RANTES (regulated on activation, normal T-cell expressed and secreted), monocyte chemotactic protein-4, and eotaxin are increased in AD skin lesions, resulting in chemotaxis of eosinophils, macrophages, and Th2 lymphocytes expressing their receptor (CCR3).

In healthy people, the skin acts as a protective barrier against external irritants, moisture loss, and infection. Proper function of the skin depends on adequate moisture and lipid content, functional immune responses, and structural integrity. **Severely dry skin is a hallmark of AD.** This results from compromise of the epidermal barrier, which leads to excess transepidermal water loss, allergen penetration, and microbial colonization. Filaggrin, a structural protein in the epidermis, and its breakdown products are critical to skin barrier function. Genetic mutations in the filaggrin gene family have been identified in up to 50% of patients with severe AD. Cytokines found in allergic inflammation, such as IL-4, IL-13, IL-22, IL-25, and tumor necrosis factor, can also reduce filaggrin expression. AD patients thereby have increased risk of bacterial, viral, and fungal infection related to impairment of innate immunity, including a loss of barrier function and impaired generation of antimicrobial peptides.

**CLINICAL MANIFESTATIONS**
AD typically begins in infancy. Approximately 50% of patients experience symptoms in the 1st yr of life, and an additional 30% are diagnosed between 1 and 5 yr of age. Intense pruritus, especially at night, and cutaneous reactivity are the cardinal features of AD. Scratching and excoriation cause increased skin inflammation that contributes to the development of more pronounced eczematous skin lesions. Foods (cow milk, egg, peanut, tree nuts, soy, wheat, fish, shellfish), aeroallergens (pollen, grass, animal dander, dust mites), infection (staphylococcus, herpes simplex, molluscum), reduced humidity, excessive sweating, and irritants (wool, acrylic, soaps, toiletries, fragrances, detergents) can exacerbate (trigger) pruritus and scratching.

Acute AD skin lesions are intensely pruritic with erythematous papules (Figs. 145-1 and 145-2). Subacute dermatitis manifests as erythematous, excoriated, scaling papules. In contrast, chronic AD is characterized by lichenification (Fig. 145-3), or thickening of the skin with accentuated surface markings, and fibrotic papules. In chronic AD, all
Atopic dermatitis (AD) is a chronic inflammatory skin disorder that typically presents in early childhood and may persist into adulthood. The diagnosis of AD is based on clinical features, which include pruritus, dry skin, and skin inflammation. Laboratory tests, such as peripheral blood eosinophilia and increased serum IgE levels, can be supportive of the diagnosis but are not diagnostic. AD is not caused by an infection, but it can be exacerbated by infections such as those caused by Staphylococcus aureus or group A streptococcus. Associated features that may help in the diagnosis of AD include a history of asthma, hay fever, atopic family history, and positive results of immediate-type allergy skin tests. The severity of AD can vary, and it may be more acute in infancy and less severe in adulthood. Associated conditions, such as psoriasis, ichthyoses, and seborrheic dermatitis, can also be seen in patients with AD.

There are no specific laboratory tests to diagnose AD. Many patients with AD have peripheral blood eosinophilia and increased serum IgE levels. Serum IgE measurement or prick skin testing can identify the allergens to which patients are sensitized. The diagnosis of clinical allergy to these allergens requires confirmation by history and environmental challenges.

**DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS**

AD is diagnosed on the basis of 3 major features: pruritus, an eczematous dermatitis that fits into a typical presentation, and a chronic or chronically relapsing course (Table 145-1). Associated features, such as a family history of asthma, hay fever, elevated IgE, and immediate skin test reactivity, are variably present.

Many inflammatory skin diseases, immunodeficiencies, skin malignancies, genetic disorders, infectious diseases, and infestations share symptoms with AD and should be considered and excluded before a diagnosis of AD is established (Table 145-2). Severe combined immunodeficiency syndrome (see Chapter 126.1) should be considered for infants presenting in the 1st yr of life with diarrhea, failure to thrive, generalized scaling rash, and recurrent cutaneous and/or systemic infection. Histiocytosis (see Chapter 507) should be excluded in any infant with AD and failure to thrive. Wiskott-Aldrich syndrome (see Chapter 126.2), an X-linked recessive disorder associated with thrombocytopenia, immune defects, and recurrent severe bacterial infections, is characterized by a rash almost indistinguishable from that in AD. One of the hyper-IgE syndromes (see Chapter 126.2) is characterized by markedly elevated serum IgE values, recurrent deep-seated bacterial infections, chronic dermatitis, and refractory dermatophytosis. Many of these patients have disease as a result of autosomal dominant STAT3 mutations. In contrast, some patients with hyper-IgE syndrome present with increased susceptibility to viral infections and an autosomal recessive pattern of disease inheritance. These patients may have a Dock 8 (Dedicator of cytokinesis 8) mutation. This diagnosis should be considered in young children with severe eczema, food allergy, and disseminated skin viral infections.

Adolescents who present with an eczematous dermatitis but no history of childhood eczema, respiratory allergy, or atopic family history may have allergic contact dermatitis (see Chapter 655.1). A contact allergen may be the problem in any patient whose AD does not respond to appropriate therapy. Sensitizing chemicals, such as parabens and lanolin, can be irritants for patients with AD and are commonly found as vehicles in therapeutic topical agents. Topical glucocorticoid contact allergy has been reported in patients with chronic dermatitis on topical corticosteroid therapy. Eczematous dermatitis has also been reported with HIV infection as well as with a variety of infestations such as scabies. Other conditions that can be confused with AD include psoriasis, ichthyoses, and seborrheic dermatitis.
**Table 145-2**  Differential Diagnosis of Atopic Dermatitis

| CONGENITAL DISORDERS                  | Netherton syndrome |
|                                      | Familial keratosis pilaris |
| CHRONIC DERMATOSES                   | Seborrheic dermatitis |
|                                      | Contact dermatitis (allergic or irritant) |
|                                      | Nummular eczema |
| Psoriasis                           | Ichthyoses |
| INFECTIONS AND INFESTATIONS         | Scabies |
|                                      | HIV-associated dermatitis |
|                                      | Dermatophytosis |
|                                      | Insect bites |
|                                      | Onchocerciasis |
| MALIGNANCIES                         | Cutaneous T-cell lymphoma (mycosis fungoides/Sézary syndrome) |
|                                      | Letterer-Siwe disease (Langerhans cell histiocytosis) |
| AUTOIMMUNE DISORDERS                 | Dermatitis herpetiformis |
|                                      | Pemphigus foliaceus |
|                                      | Graft-versus-host disease |
|                                      | Dermatomyositis |
| IMMUNODEFICIENCIES                   | Wiskott-Aldrich syndrome |
|                                      | Severe combined immunodeficiency syndrome |
|                                      | Hyperimmunoglobulin E syndromes (autosomal dominant and recessive types) |
|                                      | Immunodysregulation polyendocrinopathy enteropathy X-linked (IPEX) syndrome |
| METABOLIC DISORDERS                  | Zinc deficiency |
|                                      | Pyridoxine (vitamin B6) and niacin |
|                                      | Multiple carboxylase deficiency |
|                                      | Phenylketonuria |


**Table 145-3**  List of Aggravating Factors and Counselling for AD Patients

| Clothing: avoid skin contact with irritating fibers (wool, large-fiber textiles); do not use tight and too warm clothing to avoid excessive sweating. New nonirritating clothing designed for AD children is being evaluated |
| Tobacco: avoid exposure |
| Cool temperature in bedroom and avoid too many bed covers |
| Increase emollient use with cold weather |
| Avoid exposure to herpes sores; urgent visit if flare of unusual aspect |
| Vaccines: normal schedule in noninvolved skin, including egg-allergic patients (see text) |
| Sun exposure: no specific restriction. Usually helpful because of improvement of epidermal barrier. Encourage summer holidays in altitude or at beach resorts |
| Physical exercise, sports: no restriction. If sweating induces flares of AD, progressive adaptation to exercise. Shower and emollients after swimming pool |
| Food allergies: Maintain breast feeding until 4 mo if possible |
| Otherwise normal diet, unless an allergy work-up has proven the need to exclude a specific food |
| Indoor aeroallergens: House dust mites |
| Use adequate ventilation of housing; keep the rooms well aerated even in winter |
| Avoid wall-to-wall carpeting |
| Remove dust with a wet sponge |
| Vacuum floors and upholstery with an adequately filtered cleaner once a week |
| Avoid soft toys in bed (cradle), except washable ones |
| Wash bed sheets at a temperature higher than 55° every 10 days |
| Use bed and pillow encasings made of Gore-Tex or similar material |
| 15-20 and may induce the development of folliculitis. In these cases, less occlusive agents should be used. Several prescription (classified as a medical device) “therapeutic moisturizers/barrier creams” are available, containing components such as ceramides and filaggrin acid metabolites intended to improve skin barrier function. There are little data demonstrating their efficacy over standard emollients. |

**TREATMENT**

The treatment of AD requires a systematic, multifaceted approach that incorporates skin hydration, topical anti-inflammatory therapy, identification and elimination of flare factors (Table 145-3), and, if necessary, systemic therapy. Assessment of the severity also helps direct therapy (Table 145-4).

**Cutaneous Hydration**

Because patients with AD have impaired skin barrier function from reduced lipid levels, they present with diffuse, abnormally dry skin, or xerosis. **Moisturizers are first-line therapy.** Lukewarm soaking baths for 15-20 min followed by the application of an occlusive emollient to retain moisture provide symptomatic relief. Hydrophilic ointments of varying degrees of viscosity can be used according to the patient’s preference. Occlusive ointments are sometimes not well tolerated because of interference with the function of the eccrine sweat ducts and may induce the development of folliculitis. In these cases, less occlusive agents should be used. Several prescription (classified as a medical device) “therapeutic moisturizers/barrier creams” are available, containing components such as ceramides and filaggrin acid metabolites intended to improve skin barrier function. There are little data demonstrating their efficacy over standard emollients.

Hydration by baths or wet dressings promotes transepidermal penetration of topical glucocorticoids. Dressings may also serve as effective barriers against persistent scratching, in turn promoting healing of excoriated lesions. Wet dressings are recommended for use on severely affected or chronically involved areas of dermatitis refractory to skin care. It is critical that wet dressing therapy be followed by topical emollient application to avoid potential drying and fissuring from the therapy. Wet dressing therapy can be complicated by maceration and secondary infection and should be closely monitored by a physician.

**Topical Corticosteroids**

**Topical corticosteroids are the cornerstone of antiinflammatory treatment for acute exacerbations of AD.** Patients should be carefully instructed on their use of topical glucocorticoids in order to avoid potential adverse effects. There are 7 classes of topical glucocorticoids, ranked according to their potency as determined by vasoconstrictor assays (Table 145-5). Because of their potential adverse effects, the
Topical Calcineurin Inhibitors
The nonsteroidal topical calcineurin inhibitors are effective in reducing AD skin inflammation. Pimecrolimus cream 1% (Elidel) is indicated for mild to moderate AD. Tacrolimus ointment 0.1% and 0.03% (Protopic) is indicated for moderate to severe AD. Both are approved for short-term or intermittent long-term treatment of AD in patients ≥2 yr whose disease is unresponsive to or who are intolerant of other conventional therapies or for whom these therapies are inadvisable owing to potential risks. Topical calcineurin inhibitors may be better than topical corticosteroids in the treatment of patients whose AD is poorly responsive to topical steroids, of patients with steroid phobia, and of patients with face and neck dermatitis, in which ineffective, low-potency topical corticosteroids are usually used because of fears of steroid-induced skin atrophy.

Tar Preparations
Coal tar preparations have antipruritic and antiinflammatory effects on the skin; however, the antiinflammatory effects are usually not as pronounced as those of topical glucocorticoids or calcineurin inhibitors. Tar preparations are useful in reducing the potency of topical glucocorticoids required in long-term maintenance therapy of AD. Tar shampoos can be particularly beneficial for scalp dermatitis. Adverse effects associated with tar preparations include skin irritation, folliculitis, and photosensitivity.

Antihistamines
Systemic antihistamines act primarily by blocking the histamine H1 receptors in the dermis, thereby reducing histamine-induced pruritus. Histamine is only one of many mediators that induce pruritus of the skin, so patients may derive minimal benefit from antihistaminic therapy. Because pruritus is usually worse at night, sedating antihistamines (hydroxyzine, diphenhydramine) may offer an advantage with their soporific side effects when used at bedtime. Doxepin hydrochloride has both tricyclic antidepressant and H1- and H2-receptor blocking effects. Short-term use of a sedative to allow adequate rest may be appropriate in cases of severe nocturnal pruritus. Studies of newer nonsedating antihistamines have shown variable effectiveness in controlling pruritus in AD, although they may be useful in the small subset of patients with AD and concomitant urticaria.

Systemic Corticosteroids
Systemic corticosteroids are rarely indicated in the treatment of chronic AD. The dramatic clinical improvement that may occur with systemic corticosteroids is frequently associated with a severe rebound flare of AD after therapy discontinuation. Short courses of oral corticosteroids may be appropriate for an acute exacerbation of AD while other treatment measures are being instituted in parallel. If a short course of oral corticosteroids is given, it is important to taper the dosage and begin intensified skin care, particularly with topical corticosteroids and frequent bathing followed by application of emollients, to prevent rebound flaring of AD.

Cyclosporine
Cyclosporine is a potent immunosuppressive drug that acts primarily on T cells by suppressing cytokine gene transcription. Cyclosporine forms a complex with an intracellular protein, cyclophilin, and this complex, in turn, inhibits calcineurin, a phosphatase required for...
activation of NFAT (nuclear factor of activated T cells), a transcription factor necessary for cytokine gene transcription. Ciclosporine (5 mg/kg/day) for short-term and long-term (1 yr) use has been beneficial for children with severe, refractory AD. Possible adverse effects include renal impairment and hypertension.

**Antimetabolites**

Mycophenolate mofetil is a purine biosynthesis inhibitor used as an immunosuppressant in organ transplantation that has been used for treatment of refractory AD. Aside from immunosuppression, herpes simplex reinitis and dose-related bone marrow suppression have been reported with its use. Of note, not all patients benefit from treatment. Therefore, the medication should be discontinued if the disease does not respond within 4-8 wk. Methotrexate is an antimetabolite with potent inhibitory effects on inflammatory cytokine synthesis and cell chemotaxis. Methotrexate has been used for patients with recalcitrant AD. In AD, dosing is more frequent than the weekly dosing used for psoriasis. Azathioprine is a purine analog with antiinflammatory and antiproliferative effects that has been used for severe AD. Myelosuppression is a significant adverse effect, and thiopurine methyl transferase levels may identify individuals at risk for it. Before any of these drugs is used, patients should be referred to an AD specialist who is familiar with treatment of severe AD to weigh relative benefits of alternative therapies.

**Phototherapy**

Natural sunlight is often beneficial to patients with AD as long as sunburn and excessive sweating are avoided. Many phototherapy modalities are effective for AD, including ultraviolet A-1, ultraviolet B, narrow-band ultraviolet B, and psoralen plus ultraviolet A. Phototherapy is generally reserved for patients in whom standard treatments fail. Maintenance treatments are usually required for phototherapy to be effective. Short-term adverse effects with phototherapy include erythema, skin pain, pruritus, and pigmentation. Long-term adverse effects include predisposition to cutaneous malignancies.

**Unproven Therapies**

Other therapies that may be considered in patients with refractory AD are as follows.

**Interferon-γ**

IFN-γ is known to suppress Th2-cell function. Several studies, including a multicenter, double-blind, placebo-controlled trial and several open trials, have demonstrated that treatment with recombinant human IFN-γ results in clinical improvement of AD. Reduction in clinical severity of AD correlated with the ability of IFN-γ to decrease total circulating eosinophil counts. Influenza-like symptoms are commonly observed side effects during the treatment course.

**Omalizumab**

Treatment of patients who have severe AD and elevated serum IgE values with monoclonal anti-IgE may be considered in those with allergen-induced flares of AD. However, there have been no published double-blind, placebo-controlled trials of its use. Most reports have been case studies and show inconsistent responses to anti-IgE.

**Allergen Immunotherapy**

In contrast to its acceptance for treatment of allergic rhinitis and extrinsic asthma, immunotherapy with Aeroallergens in the treatment of AD is controversial. There are reports of both disease exacerbation and improvement. Studies suggest specific immunotherapy in patients with AD sensitized to dust mite allergen showed improvement in severity of skin disease, as well as reduction in topical steroid use.

**Probiotics**

Perinatal administration of the probiotic *Lactobacillus rhamnosus* strain GG has been shown to reduce the incidence of AD in at-risk children during the first 2 yr of life. The treatment response has been found to be more pronounced in patients with positive skin prick test results and elevated IgE values. Other studies have not demonstrated a benefit.

**Chinese Herbal Medications**

Several placebo-controlled clinical trials have suggested that patients with severe AD may benefit from treatment with traditional Chinese herbal therapy. The subjects had significantly reduced skin disease and decreased pruritus. The beneficial response of Chinese herbal therapy is often temporary, and effectiveness may wear off despite continued treatment. The possibility of hepatic toxicity, cardiac side effects, or idiosyncratic reactions remains a concern. The specific ingredients of the herbs also remain to be elucidated, and some preparations have been found to be contaminated with corticosteroids. At present, Chinese herbal therapy for AD is considered investigational.

**Vitamin D**

Vitamin D deficiency often accompanies severe AD. Vitamin D enhances skin barrier function, reduces corticosteroid requirements to control inflammation and augments skin antimicrobial function. Several small clinical studies suggest vitamin D can enhance antimicrobial peptide expression in the skin and reduce severity of skin disease especially in patients with low baseline vitamin D, for example, during the wintertime when exacerbation of AD often occurs. Patients with AD might benefit from supplementation with vitamin D, particularly if they have a documented low level or low vitamin D intake.

**AVOIDING TRIGGERS**

It is essential to identify and eliminate triggering factors, both during the period of acute symptoms and on a long-term basis to prevent recurrences (see Table 145-3).

**Irritants**

Patients with AD have a low threshold response to irritants that trigger their itch-scratch cycle. Soaps or detergents, chemicals, smoke, abrasive clothing, and exposure to extremes of temperature and humidity are common triggers. Patients with AD should use soaps with minimal defatting properties and a neutral pH. New clothing should be laundered before wearing to decrease levels of formaldehyde and other chemicals. Residual laundry detergent in clothing may trigger the itch-scratch cycle; using a liquid rather than powder detergent and adding a second rinse cycle facilitates removal of the detergent.

Every attempt should be made to allow children with AD to be normally active as possible. A sport such as swimming may be better tolerated than others that involve intense perspiration, physical contact, or heavy clothing and equipment. Rinsing off chlorine immediately and lubricating the skin after swimming are important. Although ultraviolet light may be beneficial to some patients with AD, high sun protection factor sunscreens should be used to avoid sunburn.

**Foods**

Food allergy is comorbid in approximately 40% of infants and young children with moderate to severe AD (see Chapter 151). Undiagnosed food allergies in patients with AD may induce eczematous dermatitis in some patients and urticarial reactions, wheezing, or nasal congestion in others. Increased severity of AD symptoms and younger age correlate directly with the presence of food allergy. Removal of food allergens from the diet leads to significant clinical improvement but requires a great deal of education, because most common allergens (egg, milk, peanut, wheat, soy) contaminate many foods and are difficult to avoid.

Potential allergens can be identified by a careful history and performing selective skin prick tests or in vitro blood testing for allergen-specific IgE. Negative skin and blood test results for allergen-specific IgE have a high predictive value for excluding suspected allergens. Positive results of skin or blood tests using foods often do not correlate with clinical symptoms and should be confirmed with controlled food challenges and elimination diets. Extensive elimination diets, which can be nutritionally deficient, are rarely required. Even with multiple
positive skin test results, the majority of patients react to fewer than 3 foods under controlled challenge conditions.

Aeroallergens
In older children, AD flares can occur after intranasal or epicutaneous exposure to aeroallergens such as fungi, animal dander, grass, and ragweed pollen. Avoiding aeroallergens, particularly dust mites, can result in clinical improvement of AD. Avoidance measures for dust mite–allergic patients include using dust mite–proof encasings on pillows, mattresses, and box springs; washing bedding in hot water weekly; removing bedroom carpeting; and decreasing indoor humidity levels with air conditioning.

Infections
Patients with AD have increased susceptibility to bacterial, viral, and fungal skin infections. Antistaphylococcal antibiotics are very helpful for treating patients who are heavily colonized or infected with *Staphylococcus aureus*. Erythromycin and azithromycin are usually beneficial for patients who are not colonized with a resistant *S. aureus* strain; a first-generation cephalosporin (cephalexin) is recommended for macrolide-resistant *S. aureus*. Topical mupirocin is useful in the treatment of localized impetiginous lesions, with systemic antibiotics for widespread infections. Cytokine-mediated skin inflammation contributes to skin colonization with *S. aureus*; this fact indicates the importance of combining effective anti-inflammatory therapy with antibiotics for treating moderate to severe AD to avoid the need for repeated courses of antibiotics, which can lead to the emergence of antibiotic-resistant strains of *S. aureus*. Dilute bleach baths (1/2 cup of bleach in 40 gallons of water) twice weekly may be also considered to reduce *S. aureus* colonization. In one randomized trial the group who received the bleach baths plus intranasal mupirocin (5 days/mo) had significantly decreased severity of AD at 1 and 3 mo compared with placebo. Patients rinse off after the soaking. Further studies are needed to validate this technique.

Herpes simplex virus (HSV) can provoke recurrent dermatitis and may be misdiagnosed as *S. aureus* infection. The presence of punched-out erosions, vesicles, and infected skin lesions that fail to respond to oral antibiotics suggests HSV infection, which can be diagnosed by a Giemsa-stained Tzanck smear of cells scraped from the vesicle base or by viral polymerase chain reaction or culture. Topical corticosteroids should be temporarily discontinued if HSV infection is suspected. Reports of life-threatening dissemination of HSV infections in patients with AD who have widespread disease mandate antiviral treatment. Persons with AD are also susceptible to eczema vaccinatum, which is similar in appearance to eczema herpeticum and historically follows smallpox (vaccinia virus) vaccination. Cutaneous warts and molluscum contagiosum are additional viral infections affecting children with AD. Dermatophyte infections also can contribute to exacerbation of AD. Patients with AD have been found to have a greater susceptibility to *Trichophyton rubrum* fungal infections than nonatopic control subjects. There has been particular interest in the role of *Malassezia furfur* (formerly known as *Pityrosporum ovale*) in AD because it is a lipophilic yeast commonly present in the seborrheic areas of the skin. IgE antibodies against *M. furfur* have been found in patients with head and neck dermatitis. A reduction of AD severity has been observed in those patients after treatment with antifungal agents.

COMPLICATIONS
Exfoliative dermatitis may develop in patients with extensive skin involvement. It is associated with generalized redness, scaling, weeping, crusting, systemic toxicity, lymphadenopathy, and fever, and is usually caused by superinfection (e.g., with toxin-producing *S. aureus* or HSV infection) or inappropriate therapy. In some cases, the withdrawal of systemic glucocorticoids used to control severe AD precipitates exfoliative erythroderma. Eyelid dermatitis and chronic blepharitis may result in visual impairment from corneal scarring. *Atopic keratoconjunctivitis* is usually bilateral and can have disabling symptoms that include itching, burning, tearing, and copious mucoid discharge. Vernal conjunctivitis is associated with papillary hypertrophy or cobblestoning of the upper eyelid conjunctiva. It typically occurs in younger patients and has a marked seasonal incidence with spring exacerbations. Keratoconus is a conical deformity of the cornea believed to result from chronic rubbing of the eyes in patients with AD. Cataracts may be a primary manifestation of AD or from extensive use of systemic and topical glucocorticoids, particularly around the eyes.

PROGNOSIS
AD generally tends to be more severe and persistent in young children, particularly if they have null mutations in their filaggrin genes. Periods of remission occur more frequently as patients grow older. Spontaneous resolution of AD has been reported to occur after age 5 yr in 40-60% of patients affected during infancy, particularly for mild disease. Earlier studies suggested that approximately 84% of children outgrow their AD by adolescence; however, later studies reported that AD resolves in approximately 20% of children monitored from infancy until adolescence and becomes less severe in 65%. Of those adolescents treated for mild dermatitis, >50% may experience a relapse of disease as adults, which frequently manifests as hand dermatitis, especially if daily activities require repeated hand wetting. Predictive factors of a poor prognosis for AD include widespread AD in childhood, filaggrin gene null mutations, concomitant allergic rhinitis and asthma, family history of AD in parents or siblings, early age at onset of AD, being an only child, and very high serum IgE levels.

PREVENTION
Breastfeeding or a feeding with a hypoallergenic hydrolyzed formula may be beneficial. Probiotics and prebiotics may also reduce the incidence or severity of AD, but this approach is unproven. If an infant with AD is diagnosed with food allergy, the breast feeding mother may need to eliminate the implicated food allergen from her diet. Identification and elimination of triggering factors is the mainstay for prevention of flares as well as for the long-term treatment of AD.

Emollient therapy applied to the whole body for the first few months of life may enhance the cutaneous barrier and reduce the risk of eczema.

Bibliography is available at Expert Consult.


Allergic responses to stinging or, more rarely, biting insects vary from localized cutaneous reactions to systemic anaphylaxis. Allergic reactions that are caused by inhalation of airborne particles of insect origin result in acute and chronic respiratory symptoms of seasonal or perennial rhinitis, conjunctivitis, and/or asthma.

ETIOLOGY
Most reactions to stinging and biting insects, such as those induced by wasps, mosquitoes, flies, and fleas, are limited to a primary lesion isolated to the area of the sting or bite and do not represent an allergic response. Occasionally, insect stings or bites induce pronounced localized reactions or systemic reactions that may be based on immediate or delayed hypersensitivity reactions. Systemic allergic responses to insects are attributed most typically to immunoglobulin (Ig) E antibody–mediated responses, which are caused primarily by stings from venomous insects of the order Hymenoptera and more rarely from ticks, spiders, scorpions, and Triatoma (kissing bug). Members of the order Hymenoptera include apids (honeybee, bumblebee), vespids
IgE antibody–mediated allergic responses to airborne particulate matter carrying insect emanations contribute to seasonal and perennial symptoms affecting the upper and lower airways. Seasonal allergy is attributed to exposures to a variety of insects, particularly aquatic insects such as the caddis fly and midge, or lake fly, at a time when larvae pupate and adult flies are airborne. Perennial allergy is attributed to sensitization to insects such as cockroaches and ladybugs, as well as house dust mite, which is phylogenetically related to spiders rather than insects and has 8 rather than 6 legs.

**PATHOGENESIS**

Hymenoptera venoms contain numerous components with toxic and pharmacologic activity and with allergenic potential. These constituents include vasoactive substances such as histamine, acetylcholine, and kinins; enzymes such as phospholipase and hyaluronidase; apamin; melittin; and formic acid. The majority of patients who experience systemic reactions after Hymenoptera stings have IgE-mediated sensitivity to antigenic substances in the venom. Some venom allergens are homologous among members of the Hymenoptera order; others are family specific. There is substantial cross-reactivity among vespid venoms, but these venom allergens are distinct from honeybee venom allergens.

Localized skin reactions to biting insects are caused primarily by vasoactive or irritant materials derived from insect saliva, and rarely occur from IgE-associated responses. Systemic IgE-mediated allergic reactions to salivary proteins of biting insects such as mosquitoes are reported but uncommon.

A variety of proteins derived from insects can become airborne and induce IgE-mediated respiratory responses, causing inhalant allergies. The primary allergen from the caddis fly is a hemocyanin-like protein, and that from the midge fly is derived from hemoglobin. Allergens from the cockroach are the best studied and are derived from cockroach saliva, secretions, fecal material, and debris from skin casts.

**CLINICAL MANIFESTATIONS**

Clinical reactions to stinging venomous insects are categorized as local, large local, generalized cutaneous, systemic, toxic, and delayed/late. Simple local reactions involve limited swelling and pain, and generally last <24 hr. Large local reactions develop over hours and days, involve swelling of extensive areas (>10 cm) that are contiguous with the sting site, and may last for days. Generalized cutaneous reactions typically progress within minutes and include cutaneous symptoms of urticaria, angioedema, and pruritus beyond the site of the sting. Systemic reactions are identical to anaphylaxis from other triggers and may include symptoms of generalized urticaria, laryngeal edema, bronchospasm, and hypotension. Stings from a large number of insects at once may result in toxic reactions of fever, malaise, emesis, and nausea owing to the chemical properties of the venom in large doses. Serum sickness, nephrotic syndrome, vasculitis, neuritis, or encephalopathy may occur as delayed/late reactions to stinging insects.

Insect bites are usually urticarial but may be papular or vesicular. Papular urticaria affecting the lower extremities in children is usually caused by multiple bites. Occasionally, individuals have large local reactions. IgE antibody–associated immediate- and late-phase allergic responses to mosquito bites sometimes mimic cellulitis.

Inhalant allergy caused by insects results in clinical disease similar to that induced by other inhalant allergens such as pollens. Depending on individual sensitivity and exposure, reactions may result in seasonal or perennial rhinitis, conjunctivitis, and/or asthma.

**DIAGNOSIS**

The diagnosis of allergy from stinging and biting insects is generally evident from the history of exposure, typical symptoms, and physical findings. The diagnosis of Hymenoptera allergy rests in part on the identification of venom-specific IgE by prick skin testing or in vitro testing. The primary reasons to pursue testing are to confirm reactivity when venom immunotherapy (VIT) is being considered or when it is clinically necessary to confirm venom hypersensitivity as a cause of a reaction. Venoms of 5 Hymenoptera (honeybee, yellow jacket, yellow
Venom Immunotherapy

Hymenoptera VIT is highly effective (95-97%) in decreasing the risk for severe anaphylaxis. The selection of patients for VIT depends on several factors (Table 146-1). Individuals with local reactions regardless of age are not at increased risk for severe systemic reactions on a subsequent sting and are not candidates for VIT. The risk of a systemic reaction for those who experienced a large local reaction is no more than 5-10%; testing or VIT is usually not recommended, and prescription of self-injectable epinephrine is considered optional but usually not necessary. There is growing evidence that VIT can reduce the size and duration of large, local reactions, and therefore VIT may be considered for those with frequent or unavoidable large, local reactions. Those who experience severe systemic reactions, such as airway involvement or hypotension, and have specific IgE to venom allergens should receive immunotherapy. Immunotherapy against winged Hymenoptera is not usually indicated for children ≤16 yr of age in whom stings have caused only generalized urticaria or angioedema, because their risk for a systemic reaction after a subsequent sting is approximately 10%. If a systemic reaction occurs, it is likely to be isolated skin reactions, with <5% risk of a more severe reaction and <1% risk of life-threatening anaphylaxis. The risk could be reduced to 1% after treatment with VIT, so it is an option to consider if multiple future stings are anticipated. Immunotherapy against Hymenoptera is indicated in those ≥17 yr of age who have specific IgE to venom allergens and a history of generalized urticaria or a systemic reaction, because their risk for future systemic reactions is 30-60%. VIT is usually not indicated if there is no evidence of IgE to venom.

The incidence of adverse effects in the course of treatment is not trivial in adults, as 50% experience large local reactions and about 10% experience systemic reactions. The incidence of both local and systemic reactions is much lower in children. Patients treated with honeybee venom are at higher risk for systemic reactions to VIT than those receiving treatment with vespid venom. Individuals with mast cell disorders are at increased risk for severe anaphylaxis and more frequent systemic reactions with VIT.

It is uncertain how long immunotherapy with Hymenoptera venom should continue. In general, a 3-5 year treatment duration is recommended because >80% of adults who have received 5 yr of therapy tolerate challenge stings without systemic reactions for 5-10 yr after completion of treatment. Long-term responses to treatment are even better for children. Follow-up over a mean of 18 yr of children with moderate to severe insect sting reactions who received VIT for a mean treatment period of 3-5 yr and were stung again showed a reaction rate of only 5%; untreated children experienced a reaction rate of 32%. Whereas duration of therapy with VIT may be individualized, it is clear that a significant number of untreated children retain their allergy. Lifelong treatment may be considered for those who have had severe life-threatening anaphylaxis with insect stings, those with honeybee allergy, and those with occupational exposures to Hymenoptera. Life-long VIT should also be considered for those with mast cell disorders as these individuals have a higher rate of failure of VIT and relapse when VIT is discontinued.

Less is known about the natural history of fire ant hypersensitivity and efficacy of immunotherapy for this allergy. The criteria for starting immunotherapy are similar to those for hypersensitivities to other Hymenoptera, but there is stronger consideration to treat children ≤16 yr of age with VIT if they have experienced only generalized

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**Table 146-1** Indications for Venom Immunotherapy Against Winged Hymenoptera

<table>
<thead>
<tr>
<th>SYMPTOMS</th>
<th>AGE</th>
<th>SKIN TEST/IN VITRO TEST</th>
<th>RISK OF SYSTEMIC REACTION IF UNTREATED*</th>
<th>VIT RECOMMENDED</th>
</tr>
</thead>
<tbody>
<tr>
<td>Large local reaction</td>
<td>Any</td>
<td>Usually not indicated</td>
<td>5-10%</td>
<td>Usually not indicated</td>
</tr>
<tr>
<td>Generalized cutaneous</td>
<td>≤16 yr</td>
<td>Usually not indicated</td>
<td>10%</td>
<td>Usually not indicated</td>
</tr>
<tr>
<td>reaction</td>
<td>≥17 yr</td>
<td>Positive result</td>
<td>20%</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Negative result</td>
<td>—</td>
<td>No</td>
</tr>
<tr>
<td>Systemic reaction</td>
<td>Any</td>
<td>Positive result</td>
<td>Child: 40%</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Negative result</td>
<td>Adult: 30-60%</td>
<td>Usually no</td>
</tr>
</tbody>
</table>

*Risks generally decrease after 10 yr.
urticaria. Only whole-body fire ant extract is commercially available for diagnostic skin testing and immunotherapy.

**Inhalant Allergy**
The symptoms of inhalant allergy caused by insects are managed as for other causes of seasonal or perennial rhinitis (see Chapter 143), conjunctivitis (see Chapter 147), and asthma (see Chapter 144).

**PREVENTION**
Avoidance of stings and bites is essential. To reduce the risk of stings, sensitized individuals should avoid attractants such as perfumes and bright-colored clothing outdoors, wear gloves when gardening, and wear long pants and shoes with socks when walking in the grass or through fields. Typical insect repellents do not guard against Hymenoptera. Nests of these insects should be removed if they are close to the home.

*Individuals who have had generalized cutaneous or systemic reactions to Hymenoptera stings should have immediate access to self-injectable epinephrine.* Adults responsible for allergic children, and older patients who can self-treat, must be carefully taught the indications for and technique of administration of this medication. Particular attention is necessary for children in out-of-home daycare centers, at school, or attending camps, to ensure that an emergency action plan is in place. The individual at risk for anaphylaxis from an insect sting should also wear an identification bracelet indicating the allergy.

Avoidance of the insect is the preferred management of inhalant allergy. This can prove difficult, particularly, for instance, for those living in multiple-dwelling apartments, where eradication of cockroaches is problematic. Immunotherapy for dust mites is effective and should be considered in conjunction with avoidance measures. In contrast, there is limited data regarding the efficacy of cockroach immunotherapy.

*Bibliography is available at Expert Consult.*
Bibliography
The eye is a common target of allergic disorders because of its marked vascularity and direct contact with allergens in the environment. The conjunctiva is the most immunologically active tissue of the external eye. Ocular allergies can occur as isolated target organ disease or more commonly in conjunction with nasal allergies. Ocular symptoms can significantly affect quality of life.

**CLINICAL MANIFESTATIONS**

There are a few distinct entities that constitute allergic eye disease, all of which have bilateral involvement. Sensitization is necessary for all of these except for giant papillary conjunctivitis. Vernal keratoconjunctivitis and atopic keratoconjunctivitis are potentially sight-threatening.

**Allergic Conjunctivitis**

Allergic conjunctivitis is the most common hypersensitivity response of the eye, affecting approximately 25% of the general population and 30% of children with atopy. It is caused by direct exposure of the mucosal surfaces of the eye to environmental allergens. Patients complain of variable ocular itching, rather than pain, with increased tearing. Clinical signs include bilateral injected conjunctivae with vascular congestion that may progress to chemosis, or conjunctival swelling, and a watery discharge (Fig. 147-1). Allergic conjunctivitis occurs in a seasonal or, less commonly, perennial form. **Seasonal allergic conjunctivitis** is typically associated with allergic rhinitis (see Chapter 143) and is most commonly triggered by pollens. Major pollen groups in the temperate zones include trees (late winter to early spring), grasses (late spring to early summer), and weeds (late summer to early fall), but seasons can vary significantly in different parts of the country. Mold spores can also cause seasonal allergy symptoms, principally in the summer and fall. Seasonal allergy symptoms may be aggravated by coincident exposure to perennial allergens. **Perennial allergic conjunctivitis** is triggered by allergens such as animal danders or dust mites that are present throughout the year. Symptoms are usually less severe than with seasonal allergic conjunctivitis. Because pollens and soil molds may be present intermittently by season, and exposure to allergens such as furred animals may be perennial, classification as intermittent (symptoms present <4 days/wk or for <4 wk) and persistent (symptoms present >4 days/wk and for >4 wk) has been proposed.

**Vernal Keratoconjunctivitis**

Vernal keratoconjunctivitis is a severe bilateral chronic inflammatory process of the upper tarsal conjunctival surface that occurs in a limbal or palpebral form. It may threaten eyesight if there is corneal involvement. Although vernal keratoconjunctivitis is not immunoglobulin E mediated, it occurs most frequently in children with seasonal allergies, asthma, or atopic dermatitis. Vernal keratoconjunctivitis affects boys twice as often as girls and is more common in persons of Asian and African descent. It affects primarily children in temperate areas, with exacerbations in the spring and summer. Symptoms include severe ocular itching exacerbated by exposure to irritants, light, or perspiration. In addition, patients may complain of severe photophobia, foreign-body sensation, and lacrimation. Giant papillae occur predominantly on the upper tarsal plate and are typically described as *cobblestoning* (Fig. 147-2). Other signs include a stringy or thick, roped discharge, cobblestone papillae, transient yellow-white points in the limbus (Trantas dots) and conjunctiva (Horner points), corneal “shield” ulcers, and Dennie lines (Dennie-Morgan folds), which are prominent symmetric skin folds that extend in an arc from the inner canthus beneath and parallel to the lower lid margin. Children with vernal keratoconjunctivitis have measurably longer eyelashes, which may represent a reaction to ocular inflammation.

**Atopic Keratoconjunctivitis**

Atopic keratoconjunctivitis is a chronic inflammatory ocular disorder most commonly involving the lower tarsal conjunctiva. It may threaten eyesight if there is corneal involvement. Almost all patients have atopic dermatitis, and a significant number have asthma. Atopic
Giant Papillary Conjunctivitis

Giant papillary conjunctivitis has been linked to chronic exposure to foreign bodies, such as contact lenses, both hard and soft, ocular prosthesis, and sutures. Symptoms and signs include mild bilateral ocular itching, tearing, a foreign-body sensation, and excessive ocular discomfort with mild mucoid discharge with white or clear exudate on awakening, which may become thick and stringy. Trantas dots, limbal infiltration, bulbar conjunctival hyperemia, and edema may develop.

Contact Allergy

Contact allergy typically involves the eyelids but can also involve the conjunctivae. It is being recognized more frequently in association with increased exposure to topical medications, contact lens solutions, and preservatives.

DIAGNOSIS

Nonallergic conjunctivitis can be viral, bacterial, or chlamydial in origin. It is typically unilateral but can be bilateral with symptoms initially developing in 1 eye (see Chapter 626). Symptoms include stinging or burning rather than itching and often a foreign-body sensation. Ocular discharge can be watery, mucoid, or purulent. Masqueraders of ocular allergy also include nasolacrimal duct obstruction, foreign body, blepharconjunctivitis, dry eye, uveitis, and trauma.

TREATMENT

Primary treatment of ocular allergies includes avoidance of allergens, cold compresses, and lubrication. Secondary treatment regimens include the use of oral or topical antihistamines and, if necessary, topical decongestants, mast cell stabilizers, and antiinflammatory agents (Table 147-1). Drugs with dual antihistamine and mast cell blocking activities provide the most advantageous approach in treating allergic conjunctivitis, with both fast-acting symptomatic relief and long-term anti-inflammatory effects.

Table 147-1  Topical Ophthalmic Medications for Allergic Conjunctivitis

<table>
<thead>
<tr>
<th>DRUG AND TRADE NAMES</th>
<th>MECHANISM OF ACTION AND DOSING</th>
<th>CAUTIONS AND ADVERSE EVENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azelastine hydrochloride 0.05% Optivar</td>
<td>Antihistamine Children ≥3 yr: 1 gtt bid</td>
<td>Not for treatment of contact lens–related irritation; the preservative may be absorbed by soft contact lenses. Wait at least 10 min after administration before inserting soft contact lenses.</td>
</tr>
<tr>
<td>Emedastine difumarate 0.05% Emadine</td>
<td>Antihistamine Children ≥3 yr: 1 gtt qid</td>
<td>Soft contact lenses should not be worn if the eye is red. Wait at least 10 min after administration before inserting soft contact lenses.</td>
</tr>
<tr>
<td>Levocabastine hydrochloride 0.05% Livostin</td>
<td>Antihistamine Children ≥12 yr: 1 gtt bid-qid up to 2 wk</td>
<td>Not for use in patients wearing soft contact lenses during treatment.</td>
</tr>
<tr>
<td>Pheniramine maleate</td>
<td>Antihistamine/vasoconstrictor</td>
<td>Avoid prolonged use (&gt;3-4 days) to avoid rebound symptoms. Not for use with contact lenses.</td>
</tr>
<tr>
<td>0.3%/Naphazoline hydrochloride 0.025% Naphcon-A, Opcon-A</td>
<td>Children ≥6 yr: 1-2 gtt qid</td>
<td></td>
</tr>
<tr>
<td>Cromolyn sodium 4% Crolom, Opticrom</td>
<td>Mast cell stabilizer Children ≥4 yr 1-2 gtt q4-6h</td>
<td>Can be used to treat giant papillary conjunctivitis and vernal keratitis. Not for use with contact lenses.</td>
</tr>
<tr>
<td>Lodoxamide tromethamine 0.1% Alomide</td>
<td>Mast cell stabilizer Children ≥2 yr: 1-2 gtt qid up to 3 mo</td>
<td>Can be used to treat vernal keratoconjunctivitis. Not for use in patients wearing soft contact lenses during treatment.</td>
</tr>
<tr>
<td>Nedocromil sodium 2% Alocril</td>
<td>Mast cell stabilizer Children ≥3 yr 1-2 gtt bid</td>
<td>Avoid wearing contact lenses while exhibiting the signs and symptoms of allergic conjunctivitis.</td>
</tr>
<tr>
<td>Pemirolast potassium 0.1% Alamast</td>
<td>Mast cell stabilizer Children &gt;3 yr: 1-2 gtt qid</td>
<td>Not for treatment of contact lens–related irritation; the preservative may be absorbed by soft contact lenses. Wait at least 10 min after administration before inserting soft contact lenses.</td>
</tr>
<tr>
<td>Epinastine hydrochloride 0.05% Elestat</td>
<td>Antihistamine/mast cell stabilizer Children ≥3 yr 1 gtt bid</td>
<td>Contact lenses should be removed prior to use. Wait at least 15 min after administration before inserting soft contact lenses. Not for the treatment of contact lens irritation.</td>
</tr>
</tbody>
</table>

Continued
### Topical Ophthalmic Medications for Allergic Conjunctivitis—cont’d

<table>
<thead>
<tr>
<th>DRUG AND TRADE NAMES</th>
<th>MECHANISM OF ACTION AND DOSING</th>
<th>CAUTIONS AND ADVERSE EVENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ketotifen fumarate 0.025% Zaditor</td>
<td>Antihistamine/mast cell stabilizer Children ≥3 yr 1 gtt bid q8-12h</td>
<td>Not for treatment of contact lens–related irritation; the preservative may be absorbed by soft contact lenses. Wait at least 10 min after administration before inserting soft contact lenses.</td>
</tr>
<tr>
<td>Olopatadine hydrochloride 0.1%, 0.2% Patanol Pataday</td>
<td>Antihistamine/mast cell stabilizer Children ≥3 yr: 1 gtt bid (8 hr apart) 1 gtt q day</td>
<td>Not for treatment of contact lens–related irritation; the preservative may be absorbed by soft contact lenses. Wait at least 10 min after administration before inserting soft contact lenses.</td>
</tr>
<tr>
<td>Alcaftadine, 0.25% Lastacaft Bepревe</td>
<td>Antihistamine/mast cell stabilizer Children &gt;2 yr: 1 gtt bid q8-12 hr</td>
<td>Contact lenses should be removed prior to application, may be inserted after 10 minutes. Not for the treatment of contact lens irritation.</td>
</tr>
<tr>
<td>Ketorolac tromethamine 0.5% Acular</td>
<td>NSAID Children ≥3 yr: 1 gtt qid</td>
<td>Avoid with aspirin or NSAID sensitivity. Use ocular product with caution in patients with complicated ocular surgeries, corneal denervation or epithelial defects, ocular surface diseases (e.g., dry eye syndrome), repeated ocular surgeries within a short period of time, diabetes mellitus, or rheumatoid arthritis; these patients may be at risk for corneal adverse events that may be sight-threatening. Do not use while wearing contact lenses.</td>
</tr>
<tr>
<td>Fluorometholone 0.1%, 0.25% suspension (0.1%, 0.25%) and ointment (0.1%) FML, FML Forte, Flarex</td>
<td>Fluorinated corticosteroid Children ≥2 yr, 1 gtt into conjunctival sac of affected eye(s) bid-qid. During initial 24–48 hr, dosage may be increased to 1 gtt q 4 hr. Ointment (approximately 1.3 cm in length) into the conjunctival sac of affected eye(s) 1–3 times daily. May be applied q 4 hr during initial 24–48 hr of therapy</td>
<td>If improvement does not occur after 2 days, patient should be reevaluated. Patient should remove soft contact lenses prior to administering (contains benzalkonium chloride) and delay reinsertion of lenses for ≥15 minutes after administration. Close monitoring for development of glaucoma and cataracts.</td>
</tr>
</tbody>
</table>

NSAID, nonsteroidal antiinflammatory drug.

Disease-modifying action. Children often complain of stinging or burning with use of topical ophthalmic preparations and usually prefer oral antihistamines for allergic conjunctivitis. It is important not to contaminate topical ocular medications by allowing the applicator tip to contact the eye or eyelid. Using refrigerated medications may decrease some of the discomfort associated with their use. Topical decongestants act as vasoconstrictors, reducing erythema, vascular congestion, and eyelid edema, but do not diminish the allergic response. Adverse effects of topical vasoconstrictors include burning or stinging and rebound hyperemia or conjunctivitis medicamentosa with chronic use. Combined use of an antihistamine and a vasoconstrictive agent is more effective than use of either agent alone. Use of topical nasal corticosteroids for allergic rhinoconjunctivitis decreases ocular symptoms, presumably through a naso-ocular reflex.

Tertiary treatment of ocular allergy includes topical or, rarely, oral corticosteroids and should be conducted in conjunction with an ophthalmologist. Local administration of topical corticosteroids may be associated with increased intraocular pressure, viral infections, and cataract formation. Other immunomodulatory medications, such as topical tacrolimus or topical cyclosporine are used as steroid-sparing agents by ophthalmologists. Allergen immunotherapy can be very effective in seasonal and perennial allergic conjunctivitis, especially when associated with rhinitis, and can decrease the need for oral or topical medications to control allergy symptoms.

Because vernal conjunctivitis and atopic keratoconjunctivitis can be associated with visual morbidity, if these diagnoses are suspected, the patient should be referred to an ophthalmologist.

Bibliography is available at Expert Consult.
**Bibliography**


Chapter 148

Urticaria (Hives) and Angioedema

Amy P. Stallings, Stephen C. Dreskin, Michael M. Frank, and Scott H. Sicherer

Urticaria and angioedema affect 20% of individuals at some point in their lives. Episodes of hives that last for <6 wk are considered acute, whereas those that occur on most days of the week for >6 wks are designated chronic. The distinction is important, because the causes and mechanisms of urticaria formation and the therapeutic approaches are different in each instance.

ETIOLOGY AND PATHOGENESIS

Acute urticaria and angioedema are often caused by an allergic immunoglobulin (Ig) E-mediated reaction (Table 148-1). This form of urticaria is a self-limited process that occurs when an allergen activates mast cells in the skin. Common causes of acute generalized urticaria include foods, drugs (particularly antibiotics), and stinging insect venoms. If an allergen (latex, animal dander) penetrates the skin locally, hives often can develop at the site of exposure. Acute urticaria can also result from non–IgE-mediated stimulation of mast cells,
caused by radiocontrast agents, viral agents (including hepatitis B and Epstein-Barr virus), opiates, and nonsteroidal antiinflammatory agents. The diagnosis of chronic urticaria is established when lesions occur on most days of the week for >6 wk and are not physical urticaria or recurrent acute urticaria with repeated exposures to a specific agent (Table 148-2). In about half the cases, chronic urticaria is accompanied by angioedema. Rarely, angioedema occurs without urticaria. Angioedema without urticaria is often a result of allergy, but recurrent angioedema raises a question about other diagnoses.

A typical hive is an erythematous, pruritic raised wheal that blanches with pressure, is transient, and resolves without residual lesions, unless the area was intensely scratched. In contrast, urticaria associated with serum sickness reactions, systemic lupus erythematosus or other vasculitides, in which a skin biopsy reveals a small-vessel vasculitis, often have distinguishing clinical features. Lesions that burn more than itch, last >24 hr, do not blanch, blister, heal with scarring, or are associated with bleeding into the skin (purpura) suggest urticarial vasculitis. Atypical aspects of the gross appearance of the hives or associated symptoms should heighten concern that the urticaria or angioedema may be the manifestation of a systemic disease process.

**PHYSICAL URTICARIA**

Physically induced urticaria and angioedema share the common property of being induced by an environmental stimulus, such as a change in temperature or direct stimulation of the skin with pressure, stroking, vibration, or light (Table 148-3).

**Cold-Dependent Disorders**

Cold urticaria is characterized by the development of localized pruritus, erythema, and urticaria/angioedema after exposure to a cold stimulus. Total-body exposure as seen with swimming in cold water can cause massive release of vasoactive mediators, resulting in hypotension, loss of consciousness and even death if not promptly treated. The diagnosis is confirmed by challenge testing for an isomorphic cold reaction by holding an ice cube in place on the patient’s skin for 4 min. In patients with cold urticaria, an urticarial lesion develops about 10 minutes after removal of the ice cube and upon rewarming of the chilled skin. Cold urticaria can be associated with the presence of cryoproteins, such as cold agglutinins, cryoglobulins, cryofibrinogen, and the Donath-Landsteiner antibody seen in secondary syphilis (paroxysmal cold hemoglobinuria). In patients with cryoglobulins, the isolated proteins appear to transfer cold sensitivity and activate the complement cascade upon in vitro incubation with normal plasma. The term **idiopathic cold urticaria** generally applies to patients without abnormal circulating plasma proteins such as cryoglobulins. Cold urticaria has also been reported after viral infections. Cold urticaria must be distinguished from the familial cold autoinflammatory syndrome (see “Diagnosis,” later).

**Cholinergic Urticaria**

Cholinergic urticaria is characterized by the onset of small punctate pruritic wheals surrounded by a prominent erythematous flare associated with exercise, hot showers, and sweating. Once the patient cools down, the rash usually subsides in 30-60 min. Occasionally, symptoms of more generalized cholinergic stimulation, such as lacrimation, wheezing, salivation, and syncope, are observed. These symptoms are mediated by cholinergic nerve fibers that innervate the musculature via parasympathetic neurons and innervate the sweat glands by cholinergic fibers that travel with the sympathetic nerves. Elevated plasma histamine values parallel the onset of urticaria triggered by changes in body temperature.

**Dermatographism**

The ability to write on skin, termed dermatographism (also called dermographism or urticaria factitia), may occur as an isolated...
Tables 148-3  Diagnostic Testing for Urticaria and Angioedema

<table>
<thead>
<tr>
<th>DIAGNOSIS</th>
<th>DIAGNOSTIC TESTING</th>
</tr>
</thead>
<tbody>
<tr>
<td>Food and drug reactions</td>
<td>Elimination of offending agent, skin testing, and challenge with suspected foods</td>
</tr>
<tr>
<td>Autoimmune urticaria</td>
<td>Autologous serum skin test; antihypothyroid antibodies</td>
</tr>
<tr>
<td>Thyroiditis</td>
<td>Thyroid-stimulating hormone; antihypothyroid antibodies</td>
</tr>
<tr>
<td>Infections</td>
<td>Appropriate cultures or serology</td>
</tr>
<tr>
<td>Collagen vascular diseases and cutaneous vasculitis</td>
<td>Skin biopsy, CH$_{50}$, C1q, C4, C3, factor B, immunofluorescence of tissues, antinuclear antibodies, cryoglobulins</td>
</tr>
<tr>
<td>Malignancy with angioedema</td>
<td>CH$_{50}$, C1q, C4, C1-INH determinations</td>
</tr>
<tr>
<td>Cold urticaria</td>
<td>Ice cube test</td>
</tr>
<tr>
<td>Solar urticaria</td>
<td>Exposure to defined wavelengths of light, red blood cell protoporphyrin, fecal protoporphyrin, and coproporphyrin</td>
</tr>
<tr>
<td>Dermatographism</td>
<td>Stroking with narrow object (e.g., tongue blade, fingernail)</td>
</tr>
<tr>
<td>Pressure urticaria</td>
<td>Application of pressure for defined time and intensity</td>
</tr>
<tr>
<td>Vibratory urticaria</td>
<td>Vibration for 4 min</td>
</tr>
<tr>
<td>Aquagenic urticaria</td>
<td>Challenge with tap water at various temperatures</td>
</tr>
<tr>
<td>Urticaria pigmentosa</td>
<td>Skin biopsy, test for dermographism</td>
</tr>
<tr>
<td>Hereditary angioedema</td>
<td>C4, C2, CH$_{50}$, C1-INH testing by protein and function</td>
</tr>
<tr>
<td>Familial cold urticaria</td>
<td>Challenge by cold exposure, measurement of temperature, white blood cell count, erythrocyte sedimentation rate, and skin biopsy</td>
</tr>
<tr>
<td>C3b inactivator deficiency</td>
<td>C3, factor B, C3b inactivator determinations</td>
</tr>
<tr>
<td>Chronic idiopathic urticaria</td>
<td>Skin biopsy, immunofluorescence (negative result), autologous skin test</td>
</tr>
</tbody>
</table>

Disorder or may accompany chronic urticaria or other physical urticaria, such as cholinergic and cold urticaria. It can be diagnosed by observing the skin after stroking it with a tongue depressor. In patients with dermatographism, a linear response occurs secondary to reflex vasoconstriction, followed by pruritus, erythema, and a linear flare caused by secondary dilation of the vessel and the extravasation of plasma.

**Pressure-Induced Urticaria and Angioedema**

Pressure-induced urticaria differs from most types of urticaria or angioedema in that symptoms typically occur 4-6 hr after pressure has been applied. The disorder is clinically heterogeneous. Some patients may complain of swelling secondary to pressure with normal-appearing skin (no urticaria), so the term angioedema is more appropriate. Other lesions are predominantly urticarial and may or may not be associated with significant swelling. When urticaria is present, an infiltrative skin lesion is seen, characterized by a perivascular mononuclear cell infiltrate and dermal edema similar to that seen in chronic idiopathic urticaria. Symptoms occur at sites of tight clothing; foot swelling is common after walking; and buttock swelling may be prominent after sitting for a few hours. This condition can coexist with chronic idiopathic urticaria or can occur separately. The diagnosis is confirmed by challenge testing in which pressure is applied perpendicular to the skin. This is often done with a sling attached to a 10 lb weight that is placed over the patient's arm for 20 min.

**Solar Urticaria**

Solar urticaria is a rare disorder in which urticaria develops within minutes of direct sun exposure. Typically, pruritus occurs first, in approximately 30 sec, followed by edema confined to the light-exposed area and surrounded by a prominent erythematous zone. The lesions usually disappear within 1-3 hr after cessation of sun exposure. When large areas of the body are exposed, systemic symptoms may occur, including hypotension and wheezing. Solar urticaria has been classified into 6 types, depending on (1) the wavelength of light that induces skin lesions and (2) the ability or inability to transfer the disorder passively with serum IgE. The rare inborn error of metabolism, erythropoietic protoporphyria, can be confused with solar urticaria because of the development of itching and burning of exposed skin immediately after sun exposure. In erythropoietic protoporphyria, fluorescence of ultraviolet-irradiated red blood cells can be demonstrated and protoporphyrins are found in the urine.

**Aquagenic Urticaria**

Patients with aquagenic urticaria demonstrate small wheals after contact with water, regardless of its temperature, and are thereby distinguishable from patients with cold urticaria or cholinergic urticaria. Direct application of a compress of water to the skin is used to test for the presence of aquagenic urticaria. In some of these patients, chlorine or other trace contaminants are responsible for the reaction.

**CHRONIC IDIOPATHIC URTICARIA AND ANGIOEDEMA**

A common disorder of unknown origin, chronic idiopathic urticaria and angioedema is often associated with normal routine laboratory values and no evidence of systemic disease. Chronic urticaria does not appear to result from an allergic reaction. It differs from allergen-induced skin reactions and from physically induced urticaria in that histologic studies reveal a cellular infiltrate predominantly around small venules. Skin examination reveals infiltrative hives with palpably elevated borders, sometimes varying greatly in size and/or shape but generally being rounded.

Biopsy of the typical lesion reveals non-necrotizing, perivascular, mononuclear cellular infiltration. Many types of histopathologic processes can occur in the skin and manifest as urticaria. Patients with hypocomplementemia and cutaneous vasculitis can have urticaria and/or angioedema. Biopsy of these lesions in patients with urticaria, arthralgias, myalgias, and an elevated erythrocyte sedimentation rate (ESR) as manifestations of necrotizing venulitis can reveal fibrinoid necrosis with a predominantly neutrophilic infiltrate. Yet the urticarial lesions may be clinically indistinguishable from those seen in the more typical, nonvasculitic cases.

There is an increased association of chronic urticaria with the presence of antithyroid antibodies. Affected patients generally have antibodies to thyroglobulin or a microsomal-derived antigen (peroxidase) even if they are euthyroid. The incidence of elevated thyroid antibodies in patients with chronic urticaria is ≈12%, compared with 3-6% in the general population. Although some patients show clinical reduction of the urticaria with thyroid replacement therapy, others do not. The role of thyroid autoantibodies in chronic urticaria is uncertain. It has been proposed that their presence may reflect a tendency of the patient to develop autoantibodies, but that they may not play a direct role in chronic urticaria. Of patients with chronic urticaria, 35-40% have a positive autologous serum skin test result: If serum from these patients is intradermally injected into their skin, a significant wheal and flare reaction develops. Such patients frequently have a complement-activating IgG antibody directed against the α subunit of the IgE receptor that can crosslink the IgE receptor (α subunit) and degranulate mast cells and basophils. An additional 5-10% of patients...
with chronic urticaria have anti-IgE antibodies rather than an anti-IgE receptor antibody. These patients, classified as having autoimmune urticaria, tend to have a more severe clinical course than patients without evidence of autoantibodies, but the difference is not dramatic.

**DIAGNOSIS**

The diagnosis of both acute and chronic urticaria is primarily clinical and requires that the physician be aware of the various forms of urticaria.

**Urticaria** is transient, pruritic, erythematous, raised wheals, with flat tops and edema that may become tense and painful. The lesions may coalesce and form polycyclic, serpiginous, or annular lesions (Figs. 148-1 and 148-2). Individual lesions usually last 20 min to 3 hr, and rarely more than 24 hr. The lesions often disappear only to reappear at another site. **Angioedema** involves the deeper subcutaneous tissues in locations such as the eyelids, lips, tongue, genitals, dorsum of the hands or feet, or wall of the gastrointestinal (GI) tract.

Differential diagnosis of urticaria includes cutaneous or systemic mastocytosis, complement-mediated mast cell degranulation as may occur with the presence of circulating immune complexes, malignancies, mixed connective tissue diseases, and cutaneous blisters (e.g., bullous pemphigoid; see Table 148-3). Testing for antibodies directed at the high affinity IgE receptor may be warranted in patients with intractable urticaria. Hereditary angioedema, a potentially life-threatening form of angioedema usually associated with deficient C1 inhibitor activity, is the most important familial form of angioedema (see Chapter 134.3), but is not associated with typical urticaria. In patients with eosinophilia, stools should be obtained for ova and parasite testing, because infection with helminthic parasites has been associated with urticaria. A syndrome of episodic angioedema/urticaria and fever with associated eosinophilia has been described in both adults and children. In contrast to other hypereosinophilic syndromes, this entity has a benign course.

Skin biopsy for diagnosis of possible **urticarial vasculitis** is recommended for urticarial lesions that persist at the same location for >24 hr, those with pigmented or purpuric components, and those that burn more than itch. Collagen vascular diseases such as systemic lupus may manifest urticarial vasculitis as a presenting feature. The skin biopsy in urticarial vasculitis typically shows endothelial cell swelling of postcapillary venules with necrosis of the vessel wall, perivascular neutrophil infiltrate, diapedesis of red blood cells, and fibrin deposition associated with deposition of immune complexes.

**Mastocytosis** is characterized by mast cell hyperplasia in the bone marrow, liver, spleen, lymph nodes, and skin. Clinical effects of mast cell activation are common, including pruritus, flushing, urtication, abdominal pain, nausea, and vomiting. The diagnosis is confirmed by a bone marrow biopsy showing increased numbers of spindle-shaped mast cells that express CD2 and CD25. **Urticaria pigmentosa** is the most common skin manifestation of mastocytosis and may occur as an isolated skin finding. It appears as small, yellow-tan to reddish brown macules or raised papules that urticate on scratching (Darier sign). This sign can be masked by antihistamines. The diagnosis is confirmed by a skin biopsy that shows increased numbers of dermal mast cells.

Physical urticaria should be considered in any patient with chronic urticaria and a suggestive history (see Table 148-3). Papular urticaria commonly occurs in small children, generally on the extremities. It manifests as grouped or linear, highly pruritic wheals or papules mainly on exposed skin at the sites of insect bites.

Exercise-induced anaphylaxis manifests as varying combinations of pruritus, urticaria, angioedema, wheezing, laryngeal obstruction, or hypotension after exercise (see Chapter 149). Cholinergic urticaria is differentiated by positive results of heat challenge tests and the rare occurrence of anaphylactic shock. The combination of ingestion of various food allergens (shrimp, celery, or wheat) and post-prandial exercise has been associated with urticaria/angioedema and
anaphylaxis. In patients with this combination disorder, food or exercise alone does not produce the reaction.

Muckle-Wells syndrome and familial cold autoinflammatory syndrome are rare, dominantly inherited conditions associated with recurrent urticaria-like lesions. Muckle-Wells syndrome is characterized by arthritis and joint pain that usually appears in adolescence. It is associated with progressive nerve deafness, recurrent fever, elevated ESR, hypergammaglobulinemia, renal amyloidosis, and a poor prognosis. Familial cold autoinflammatory syndrome is characterized by a cold-induced rash that has urticarial features but is rarely pruritic. Cold exposure leads to additional symptoms such as conjunctivitis, sweating, headache, and nausea. Patient longevity is usually normal.

**TREATMENT**

Acute urticaria is a self-limited illness requiring little treatment other than antihistamines and avoidance of any identified trigger. Hydroxyzine and diphenhydramine are sedating but are effective and commonly used for treatment of urticaria. Loratadine, fexofenadine, and cetirizine are also effective and are preferable because of reduced frequency of drowsiness and longer duration of action (Table 148-4). Epinephrine 1:1,000, 0.01 mL/kg (maximum: 0.3 mL) intramuscularly usually provides rapid relief of acute, severe urticaria/angioedema but is seldom required. A short course of oral corticosteroids should be given only for very severe episodes of urticaria and angioedema that are unresponsive to antihistamines.

The best treatment of physical urticaria is avoidance of the stimulus. Antihistamines are also helpful. Cyproheptadine in divided doses is the drug of choice for cold-induced urticaria. Treatment of dermatographism consists of local skin care and antihistamines; for severe symptoms, high doses may be needed. The initial objective of therapy is to decrease pruritus so that the stimulation for scratching is diminished. A combination of antihistamines, sunscreens, and avoidance of sunlight is helpful for most patients.

Chronic urticaria only rarely responds favorably to dietary manipulation. Removal of recognized urticarial aggravators such as salicylates and β-blockers should be considered. The mainstay of therapy is the use of nonsedating or low-sedating H1 antihistamines. In those patients not showing response to standard doses, pushing the H1 blockade with higher than the usual recommended doses of these agents is a common next approach. The 3-drug combination of H1 and H2 antihistamine combined with a leukotriene receptor antagonist (montelukast) is helpful for many patients. If hives persist after maximal H1- and/or H2-receptor blockade has been achieved, a brief course of oral corticosteroids may be considered, but long-term steroid use is best avoided. Treatment with cyclosporine 4-6 mg/kg/day has been effective in some adults with chronic urticaria but its use is limited by hypertension and/or nephrotoxicity. Immunomodulatory agents such as omalizumab (anti-IgE antibody) that have been used with success in cases of chronic urticarial that are refractory to other therapies, but are not approved for the treatment of this condition by the FDA. These include omalizumab (anti-IgE), cyclosporine, hydroxychloroquine, sulfasalazine, colchicine, dapsone, mycophenolate, intravenous immunoglobulin, and plasmapheresis.

**HEREDITARY ANGIOEDEMA**

Hereditary angioedema (HAE) (types 1 and 2) is an inherited autosomal dominant disease caused by low functional levels of the plasma protein C1 inhibitor (C1-INH) (see Chapter 134). Patients typically report episodic attacks of angioedema or deep localized swelling, most commonly on a hand or foot, that begin during childhood and become much more severe during adolescence. Cutaneous nonpitting, nonpruritic edema not associated with urticaria is the most common symptom. The swelling usually becomes more severe over about 1.5 days and then resolves over about the same period. In some patients attacks are preceded by the development of a rash, that is erythematous, that is not raised, and not pruritic. The second major symptom complex noted by patients is attacks of severe abdominal pain caused by edema of the mucosa of any portion of the GI tract. The intensity of the pain can approximate that of an acute abdomen, often resulting in unnecessary surgery. Either constipation or diarrhea during these attacks can be noted. The GI edema generally follows the same time course to resolution as the cutaneous attacks, and often does not occur at the same time as the peripheral edema. Patients usually have a prodrome, a tightness or tingling in the area that will swell, lasting most frequently for several hours, followed by the development of angioedema.

Laryngeal edema, the most feared complication of HAE, can cause complete respiratory obstruction. Although life-threatening attacks are infrequent, more than half of patients with HAE experience laryngeal involvement at some time during their lives. Dental work with the injection of procaine HCL (Novocain) into the gums is a common precipitant, but laryngeal edema can be spontaneous. The clinical condition may deteriorate rapidly, progressing through mild discomfort to complete airway obstruction over a period of hours. Soft-tissue edema can be readily seen when the disease involves the throat and uvula. If this edema progresses to difficulty swallowing secretions or a change in the tone of the voice, the patient may require emergency intubation or even tracheostomy to ensure an adequate airway. Other presentations are less common. These patients typically do not respond well to treatment with epinephrine, antihistamines, or glucocorticoids.

In most cases the cause of the attack is unknown, but in some patients trauma or emotional stress clearly precipitates attacks. Drugs like angiotensin-converting enzyme inhibitors that inhibit the degradation of bradykinin make the disease strikingly worse, and estrogens also make attacks more severe. In some females menstruation also regularly induces attacks. The frequency of attacks varies greatly among

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**Table 148-4**

<table>
<thead>
<tr>
<th>CLASS/DRUG</th>
<th>Treatment of Urticaria and Angioedema</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ANTIHISTAMINES, TYPE H1 (SECOND GENERATION)</strong></td>
<td></td>
</tr>
<tr>
<td>Fexofenadine</td>
<td>6-11 yr: 30 mg</td>
</tr>
<tr>
<td>&gt;12 yr: 60 mg</td>
<td>Adult: 180 mg</td>
</tr>
<tr>
<td>Loratadine</td>
<td>2-5 yr: 5 mg</td>
</tr>
<tr>
<td>&gt;6 yr: 10 mg</td>
<td></td>
</tr>
<tr>
<td>Desloratadine</td>
<td>6-11 mo: 1 mg</td>
</tr>
<tr>
<td>12 mo-5 yr: 1.25 mg</td>
<td></td>
</tr>
<tr>
<td>6-11 yr: 2.5 mg</td>
<td></td>
</tr>
<tr>
<td>&gt;12 yr: 5 mg</td>
<td></td>
</tr>
<tr>
<td>Cetirizine</td>
<td>6-23 mo: 2.5 mg</td>
</tr>
<tr>
<td>2-6 yr: 2.5-5mg</td>
<td></td>
</tr>
<tr>
<td>Levocetirizine</td>
<td>&gt;6 yr: 5-10 mg</td>
</tr>
<tr>
<td>6 mo-3 yr: 1.25 mg</td>
<td></td>
</tr>
<tr>
<td>6-11 yr: 2.5 mg</td>
<td></td>
</tr>
<tr>
<td>&gt;12 yr: 5 mg</td>
<td></td>
</tr>
<tr>
<td><strong>ANTIHISTAMINES, TYPE H2</strong></td>
<td></td>
</tr>
<tr>
<td>Cimeditine</td>
<td>Infants: 10-20 mg/kg/day</td>
</tr>
<tr>
<td>Children: 20-40 mg/kg/day</td>
<td></td>
</tr>
<tr>
<td>Ranitidine</td>
<td>1 mo-16 yr: 5-10 mg/kg/day</td>
</tr>
<tr>
<td>Famotidine</td>
<td>3-12 mo: 1 mg/kg/day</td>
</tr>
<tr>
<td>1-16 yr: 1-2 mg/kg/day</td>
<td></td>
</tr>
<tr>
<td><strong>LEUKOTRIENE PATHWAY MODIFIERS</strong></td>
<td></td>
</tr>
<tr>
<td>Montelukast</td>
<td>12 mo-5 yr: 4 mg</td>
</tr>
<tr>
<td>6-14 yr: 5 mg</td>
<td></td>
</tr>
<tr>
<td>&gt;14 yr: 10 mg</td>
<td></td>
</tr>
<tr>
<td>Zafirlukast</td>
<td>5-11 yr: 10 mg</td>
</tr>
<tr>
<td><strong>IMMUNOMODULATORY DRUGS</strong></td>
<td></td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>4-6 mg/kg/day</td>
</tr>
<tr>
<td>Sulfasalazine</td>
<td>&gt;6 yr: 30 mg/kg/day</td>
</tr>
<tr>
<td>Intravenous immunoglobulin (IVIG)</td>
<td>400 mg/kg/day</td>
</tr>
</tbody>
</table>

*Monitor blood pressure and serum creatinine, potassium, and magnesium levels monthly.

*Monitor complete blood count and liver function tests at baseline, every 2 wk for 3 mo, and then every 1-3 mo.
affected individuals and at different times in the same individual. Some individuals experience weekly episodes, whereas others may go years between attacks. Episodes can start at any age.

C1-INH is a member of the serpin family of proteases, similar to α-antitrypsin, antithrombin III, and angiotensinogen. These proteins stoichiometrically inactivate their target proteases by forming stable, 1:1 complexes with the protein to be inhibited. Synthesized primarily by hepatocytes, C1-INH is also synthesized by monocytes. The regulation of the protein production is not completely understood, but it is believed that androgens may stimulate C1-INH synthesis, because patients with the disorder respond clinically to androgen therapy with raised serum levels of C1-INH. C1-INH deficiency is an autosomal dominant disease, with as many as 25% of patients giving no family history. Because all C1-INH–deficient patients are heterozygous for this gene defect, it is believed that half the normal level of C1-INH is not sufficient to prevent attacks.

Although named for its action on the first component of complement (C1 esterase), C1-INH also inhibits components of the fibrinolytic, clotting, and kinin pathways. Specifically, C1-INH inactivates plasmin–activated Hageman factor (factor XII), activated factor XI, plasma thromboplastin antecedent, and kallikrein. Within the complement system, C1-INH blocks the activation of C1 and the rest of the classic complement pathway by binding to C1r and C1s. Without adequate C1-INH, unchecked activation of C1 causes cleavage of C4 and C2, the following proteins in the complement cascade. Levels of C3 are normal. The major factor responsible for the edema formation is now known to be bradykinin, an important nonapeptide mediator that can induce leakage of postcapillary venules. Bradykinin is derived from cleavage of the circulating protein high molecular weight kininogen by the plasma enzyme kallikrein.

Two genetic types of C1-INH deficiency are described that result in essentially the same phenotypic expression. The C1-INH gene is located on chromosome 11 in the p11-q13 region. The inheritance is autosomal dominant with incomplete penetrance. Persons inheriting the abnormal gene can have a clinical spectrum ranging from asymptomatic to severely affected. Type 1 HAE is the most common form, accounting for approximately 85% of cases. Synthesis of C1-INH is blocked at the site of the faulty allele or the protein is not secreted normally because of faulty protein processing, but secretion occurs at the normal allele. The result is secretion of the normal protein, yielding quantitative serum concentrations of C1-INH that are approximately 20-40% of normal. Type 2 HAE accounts for approximately 15% of cases. Mutations of one of the amino acids near the active site of the inhibitor lead to synthesis of nonfunctional C1-INH protein and again less than half of the normal functioning protein. Patients with type 2 HAE have either normal or increased concentrations of the protein and low values in assays of C1-INH function.

A clinical syndrome resembling HAE and termed type 3 HAE has been described that affects mostly women and has a tendency to cause fewer abdominal attacks and more upper airway attacks. In this condition, no abnormalities of complement or of C1-INH have been described. Approximately 20% of affected patients have been found to have a gain-of-function abnormality of clotting factor XII, but the fundamental cause is still unknown.

The FDA has approved purified C1-INH for prophylaxis to prevent attacks. Androgens like the gonadotropin inhibitor danazol were previously used to prevent attacks. Weak androgens have many side affects that preclude their use in some patients. Their use in children is problematic because of the possibility of premature closure of the epiphyses, and these agents are not used in pregnant women. The fibrinolysis inhibitor ε-aminocaproic acid is also effective in preventing attacks and has been used in children, but its use was attended by the development of severe fatigue and muscle weakness over time.

In 2008, the FDA approved, for adolescents and older, the use of purified C1-INH (Cinryze), prepared from human plasma given intravenously for prophylaxis of this disease following clinical trials. The half-life of this plasma protein is relatively short, on the order of 40 hr, and the approved regimen is 1,000 units given twice a week. In 2009, a similar purified C1-inhibitor product, Berinert, used as 20 units/kg intravenously, was approved for the treatment of acute attacks. A recombinant C1-INH product has been approved for treatment of acute attacks in Europe, but is not currently approved for treatment in the United States. In 2009, a kallikrein inhibitor, ecallantide, given subcutaneously, was approved by the FDA for acute treatment in patients age 16 yr and older. This 60 amino acid peptide causes anaphylaxis in the rare patient, and is approved to be given only by medical personnel. In 2010, a bradykinin type 2 receptor antagonist, icatibant was approved for acute treatment in patients age 18 yr and older. All treatments are most effective when given early in an attack, and begin to have noticeable effect after about 1-4 hr after treatment.

Bibliography is available at Expert Consult.
Bibliography


Anaphylaxis is defined as a serious allergic reaction that is rapid in onset and may cause death. Anaphylaxis in children, particularly infants, is underdiagnosed. Anaphylaxis occurs when there is a sudden release of potent biologically active mediators from mast cells and basophils, leading to cutaneous (urticaria, angioedema, flushing), respiratory (bronchospasm, laryngeal edema), cardiovascular (hypotension, dysrhythmias, myocardial ischemia), and gastrointestinal (nausea, colicky abdominal pain, vomiting, diarrhea) symptoms (Table 149-1).

**ETIOLOGY**
The most common causes of anaphylaxis in children are different for hospital and community settings. Anaphylaxis occurring in the hospital results primarily from allergic reactions to medications and latex. Food allergy is the most common cause of anaphylaxis occurring outside the hospital, accounting for about half of the anaphylactic reactions reported in pediatric surveys from the United States, Italy, and South Australia (Table 149-2). Peanut allergy is an important cause of food-induced anaphylaxis, accounting for the majority of fatal and near-fatal reactions. In the hospital, latex is a particular problem for children undergoing multiple operations, such as patients with spina bifida and urologic disorders, and has prompted many hospitals to switch to latex-free products. Patients with latex allergy may also experience food-allergic reactions from homologous proteins in foods such as bananas, kiwi, avocado, chestnut, and passion fruit. Anaphylaxis to galactose-α-1,3-galactose has been reported 3-6 hr after eating meat.

**EPIDEMIOLOGY**
The overall annual incidence of anaphylaxis in the United States is estimated at 50 cases/100,000 persons/yr, totaling >150,000 cases/yr, with the highest rate for the pediatric age group (0-19 yr) at 70/100,000 persons/yr. An Australian parental survey found that 0.59% of children 3-17 yr of age had experienced at least 1 anaphylactic event. Having asthma and the severity of asthma are important anaphylaxis risk factors (Table 149-3).

**PATHOGENESIS**
Principal pathologic features in fatal anaphylaxis include acute bronchial obstruction with pulmonary hyperinflation, pulmonary edema, intraalveolar hemorrhaging, visceral congestion, laryngeal edema, and urticaria and angioedema. Acute hypotension is attributed to vasomotor dilation and/or cardiac dysrhythmias.

Most cases of anaphylaxis are believed to be the result of activation of mast cells and basophils via cell-bound allergen-specific
### Table 149-1  |  Symptoms and Signs of Anaphylaxis in Infants

<table>
<thead>
<tr>
<th>ANAPHYLAXIS SYMPTOMS THAT INFANTS CANNOT DESCRIBE</th>
<th>ANAPHYLAXIS SIGNS THAT MAY BE DIFFICULT TO INTERPRET/UNHELPFUL IN INFANTS, AND WHY</th>
<th>ANAPHYLAXIS SIGNS IN INFANTS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>GENERAL</strong>&lt;br&gt;Feeling of warmth, weakness, anxiety, apprehension, impending doom</td>
<td>Nonspecific behavioral changes such as persistent crying, fussing, irritability, fright, suddenly becoming quiet</td>
<td></td>
</tr>
<tr>
<td><strong>SKIN/MUCUS MEMBRANES</strong>&lt;br&gt;Itching of lips, tongue, palate, uvula, ears, throat, nose, eyes, etc.; mouth-tingling or metallic taste</td>
<td>Flushing (may also occur with fever, hyperthermia, or crying spells)</td>
<td>Rapid onset of hives (potentially difficult to discern in infants with acute atopic dermatitis; scratching and excoriations will be absent in young infants); angioedema (face, tongue, oropharynx)</td>
</tr>
<tr>
<td><strong>RESPIRATORY</strong>&lt;br&gt;Nasal congestion, throat tightness; chest tightness; shortness of breath</td>
<td>Hoarseness, dysphonia (common after a crying spell); drooling or increased secretions (common in infants)</td>
<td>Rapid onset of coughing, choking, stridor, wheezing, dyspnea, apnea, cyanosis</td>
</tr>
<tr>
<td><strong>GASTROINTESTINAL</strong>&lt;br&gt;Dysphagia, nausea, abdominal pain/cramping</td>
<td>Spitting up/regurgitation (common after feeds), loose stools (normal in infants, especially if breastfed); colicky abdominal pain</td>
<td>Sudden, profuse vomiting</td>
</tr>
<tr>
<td><strong>CARDIOVASCULAR</strong>&lt;br&gt;Feeling faint, presyncope, dizziness, confusion, blurred vision, difficulty in hearing</td>
<td>Hypotension (need appropriate-size blood pressure cuff; low systolic blood pressure for children is defined as &lt;70 mm Hg from 1 mo to 1 yr, and less than (70 mm Hg + [2 × age in yr]) from 1-10 yr; tachycardia, defined as &gt;140 beats/min from 3 mo to 2 yr, inclusive; loss of bowel and bladder control (ubiquitous in infants)</td>
<td>Weak pulse, arrhythmia, diaphoresis/sweating, collapse/unconsciousness</td>
</tr>
<tr>
<td><strong>CENTRAL NERVOUS SYSTEM</strong>&lt;br&gt;Headache</td>
<td>Drowsiness, somnolence (common in infants after feeds)</td>
<td>Rapid onset of unresponsiveness, lethargy, or hypotonia; seizures</td>
</tr>
</tbody>
</table>


### Table 149-2  |  Anaphylaxis Triggers in the Community*

<table>
<thead>
<tr>
<th>ALLERGEN TRIGGERS (IgE-DEPENDENT IMMUNOLOGIC MECHANISMS)*</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FOODS</strong>&lt;br&gt;(e.g., peanut, tree nuts, shellfish, fish, milk, egg, wheat, soy, sesame, meat [galactose-α-1,3-galactose])</td>
<td></td>
</tr>
<tr>
<td>Food additives (e.g., spices, colorants, vegetable gums, and contaminants)</td>
<td></td>
</tr>
<tr>
<td>Stinging insects: Hymenoptera species (e.g., bees, yellow jackets, wasps, hornets, and fire ants)</td>
<td></td>
</tr>
<tr>
<td>Medications (e.g., β-lactam antibiotics, ibuprofen)</td>
<td></td>
</tr>
<tr>
<td>Biologic agents (e.g., monoclonal antibodies [infliximab, omalizumab] and allergens [challenge tests, specific immunotherapy])</td>
<td></td>
</tr>
<tr>
<td>Natural rubber latex</td>
<td></td>
</tr>
<tr>
<td>Vaccines</td>
<td></td>
</tr>
<tr>
<td>Inhalants (rare) (e.g., horse or hamster dander, grass pollen)</td>
<td></td>
</tr>
<tr>
<td>Previously unrecognized allergens (foods, venoms, biting insect saliva, medications, biologic agents)</td>
<td></td>
</tr>
<tr>
<td><strong>OTHER IMMUNE MECHANISMS (IGE INDEPENDENT)</strong></td>
<td></td>
</tr>
<tr>
<td>IgG mediated (infliximab, high-molecular-weight dextran)</td>
<td></td>
</tr>
<tr>
<td>Immune aggregates (IVIG)</td>
<td></td>
</tr>
<tr>
<td>Drugs (aspirin, NSAID, opiates, contrast material, ethylene oxide/dialysis tubing)</td>
<td></td>
</tr>
<tr>
<td>Complement activation</td>
<td></td>
</tr>
<tr>
<td>Physical factors (e.g., exercise¹, cold, heat, sunlight/ultraviolet radiation)</td>
<td></td>
</tr>
<tr>
<td>Ethanol</td>
<td></td>
</tr>
<tr>
<td>Idiopathic*</td>
<td></td>
</tr>
</tbody>
</table>

*In the pediatric population, some anaphylaxis triggers, such as hormones (progesterone), seminal fluid, and occupational allergens, are uncommon, as is idiopathic anaphylaxis.

¹Exercise with or without a cotrigger, such as a food or medication, cold air, or cold water.

IVIG, intravenous immunoglobin; NSAID, nonsteroidal antiinflammatory drug.

imunoglobulin (Ig) E molecules. Patients initially must be exposed to the responsible allergen to generate allergen-specific antibodies. In many cases, the child and the parent are unaware of the initial exposure, which may be from passage of food proteins in maternal breast milk or skin exposures. When the child is reexposed to the sensitizing allergen, mast cells and basophils, and possibly other cells, such as macrophages, release a variety of mediators (histamine, tryptase) and cytokines that can produce allergic symptoms in any or all target organs. Clinical anaphylaxis may also be caused by mechanisms other than IgE-mediated reactions, including direct release of mediators from mast cells by medications and physical factors (morphine, exercise, cold), disturbances of leukotriene metabolism (aspirin and nonsteroidal antiinflammatory drugs), immune aggregates and complement activation (blood products), probable complement activation (radiocontrast dyes, dialysis membranes), and IgG-mediated reactions (high-molecular-weight dextran, chimeric or humanized monoclonal antibodies) (see Table 149-2).

**CLINICAL MANIFESTATIONS AND DIAGNOSIS**

The onset of symptoms may vary depending on the cause of the reaction. Reactions from ingested allergens (foods, medications) are delayed in onset (minutes to 2 hr) compared with those from injected allergens (insect sting, medications) and tend to have more gastrointestinal symptoms. Initial symptoms may include any of the following constellation of symptoms: pruritus about the mouth and face; a sensation of warmth, weakness, and apprehension (sense of doom); flushing, urticaria and angioedema, oral or cutaneous pruritus, tightness in the throat, dry staccato cough and hoarseness, periorcular pruritus, nasal congestion, sneezing, dyspnea, deep cough and wheezing; nausea, abdominal cramping, and vomiting, especially with ingested allergens; uterine contractions (manifesting as lower back pain); and faintness and loss of consciousness in severe cases. Some degree of obstructive laryngeal edema is typically encountered with severe reactions. Cutaneous symptoms may be absent in up to 20% of cases, and the acute onset of severe bronchospasm in a previously well asthmatic person should suggest the diagnosis of anaphylaxis. Sudden collapse in the absence of cutaneous symptoms should also raise suspicion of vasovagal collapse, myocardial infarction, aspiration, pulmonary embolism, or seizure disorder. Laryngeal edema, especially with abdominal pain, may also be a result of hereditary angioedema (see Chapter 148). Symptoms in infants may not be easy to identify (see Table 149-1).

**LABORATORY FINDINGS**

Laboratory studies may indicate the presence of IgE antibodies to a suspected causative agent, but this result is not definitive. Plasma histamine is elevated for a brief period but is unstable and difficult to measure in a clinical setting. Plasma tryptase is more stable and remains elevated for several hours but often is not elevated, especially in food-induced anaphylactic reactions.

**DIAGNOSIS**

A National Institutes of Health–sponsored expert panel has recommended an approach to the diagnosis of anaphylaxis (Table 149-4). The differential diagnosis includes other forms of shock (hemorrhagic, cardiogenic, septic), vasopressor reactions including flush syndromes such as carcinoid syndrome, excess histamine syndromes (systemic mastocytosis), ingestion of monosodium glutamate, scombroidosis, and hereditary angioedema. In addition, panic attack, vocal cord dysfunction, pheochromocytoma, and red man syndrome (caused by vancomycin) should be considered.
TREATMENT

Anaphylaxis is a medical emergency requiring aggressive management with intramuscular (first line) or intravenous epinephrine, intramuscular or intravenous H₁ and H₂ antihistamine antagonists, oxygen, intravenous fluids, inhaled β-agonists, and corticosteroids (Table 149-5, Fig. 149-1). The initial assessment should ensure an adequate airway with effective respiration, circulation, and perfusion. Epinephrine is the most important medication, and there should be no delay in its administration. Epinephrine should be given by the intramuscular route to the lateral thigh (1:1000 dilution, 0.01 mg/kg; max 0.5 mg). For children ≥12 yr, many recommend the 0.5 mg intramuscular dose. The intramuscular dose can be repeated 2 or 3 times at intervals of 5-15 min if an intravenous continuous epinephrine infusion has not yet been started and symptoms persist. The 1:10,000 dilution of epinephrine should be used for intravenous administration. If IV access is not readily available, then epinephrine can be administered via the endotracheal or intraosseous routes. Anaphylaxis refractory to repeated doses of epinephrine has anecdotally been treated with glucagon or methylene blue. The patient should be placed in a supine position and lower extremities elevated when there is concern for hemodynamic compromise. Fluids are also important in patients with shock. Other drugs (antihistamines, glucocorticosteroids) have a secondary role in the management of anaphylaxis. Patients may experience biphasic anaphylaxis, which occurs when anaphylactic symptoms recur after apparent resolution. The mechanism of this phenomenon is unknown, but it appears to be more common when therapy is initiated late and symptoms at presentation are more severe. It does not appear to be affected by the administration of corticosteroids during the initial therapy. More than 90% of biphasic responses occur within 4 hr, so patients should be observed for at least 4 hr before being discharged from the emergency department. Referrals should be made to appropriate specialists for further evaluation and follow-up.

Figure 149-1 Algorithm for the treatment of anaphylactic event in the outpatient setting. IV, Intravenous. (From Lieberman P, Nicklas RA, Oppenheimer J, et al: The diagnosis and management of anaphylaxis practice parameter: 2010 update, J Allergy Clin Immunol 126:477–480 e471–442, 2010 [Fig. E2].)
### Table 149-5  Management of a Patient with Anaphylaxis

<table>
<thead>
<tr>
<th>TREATMENT</th>
<th>MECHANISM(S) OF EFFECT</th>
<th>DOSAGE(S)</th>
<th>COMMENTS; ADVERSE REACTIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PATIENT EMERGENCY MANAGEMENT</strong> (DEPENDENT ON SEVERITY OF SYMPTOMS)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epinephrine (adrenaline)</td>
<td>$\alpha$, $\beta$, $\beta_2$ adrenergic effects</td>
<td>0.01 mg/kg up to 0.5 mg IM in lateral thigh</td>
<td>Tachycardia, hypertension, nervousness, headache, nausea, irritability, and tremor</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Weight 8-25 kg: Adrenaclick, Auvi-Q, EpiPen Jr (0.15 mg) IM</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Weight &gt;25 kg: Adrenaclick, Auvi-Q, EpiPen (0.3 mg) IM</td>
<td></td>
</tr>
<tr>
<td>Cetirizine (liquid)</td>
<td>Antihistamine (competitive of H$_1$ receptor)</td>
<td>Cetirizine liquid–5 mg/5 mL</td>
<td>Hypotension, tachycardia, and somnolence</td>
</tr>
<tr>
<td>Alt: diphenhydramine</td>
<td>Antihistamine (competitive of H$_1$ receptor)</td>
<td>1.25 mg/kg up to 50 mg PO or IM</td>
<td>Hypotension, tachycardia, somnolence, and paradoxical excitement</td>
</tr>
<tr>
<td>Transport to an Emergency Facility</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>EMERGENCY PERSONNEL MANAGEMENT</strong> (DEPENDENT ON SEVERITY OF SYMPTOMS)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epinephrine (adrenaline)</td>
<td>$\alpha$, $\beta$, $\beta_2$ adrenergic effects</td>
<td>0.01 mg/kg up to 0.5 mg IM in lateral thigh</td>
<td>Tachycardia, hypertension, nervousness, headache, nausea, irritability, and tremor</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Epinephrine autoinjector: 0.15 mg for 8-25 kg kg, 0.3 mg for &gt;25 kg</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.01 mL/kg/dose of 1:1,000 solution up to 0.5 mL IM</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>May repeat every 10-15 min For severe hypotension: 0.01 mL/kg/ dose of 1:10,000 slow IV push</td>
<td></td>
</tr>
<tr>
<td>Supplemental oxygen and airway management</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Volume expanders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crystalloids (normal saline or Ringer lactate)</td>
<td>30 mL/kg in 1st hr</td>
<td>Rate titrated against blood pressure response If tolerated, place patient supine with legs raised</td>
<td></td>
</tr>
<tr>
<td>Colloids (hydroxyethyl starch)</td>
<td>10 mL/kg rapidly followed by slow infusion</td>
<td>Rate titrated against blood pressure response If tolerated, place patient supine with legs raised</td>
<td></td>
</tr>
<tr>
<td><strong>Antihistamines</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cetirizine (liquid)</td>
<td>Antihistamine (competitive of H$_1$ receptor)</td>
<td>Cetirizine liquid–5 mg/5 mL</td>
<td>Hypotension, tachycardia, and somnolence</td>
</tr>
<tr>
<td>Alt: diphenhydramine</td>
<td>Antihistamine (competitive of H$_1$ receptor)</td>
<td>1.25 mg/kg up to 50 mg PO or IM</td>
<td>Hypotension, tachycardia, somnolence, and paradoxical excitement</td>
</tr>
<tr>
<td>Ranitidine</td>
<td>Antihistamine (competitive of H$_2$ receptor)</td>
<td>1 mg/kg up to 50 mg IV Should be administered slowly</td>
<td>Headache, mental confusion</td>
</tr>
<tr>
<td>Alt: cimetidine</td>
<td>Antihistamine (competitive of H$_2$ receptor)</td>
<td>4 mg/kg up to 200 mg IV Should be administered slowly</td>
<td></td>
</tr>
<tr>
<td><strong>Corticosteroids</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methylprednisolone</td>
<td>Antiinflammatory</td>
<td>Solu-Medrol (IV) 1-2 mg/kg up to 125 mg IV Depo-Medrol (IM) 1 mg/kg up to 80 mg IM</td>
<td>Hypertension, edema, nervousness, and agitation</td>
</tr>
<tr>
<td>Prednisone</td>
<td>Antiinflammatory</td>
<td>1 mg/kg up to 75 mg PO</td>
<td>Hypertension, edema, nervousness, and agitation</td>
</tr>
<tr>
<td>Nebulized albuterol</td>
<td>$\beta$-Agonist</td>
<td>(0.83 mg/mL [3 mL]) via mask with O$_2$</td>
<td>Palpitations, nervousness, central nervous system stimulation, tachycardia; use to supplement epinephrine when bronchospasm appears unresponsive; may repeat</td>
</tr>
<tr>
<td><strong>POSTEMERGENCY MANAGEMENT</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antihistamine</td>
<td>Cetirizine (5-10 mg qd) or loratadine (5-10 mg qd) for 3 days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>Optional: Oral prednisone (1 mg/kg up to 75 mg) daily for 3 days</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Preventive treatment**
- Prescription for epinephrine autoinjector and antihistamine
- Provide written plan outlining patient emergency management (may download form from [http://www.foodallergy.org](http://www.foodallergy.org))
- Follow-up evaluation to determine/confirm etiology
- Immunotherapy for insect sting allergy

**Patient education**
- Instruction on avoidance of causative agent
- Information on recognizing early signs of anaphylaxis
- Stress early treatment of allergic symptoms to avoid systemic anaphylaxis
- Encourage wearing medical identification jewelry

IM, intramuscularly; IV, intravenously; PO, by mouth.
PREVENTION

For patients experiencing anaphylactic reactions, the triggering agent should be avoided and education regarding early recognition of anaphylactic symptoms and administration of emergency medications should be provided. Patients with food allergies must be educated in allergen avoidance, including active reading of food ingredient labels and knowledge of potential contamination and high-risk situations. Any child with food allergy and a history of asthma, peanut, tree nut, fish or shellfish allergy, or a previous anaphylactic reaction should be given an epinephrine autoinjector (Adrenaclick, Auvi-Q, EpiPen), liquid cetirizine (or alternatively, diphenhydramine), and a written emergency plan in case of accidental ingestion. A form can be downloaded from Food Allergy Research & Education at http://www.foodallergy.org.

In cases of food-associated exercise-induced anaphylaxis, children must not exercise within 2-3 hr of ingesting the triggering food and, like children with exercise-induced anaphylaxis, should exercise with a friend, learn to recognize the early signs of anaphylaxis (sensation of warmth and facial pruritus), stop exercising, and seek help immediately if symptoms develop. Children experiencing a systemic anaphylactic reaction including respiratory symptoms to an insect sting should be evaluated and treated with immunotherapy, which is more than 90% protective. Reactions to medications can be reduced and minimized by using oral medications in preference to injected forms and avoidance of cross-reacting medications. Low osmolarity radiocontrast dyes and pretreatment can be used in patients in whom previous reactions are suspected. The use of nonlatex gloves and materials should be used in children undergoing multiple operations. Any child who is at risk for anaphylaxis should receive emergency medications (including epinephrine autoinjector), education on identification of signs and symptoms of anaphylaxis and proper administration of medications, and a written emergency plan in case of accidental exposure, and encouraged to wear medical identification jewelry.

Bibliography is available at Expert Consult.
Bibliography


Serum sickness is a systemic, immune complex–mediated hypersensitivity vasculitis classically attributed to the therapeutic administration of foreign serum proteins or other medications (Table 150-1).

**ETIOLOGY**
Immune complexes involving heterologous (animal) serum proteins and complement activation are important pathogenic mechanisms in serum sickness. Antibody therapies derived from the horse or sheep are available for treatment of envenomation by the black widow spider and a variety of snakes, for treatment of botulism, and for immunosuppression (antithymocyte globulin). The availability of alternative medical therapies, modified or bioengineered antibodies, and biologics of human origin have supplanted the use of nonhuman antisera, reducing the risk of serum sickness. A *serum sickness–like reaction* may be attributed to drug allergy, triggered by antibiotics (particularly cefaclor). In contrast to a true serum sickness, serum sickness–like reactions do not exhibit the immune complexes, hypocomplementemia, vasculitis, and renal lesions that are seen in serum sickness reactions.

**PATHOGENESIS**
Serum sickness is a classic example of a type III hypersensitivity reaction caused by antigen–antibody complexes. In the rabbit model using bovine serum albumin as the antigen, symptoms develop with the appearance of antibody against the injected antigen. As free antigen concentration falls and antibody production increases over days, antigen–antibody complexes of various sizes develop in a manner analogous to a precipitin curve. Whereas small complexes usually circulate harmlessly and large complexes are cleared by the reticuloendothelial system, intermediate-sized complexes that develop at the point of slight antigen excess may deposit in blood vessel walls and tissues. There the immune microprecipitates induce vascular (leukocytoclastic vasculitis with immune complex deposition) and tissue damage through activation of complement and granulocytes.

Complement activation (C3a, C5a) promotes chemotaxis and adherence of neutrophils to the site of immune complex deposition. The processes of immune complex deposition and of neutrophil accumulation may be facilitated by increased vascular permeability, owing to the release of vasoactive amines from tissue mast cells. Mast cells may be activated by binding of antigen to immunoglobulin (Ig) E or through contact with anaphylatoxins (C3a). Tissue injury results from the liberation of proteolytic enzymes and oxygen radicals from the neutrophils.

**CLINICAL MANIFESTATIONS**
The symptoms of serum sickness generally begin 7-12 days after injection of the foreign material, but may appear as late as 3 wk afterward. The onset of symptoms may be accelerated if there has been earlier exposure or previous allergic reaction to the same antigen. A few days before the onset of generalized symptoms, the site of injection may become edematous and erythematous. Symptoms usually include fever, malaise, and rashes. Urticaria and morbilliform rashes are the predominant types of skin eruptions. In a prospective study of serum sickness induced by administration of equine antithymocyte globulin, an initial rash was noted in most patients. It began as a thin serpiginous band of erythema along the sides of the hands, fingers, feet, and toes at the junction of the palmar or plantar skin with the skin of the dorsolateral surface. In most patients, the band of erythema was replaced

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*Based on review of most current literature. Other medications that are not listed are also cited to cause serum sickness.

HIV, human immunodeficiency virus.

by petechiae or purpura, presumably because of low platelet counts or local damage to small blood vessels. Additional symptoms include edema, myalgia, lymphadenopathy, symmetric arthralgia or arthritis involving multiple joints, and gastrointestinal complaints, including pain, nausea, diarrhea, and melena. Symptoms typically resolve within 2 wk of removal of the offending agent, although in unusual cases, symptoms can persist for as long as 2-3 mo.

Carditis, glomerulonephritis, Guillain-Barré syndrome, and peripheral neuritis are rare complications. Serum sickness–like reactions from drugs are characterized by fever, pruritus, urticaria, and arthralgias that usually begin 1-3 wk after drug exposure. The urticarial skin eruption becomes increasingly erythematous as the reaction progresses and can evolve into dusky centers with round plaques.

DIFFERENTIAL DIAGNOSIS
The differential diagnosis of serum sickness and serum sickness-like reactions includes viral illnesses with exanthems, hypersensitivity vasculitis, Kawasaki disease, acute rheumatic fever, acute meningococcal or gonococcal infection, endocarditis, systemic onset juvenile idiopathic arthritis (Still disease), Lyme disease, hepatitis and other types of drug reactions (see Chapter 152).

DIAGNOSIS
In most cases, the diagnosis of serum sickness is made clinically based upon the characteristic pattern of acute or subacute onset of a rash, fever, and severe arthralgia and myalgia disproportionate to the degree of swelling, occurring after exposure to a potential culprit.

The patients who appear moderately or severely ill, or who are not taking a medication that can be readily identified as the culprit, should be evaluated with the following laboratory tests:

- Complete blood count and differential; thrombocytopenia is often present.
- Erythrocyte sedimentation rate and C-reactive protein; erythrocyte sedimentation rate is usually elevated.
- Urinalysis; mild proteinuria, hemoglobinuria, and microscopic hematuria may be seen.
- Serum chemistries, including blood urea nitrogen, creatinine, and liver function tests.
- Complement studies, including CH50, C3, and C4; serum complement levels (C3 and C4) are generally decreased and reach a nadir at about day 10. C3a anaphylatoxin may be increased.
- Testing for specific infectious diseases, if indicated by the history or physical examination.
- Appropriate viral or bacterial cultures if an infection is suspected.

Skin biopsies are not usually necessary for confirming the diagnosis, because the findings are variable and not specific for serum sickness. Direct immunofluorescence studies of skin lesions often reveal immune deposits of IgM, IgA, IgE, or C3.

TREATMENT
There are no evidence-based guidelines or controlled trials upon which to base therapy recommendations. Treatment is primarily supportive, consisting of discontinuation of the offending agent, antihistamines for pruritus, and nonsteroidal antiinflammatory agents and analgesics for low-grade fever and mild arthralgia. When the symptoms are especially severe, for example, fever >38.5°C (101.3°F), severe arthralgia or myalgia, or renal dysfunction, systemic corticosteroids can be used. Prednisone (1-2 mg/kg/day, max 60 mg/day) for 1-2 wk is usually sufficient. Once the offending agent is discontinued and depending on its half-life, symptoms resolve spontaneously in 1-4 wk. Symptoms lasting longer suggest another diagnosis.

PREVENTION
The primary mode of prevention of serum sickness is to seek alternative therapies. In some cases, non–animal-derived formulations may be available (human-derived botulinum immune globulin). Other alternatives are partially digested antibodies of animal origin and engineered (humanized) antibodies. The potential of these therapies to elicit serum sickness–like disease appears low. When only animal-derived antitoxin/antivenom is available, skin tests should be performed before administration of serum, but this procedure indicates the risk only of anaphylaxis, not of serum sickness. For patients who have evidence of anaphylactic sensitivity to horse serum, a risk-to-benefit assessment must be made to determine the need to proceed with treatment. If needed, the serum can usually be successfully administered by a process of rapid desensitization using protocols of gradual administration outlined by the manufacturers. Serum sickness is not prevented by desensitization or by pretreatment with corticosteroids.

Bibliography is available at Expert Consult.
Chapter 150  Serum Sickness

Bibliography


Adverse reactions to foods consist of any untoward reaction following the ingestion of a food or food additive and are classically divided into food intolerances (e.g., lactose intolerance), which are adverse physiologic responses, and food allergies, which are adverse immunologic responses and can be immunoglobulin (Ig) E-mediated or non–IgE-mediated (Tables 151-1 to 151-3). Like other atopic disorders, food allergies appear to have increased over the past 3 decades, primarily in countries with a Western lifestyle. Worldwide, estimates of food allergy prevalence range from 1-10%; in the United States, food allergies affect an estimated 3.5% of the U.S. population. Up to 6% of children experience food allergic reactions in the 1st 3 yr of life, including approximately 2.5% with cow’s milk allergy, 1.5% with egg allergy, and 1% with peanut allergy. Peanut allergy prevalence tripled over the past decade. Most children “outgrow” milk and egg allergies, with approximately 50% doing so by school-age. In contrast, approximately 80-90% of children with peanut, nut, or seafood allergy retains their allergy for life.

PATHOGENESIS

Food intolerances are the result of a variety of mechanisms, whereas food allergy is predominantly caused by IgE-mediated and/or cell-mediated mechanisms. In susceptible individuals exposed to certain allergens, food-specific IgE antibodies are formed that bind to Fcε receptors on mast cells, basophils, macrophages, and dendritic cells. When food allergens penetrate mucosal barriers and reach cell-bound IgE antibodies, mediators are released that induce vasodilation, smooth muscle contraction, and mucus secretion, which result in symptoms of immediate hypersensitivity (allergy). Activated mast cells and macrophages may release several cytokines that attract and activate other cells, such as eosinophils and lymphocytes, leading to prolonged inflammation. Symptoms elicited during acute IgE-mediated reactions can affect the skin (urticaria, angioedema, flushing), gastrointestinal tract (oral pruritus, angioedema, nausea, abdominal pain, vomiting, diarrhea), respiratory tract (nasal congestion, rhinorrhea, nasal pruritus, sneezing, laryngeal edema, dyspnea, wheezing), and cardiovascular system (dysrhythmias, hypotension, loss of consciousness). In the other major form of food allergies, lymphocytes, primarily food allergen–specific T cells, secrete excessive amounts of various
Giardia, Akis simplex

Differential Diagnosis of Adverse Food Reactions

<table>
<thead>
<tr>
<th>FOOD</th>
<th>USUAL AGE AT ONSET OF ALLERGY</th>
<th>CROSS REACTIVITY</th>
<th>USUAL AGE AT RESOLUTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hen's egg white</td>
<td>0-1 yr</td>
<td>Other avian eggs</td>
<td>7 yr (75% of cases resolve)*</td>
</tr>
<tr>
<td>Cow's milk</td>
<td>0-1 yr</td>
<td>Goat's milk, sheep's milk, buffalo milk</td>
<td>5 yr (76% of cases resolve)*</td>
</tr>
<tr>
<td>Peanuts</td>
<td>1-2 yr</td>
<td>Other legumes, peas, lentils; coreactivity with tree nuts</td>
<td>Persistent (20% of cases resolve)</td>
</tr>
<tr>
<td>Tree nuts</td>
<td>1-2 yr; in adults, onset occurs after cross reactivity to birch pollen</td>
<td>Other tree nuts; coreactivity with peanuts</td>
<td>Persistent (9% of cases resolve)</td>
</tr>
<tr>
<td>Fish</td>
<td>Late childhood and adulthood</td>
<td>Other fish (low cross-reactivity with tuna and swordfish)</td>
<td>Persistent†</td>
</tr>
<tr>
<td>Shellfish</td>
<td>Adulthood (in 60% of patients with this allergy)</td>
<td>Other shellfish</td>
<td>Persistent</td>
</tr>
<tr>
<td>Wheat*</td>
<td>6-24 mo</td>
<td>Other grains containing gluten (rye, barley)</td>
<td>5 yr (80% of cases resolve)</td>
</tr>
<tr>
<td>Soybeans*</td>
<td>6-24 mo</td>
<td>Other legumes</td>
<td>2 yr (67% of cases resolve)</td>
</tr>
<tr>
<td>Kiwi</td>
<td>Any age</td>
<td>Banana, avocado, latex</td>
<td>Unknown</td>
</tr>
<tr>
<td>Apples, carrots, and peaches†</td>
<td>Late childhood and adulthood</td>
<td>Birch pollen, other fruits, nuts</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

*Recent studies suggest that resolution may occur at a later age, especially in children with multiple food allergies and lifetime peak food-specific IgE >50 kU/L.
†Fish allergy that is acquired in childhood can resolve.
‡Allergy to fresh apples, carrots, and peaches (oral allergy syndrome) is commonly caused by heat-labile proteins. Fresh fruit causes oral pruritus, but cooked fruit is tolerated. There is generally no risk of anaphylaxis, although in rare cases, allergies to cross-reactive lipid transfer protein can cause anaphylaxis after ingestion of fruits (e.g., peach) and vegetables.

cytokines that lead to a “delayed,” more chronic inflammatory process affecting the skin (pruritus, erythematous rash), gastrointestinal tract (failure to thrive, early satiety, abdominal pain, vomiting, diarrhea), or respiratory tract (food-induced pulmonary hemosiderosis). Mixed IgE and cellular responses to food allergens can also lead to chronic disorders such as atopic dermatitis, asthma, and allergic eosinophilic esophagitis and gastroenteritis.

Children in whom IgE-mediated food allergies develop may be sensitized by food allergens penetrating the gastrointestinal barrier, referred to as class 1 food allergens, or by food allergens that are partially homologous to plant pollens penetrating the respiratory tract, referred to as class 2 food allergens. Any food may serve as a class 1 food allergen, but egg, milk, peanuts, tree nuts, fish, soy, and wheat account for 90% of food allergies during childhood. Many of the major allergenic proteins of these foods have been characterized. There is variable but significant cross-reactivity with other proteins within an individual food group. Exposure and sensitization to these proteins often occur very early in life. Virtually all milk allergies develop by 12 mo of age and all egg allergies by 18 mo of age, and the median age of first peanut allergic reactions is 14 mo. Because allergic reactions to these high-risk allergens occur in infancy, it was once thought that avoidance of these foods and delayed introduction to the diet would prevent allergy. Indeed, the opposite is probably true and delayed introduction of these foods actually increases the risk of allergy. Current recommendations are to introduce egg, peanut products, fish, wheat, and other allergenic foods after 4-6 mo of exclusive breast feeding (Table 151-4).

Class 2 food allergens are typically vegetable, fruit or nut proteins that are partially homologous with pollen proteins (see Table 151-3). With the development of seasonal allergic rhinitis from birch, grass, or ragweed pollens, subsequent ingestion of certain uncooked fruits or vegetables provokes the oral allergy syndrome. Intermittent ingestion of allergenic foods may lead to acute symptoms such as urticaria or angioedema, whereas prolonged exposure may lead to chronic disorders such as atopic dermatitis and asthma. Cell-mediated sensitivity typically develops to class 1 allergens.

CLINICAL MANIFESTATIONS

From a clinical and diagnostic standpoint, it is most useful to subdivide food hypersensitivity disorders according to the predominant target organ (Table 151-5) and immune mechanism (see Table 151-1).

Gastrointestinal Manifestations

Gastrointestinal food allergies are often the first form of allergy to affect infants and young children and typically manifest as irritability, vomiting or “spitting-up,” diarrhea, and poor weight gain. Cell-mediated hypersensitivities without IgE involvement predominate, making standard allergy tests such as prick skin tests and in vitro tests for food-specific IgE antibodies of little diagnostic value.

Food protein–induced enterocolitis syndrome (FPIES) typically manifests in the first several months of life as irritability, intermittent vomiting and protracted diarrhea, and may result in dehydration (Table 151-6). Vomiting generally occurs 1-3 hr after feeding, and continued exposure may result in abdominal distention, bloody diarrhea, anemia, and failure to thrive. Symptoms are most commonly provoked by cow’s milk or soy protein–based formulas. A similar enterocolitis syndrome occurs in older infants and children from rice, oat, wheat, egg, peanut, nut, chicken, turkey, or fish. Hypotension occurs in approximately 15% of cases after allergen ingestion and may initially be thought to be caused by sepsis. FPIES usually resolves by age 3 yr.

Food protein-induced proctocolitis presents in the first few mo of life as blood-streaked stools in otherwise healthy infants (see Table 151-6). Approximately 60% of cases occur among breastfed infants, with the remainder largely among infants fed cow’s milk or soy

<table>
<thead>
<tr>
<th>Table 151-5</th>
<th>Symptoms of Food-Induced Allergic Reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>TARGET ORGAN</td>
<td>IMMEDIATE SYMPTOMS</td>
</tr>
<tr>
<td>Cutaneous</td>
<td>Erythema</td>
</tr>
<tr>
<td>Urticaria</td>
<td>Pruritus</td>
</tr>
<tr>
<td>Morbilliform eruption</td>
<td>Angioedema</td>
</tr>
<tr>
<td>Ocular</td>
<td>Pruritus</td>
</tr>
<tr>
<td>Conjunctival erythema</td>
<td>Tearing</td>
</tr>
<tr>
<td>Periorbital edema</td>
<td></td>
</tr>
<tr>
<td>Upper respiratory</td>
<td>Nasal congestion</td>
</tr>
<tr>
<td>Pruritus</td>
<td>Chest tightness</td>
</tr>
<tr>
<td>Rhinorrhea</td>
<td>Dyspnea</td>
</tr>
<tr>
<td>Sneezing</td>
<td>Wheezing</td>
</tr>
<tr>
<td>Laryngeal edema</td>
<td>Intercostal retractions</td>
</tr>
<tr>
<td>Hoarseness</td>
<td>Dry staccato cough</td>
</tr>
<tr>
<td>Lower respiratory</td>
<td>Cough</td>
</tr>
<tr>
<td>Cough</td>
<td>Colicky abdominal pain</td>
</tr>
<tr>
<td>Chest tightness</td>
<td>Reflux</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>Vomiting</td>
</tr>
<tr>
<td>Wheezing</td>
<td>Diarrhea</td>
</tr>
<tr>
<td>Intercostal retractions</td>
<td></td>
</tr>
<tr>
<td>Accessory muscle use</td>
<td></td>
</tr>
<tr>
<td>GI (oral)</td>
<td>Angioedema of the lips, tongue, or palate</td>
</tr>
<tr>
<td>Oral pruritus</td>
<td>Tongue swelling</td>
</tr>
<tr>
<td>GI (lower)</td>
<td>Nausea</td>
</tr>
<tr>
<td>Nausea</td>
<td>Colicky abdominal pain</td>
</tr>
<tr>
<td>Reflux</td>
<td>Vomiting</td>
</tr>
<tr>
<td>Vomiting</td>
<td>Diarrhea</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>Hematochezia</td>
</tr>
<tr>
<td>Hematochezia</td>
<td>Irritability and food refusal with weight loss</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Tachycardia (occasionally bradycardia in anaphylaxis)</td>
</tr>
<tr>
<td>Hypotension</td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td></td>
</tr>
<tr>
<td>Fainting</td>
<td></td>
</tr>
<tr>
<td>Loss of consciousness</td>
<td></td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>Uterine contractions</td>
</tr>
<tr>
<td>Sense of “impending doom”</td>
<td></td>
</tr>
</tbody>
</table>

Note: This table is presented as Table IV in the Guidelines.

GI, gastrointestinal

### Table 151-6  Food Protein-Induced Gastrointestinal Syndromes

<table>
<thead>
<tr>
<th></th>
<th>FPIES</th>
<th>PROCTOCOLITIS</th>
<th>ENTEROPATHY</th>
<th>EOSINOPHILIC GASTROENTEROPATHIES*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age at onset</strong></td>
<td>1 day–1 year</td>
<td>1 day–6 months</td>
<td>Dependent of age of exposure to antigen, cow’s milk and soy up to 2 yr</td>
<td>Infant to adolescent</td>
</tr>
<tr>
<td><strong>Food proteins implicated</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Most common</strong></td>
<td>Cow’s milk, soy</td>
<td>Cow’s milk, soy</td>
<td>Cow’s milk, soy</td>
<td>Cow’s milk, soy, egg white, wheat, peanut</td>
</tr>
<tr>
<td><strong>Less common</strong></td>
<td>Rice, chicken, turkey, fish, pea</td>
<td>Egg, corn, chocolate</td>
<td>Wheat, egg</td>
<td>Meats, corn, rice, fruits, vegetables, fish</td>
</tr>
<tr>
<td><strong>Multiple food hypersensitivities</strong></td>
<td>&gt;50% both cow’s milk and soy</td>
<td>40% both cow’s milk and soy</td>
<td>Rare</td>
<td>Common</td>
</tr>
<tr>
<td><strong>Feeding at the time of onset</strong></td>
<td>Formula</td>
<td>&gt;50% exclusive breastfeeding</td>
<td>Formula</td>
<td>Formula</td>
</tr>
<tr>
<td><strong>Atopic background</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Family history of atopy</strong></td>
<td>40-70%</td>
<td>25%</td>
<td>Unknown</td>
<td>~50% (often history of eosinophilic esophagitis)</td>
</tr>
<tr>
<td><strong>Personal history of atopy</strong></td>
<td>30%</td>
<td>22%</td>
<td>22%</td>
<td>~50%</td>
</tr>
<tr>
<td><strong>Symptoms</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Emesis</strong></td>
<td>Prominent</td>
<td>No</td>
<td>Intermittent</td>
<td>Intermittent</td>
</tr>
<tr>
<td><strong>Diarrhea</strong></td>
<td>Severe</td>
<td>Moderate</td>
<td>Moderate</td>
<td>Moderate</td>
</tr>
<tr>
<td><strong>Bloody stools</strong></td>
<td>Severe</td>
<td>Moderate</td>
<td>Rare</td>
<td>Moderate</td>
</tr>
<tr>
<td><strong>Edema</strong></td>
<td>Acute, severe</td>
<td>No</td>
<td>Moderate</td>
<td>Moderate</td>
</tr>
<tr>
<td><strong>Shock</strong></td>
<td>15% Moderate</td>
<td>No</td>
<td>No</td>
<td>Moderate</td>
</tr>
<tr>
<td><strong>Failure to thrive</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Laboratory findings</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Anemia</strong></td>
<td>Moderate</td>
<td>Mild</td>
<td>Moderate</td>
<td>Mild-moderate</td>
</tr>
<tr>
<td><strong>Hypoalbuminemia</strong></td>
<td>Acute</td>
<td>Rare</td>
<td>Moderate</td>
<td>Mild-severe</td>
</tr>
<tr>
<td><strong>Methemoglobinemia</strong></td>
<td>May be present</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td><strong>Allergy evaluation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Food prick skin test</strong></td>
<td>Negative†</td>
<td>Negative</td>
<td>Negative</td>
<td>Positive in ~50%</td>
</tr>
<tr>
<td><strong>Serum food allergen IgE</strong></td>
<td>Negative†</td>
<td>Negative</td>
<td>Negative</td>
<td>Positive in ~50%</td>
</tr>
<tr>
<td><strong>Total IgE</strong></td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal to elevated</td>
</tr>
<tr>
<td><strong>Peripheral blood eosinophilia</strong></td>
<td>No</td>
<td>Occasional</td>
<td>Occasional</td>
<td>Present in &lt;50%</td>
</tr>
<tr>
<td><strong>Biopsy findings</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Colitis</strong></td>
<td>Prominent</td>
<td>Focal</td>
<td>No</td>
<td>May be present</td>
</tr>
<tr>
<td><strong>Lymph nodular hyperplasia</strong></td>
<td>No</td>
<td>Common</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Eosinophils</strong></td>
<td>Prominent</td>
<td>Prominent</td>
<td>Few</td>
<td>Prominent; also neutrophilic infiltrates, papillary elongation and basal zone hyperplasia</td>
</tr>
<tr>
<td><strong>Food challenge</strong></td>
<td>Vomiting in 2-4 hr, diarrhea in 5-8 hr</td>
<td>Rectal bleeding in 6-72 hr</td>
<td>Vomiting, diarrhea, or both in 40-72 hr</td>
<td>Vomiting and diarrhea in hours to days</td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td>Protein elimination, 80% respond to casein hydrolysate and symptoms clear in 3-10 days; rechallenge in 1.5-2 yr</td>
<td>Protein elimination, symptoms clear in 3 days with casein hydrolysate, resume/continue breastfeeding on maternal antigen-restricted diet</td>
<td>Protein elimination, symptoms clear in 1-3 wk, rechallenge and biopsy in 1-2 yr</td>
<td>Protein elimination, good response to casein hydrolysate, excellent response to elemental diet, symptoms clear within 2-3 wk, excellent acute response to steroids; rechallenge and biopsy in 1-2 yr</td>
</tr>
<tr>
<td><strong>Natural history</strong></td>
<td>Cow’s milk: 60% resolved by 2 yr Soy: 25% resolved by 2 yr</td>
<td>Resolved by 9-12 months</td>
<td>Most cases resolve in 2-3 yr</td>
<td>Typically a prolonged, relapsing course</td>
</tr>
<tr>
<td><strong>Reintroduction of the food</strong></td>
<td>Inpatient food challenge</td>
<td>At home, gradually advancing from 1 oz to full feedings over 2 weeks</td>
<td>Home, gradually advancing</td>
<td>Home, gradually advancing</td>
</tr>
</tbody>
</table>

*Eosinophilic gastroenteropathies encompass esophagitis, gastritis, gastroenterocolitis.
†If positive, may be a risk factor for persistent disease.
FPIES, food protein-induced enterocolitis syndrome.
protein–based formula. Blood loss is typically modest, but can occasionally produce anemia.

**Food protein–induced enteropathy** often manifests in the first several months of life as diarrhea, often with steatorrhea and poor weight gain (see Table 151-6). Symptoms include protracted diarrhea, vomiting in up to 65% of cases, failure to thrive, abdominal distention, early satiety, and malabsorption. Anemia, edema, and hypoproteinemias can occur occasionally. **Cow’s milk sensitivity** is the most common cause of this food protein–induced enteropathy in young infants, but it also has been associated with sensitivity to soy, egg, wheat, rice, chicken, and fish in older children. **Celiac disease**, the most severe form of protein-induced enteropathy, occurs in about 1:100 of the U.S. population, although it may be “silent” in many patients (see Chapter 338.2). The full-blown form is characterized by extensive loss of absorptive villi and hyperplasia of the crypts, leading to malabsorption, chronic diarrhea, steatorrhea, abdominal distention, flatulence, and weight loss or failure to thrive. Oral ulcers and other extraintestinal symptoms secondary to malabsorption may occur. Genetically susceptible individuals (HLA-DQ2 or HLA-DQ8) demonstrate a cell-mediated response to tissue transglutaminase deamidated gliadin (a fraction of gluten), which is found in wheat, rye, and barley.

**Eosinophilic esophagitis** (EoE) may appear from infancy through adolescence, more frequently in boys (see Chapter 324). In young children, it is primarily cell mediated and manifests as chronic gastroesophageal reflux, intermittent emesis, food refusal, abdominal pain, dysphagia, irritability, sleep disturbance, and failure to respond to conventional reflux medications. EoE is a clinicopathologic diagnosis. The diagnosis is confirmed when 15 eosinophils per high-power field are present on esophageal biopsy during treatment with proton pump inhibitors. **Eosinophilic gastroenteritis** occurs at any age and causes symptoms similar to those of EoE as well as prominent weight loss or failure to thrive, both of which are the hallmarks of this disorder. More than 50% of patients with this disorder are atopic, however food-induced IgE-mediated reactions have been implicated only in a minority of patients. Generalized edema secondary to hypoalbuminemia may occur in some infants with marked protein-losing enteropathy.

**Oral allergy syndrome** (pollen-associated food allergy syndrome) is an IgE-mediated hypersensitivity that occurs in many older children with birch and ragweed pollen-induced allergic rhinitis. Symptoms are usually confined to the oropharynx and consist of the rapid onset of oral pruritus, tingling and angioedema of the lips, tongue, palate, and throat, and occasionally a sensation of pruritus in the ears and tightness in the throat. Symptoms are generally short lived and are caused by local mast cell activation following contact with fresh fruit and vegetable proteins that cross-react with birch pollen (apple, carrot, potato, celery, hazel nuts, kiwi, cherry, pear), grass pollen (potato, tomato, watermelon, kiwi), and ragweed pollen (banana, melons such as watermelon and cantaloupe).

**Acute gastrointestinal** allergy generally manifests as acute abdominal pain and vomiting that accompany IgE-mediated allergic symptoms in other target organs.

### Skin Manifestations

Cutaneous food allergies are also common in infants and young children.

**Atopic dermatitis** is a form of eczema that generally begins in early infancy and is characterized by pruritus, a chronically relapsing course, and association with asthma and allergic rhinitis (see Chapter 145). Although not often apparent from history, at least 30% of children with moderate to severe atopic dermatitis have food allergies. The younger the child and the more severe the eczema, the more likely food allergy is playing a role in the disorder.

**Acute urticaria and angioedema** are among the most common symptoms of food allergic reactions (see Chapter 148). The onset of symptoms may be very rapid, within minutes after ingestion of the responsible allergen. Symptoms result from activation of IgE-bearing mast cells by food allergens that are absorbed and circulated rapidly throughout the body. Foods most commonly incriminated in children include egg, milk, peanuts, and nuts, although reactions to various seeds (sesame, poppy) and fruits (kiwi) are becoming more common. Chronic urticaria and angioedema are rarely caused by food allergies.

**Perioral dermatitis** is often a contact dermatitis caused by substances in toothpaste, gums, lipstick, to medications. **Perioral flushing** is often noted in infants fed citrus fruits and may be caused by benzoyl alcohol in the food. It may also occur during nursing. In both situations, it is benign. Flushing may also be caused by auriculotemporal nerve (Frey) syndrome (familial, forces delivery), which resolves spontaneously.

### Respiratory Manifestations

Respiratory food allergies are uncommon as isolated symptoms. Although many parents believe that nasal congestion in infants is often caused by milk allergy, studies show this not to be the case. **Food-induced rhinoconjunctivitis** symptoms typically accompany allergic symptoms in other target organs, such as skin, and consist of typical allergic rhinitis symptoms (periorbital pruritus and tearing, nasal congestion and pruritus, sneezing, rhinorrhea). Wheezing occurs in approximately 25% of IgE-mediated food allergic reactions, but only approximately 10% of asthmatic patients have food-induced respiratory symptoms.

**Anaphylaxis**

Anaphylaxis is defined as a serious, multisystem allergic reaction that is rapid in onset and potentially fatal. Food allergic reactions are the single most common cause of anaphylaxis seen in hospital emergency departments in the United States. In addition to the rapid onset of cutaneous, respiratory, and gastrointestinal symptoms, patients may demonstrate cardiovascular symptoms, including hypotension, vascular collapse, and cardiac dysrhythmias, which are presumably caused by massive mast cell–mediator release. **Food-associated exercise-induced anaphylaxis** occurs more frequently among teenage athletes, especially females (see Chapter 149).

### Diagnosis

A thorough medical history is necessary to determine whether a patient’s symptomatology represents an adverse reaction (see Table 151-2), whether the adverse food reaction is an intolerance or food allergic reaction, and if the latter, whether it is likely to be an IgE-mediated or a cell–mediated response (Fig. 151-1). The following facts should be established: (1) the food suspected of provoking the reaction and the quantity ingested, (2) the interval between ingestion and the development of symptoms, (3) the types of symptoms elicited by the ingestion, (4) whether ingesting the suspected food produced similar symptoms on other occasions, (5) whether other inciting factors, such as exercise, are necessary, and (6) the interval from the last reaction to the food.

Prick skin tests and in vitro laboratory tests are useful for demonstrating IgE sensitization, defined as presence of food-specific IgE antibodies. Many fruits and vegetables require prick–prick skin testing with fresh produce because labile proteins are destroyed during commercial preparation. A negative skin test result virtually excludes an IgE-mediated form of food allergy. Conversely, the majority of children with positive skin test responses to a food do not react when the food is ingested, so more definitive tests, such as quantitative IgE tests or food elimination and challenge, are often necessary to establish a diagnosis of food allergy. Serum food-specific IgE levels ≥15 kU/L for milk (≥5 kU/L for children <1 yr), 77 kU/L for egg (≥2 kU/L for children <2 yr), and 144 kU/L for peanut are associated with a >95% likelihood of clinical reactivity to these foods in children with suspected reactivity. In the absence of a clear history of reactivity to a food and evidence of food-specific IgE antibodies, definitive studies must be performed before recommendations are made for avoidance or the use of highly restrictive diets that may be nutritionally deficient, logistically impractical, disruptive to the family, expensive, and a potential source of future feeding disorders. IgE-mediated food allergic reactions are generally very food specific, so the use of broad exclusionary diets, such as avoidance of all legumes, cereal grains, or animal products, is not warranted (Tables 151-3 and 151-7).
Figure 151-1 General scheme for diagnosis of food allergy. (From Sicherer SH: Food allergy, Lancet 360:701–710, 2002.)

Table 151-7 Clinical Implications of Cross-Reactive Proteins in IgE-Mediated Allergy

<table>
<thead>
<tr>
<th>FOOD FAMILY</th>
<th>RISK OF ALLERGY TO ≥1 MEMBER (% APPROXIMATE)</th>
<th>FEATURE(S)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Legumes</td>
<td>5</td>
<td>Main causes of reactions are peanut, soybean, lentil, lupine, and garbanzo (chickpea)</td>
</tr>
<tr>
<td>Tree nuts (e.g., almond, cashew, hazelnut, walnut, brazil)</td>
<td>35</td>
<td>Reactions are often severe</td>
</tr>
<tr>
<td>Fish</td>
<td>50</td>
<td>Reactions can be severe</td>
</tr>
<tr>
<td>Shellfish</td>
<td>75</td>
<td>Reactions can be severe</td>
</tr>
<tr>
<td>Grains</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Mammalian milks</td>
<td>90</td>
<td>Cow’s milk is highly cross reactive with goat’s or sheep’s milk (92%) but not with mare’s milk (4%)</td>
</tr>
<tr>
<td>Rosaceae (pitted fruits)</td>
<td>55</td>
<td>Risk of reactions to more than three related foods is very low (&lt;10%), symptoms are usually mild (oral allergy syndrome)</td>
</tr>
<tr>
<td>Latex-food</td>
<td>35</td>
<td>For individuals allergic to latex, banana, kiwi, fig, chestnut, and avocado are the main causes of reactions</td>
</tr>
<tr>
<td>Food-latex</td>
<td>11</td>
<td>Individuals allergic to banana, kiwi, fig, chestnut, and avocado may be at an increased risk of reactions to latex</td>
</tr>
</tbody>
</table>

and may prevent the development of allergies later in life. Use of partially hydrolyzed whey formulas may be beneficial if breast feeding cannot be continued for 4-6 mo or after weaning, especially to prevent eczema in high risk families, but his approach remains controversial. Probiotic supplements may also reduce the incidence and severity of eczema. Because some skin preparations contain peanut oil, which may sensitize young infants, especially those with cutaneous inflammation, such preparations should be avoided.

Bibliography is available at Expert Consult.

There are no laboratory studies to help identify foods responsible for cell-mediated reactions. Consequently, elimination diets followed by food challenges are the only way to establish the diagnosis. Allergists experienced in dealing with food allergic reactions and able to treat anaphylaxis should perform food challenges. Before a food challenge is initiated, the suspected food should be eliminated from the diet for 10-14 days for IgE-mediated food allergy and up to 8 wk for some cell-mediated disorders, such as EoE. Some children with cell-mediated reactions to cow’s milk do not tolerate hydrolysate formulas and must receive amino acid–derived formulas. If symptoms remain unchanged despite appropriate elimination diets, it is unlikely that food allergy is responsible for the child’s disorder.

**TREATMENT**

Appropriate identification and elimination of foods responsible for food hypersensitivity reactions are the only validated treatments for food allergies. Complete elimination of common foods (milk, egg, soy, wheat, rice, chicken, fish, peanut, nuts) is very difficult because of their widespread use in a variety of processed foods. The lay organization Food Allergy Research and Education (FARE, www.foodallergy.org) provides excellent information to help parents deal with both the practical and emotional issues surrounding these diets. Validated educational materials are also available through the Consortium of Food Allergy Research (www.cofargroup.org). Children with asthma and IgE-mediated food allergy, peanut or nut allergy, or a history of a previous severe reaction should be given self-injectable epinephrine and a written emergency plan in case of accidental ingestion (see Chapter 149). Because many food allergies are outgrown, children should be reevaluated periodically by an allergist to determine whether they have lost their clinical reactivity. A number of clinical trials are beginning to evaluate the efficacy of oral, sublingual, and epicutaneous (patch) immunotherapy for the treatment of IgE-mediated food allergies (milk, egg, peanut). Combining oral immunotherapy with anti-IgE treatment (omalizumab) may be even more effective than oral immunotherapy alone. Furthermore, extensively heated milk or egg in baked products are tolerated by the majority of milk and egg allergic children. Regular ingestion of baked products with milk and egg appears to accelerate resolution of milk and egg allergy. Management of egg-allergic children who require immunizations is noted in Table 151-8.

**PREVENTION**

There is no consensus as to whether food allergies can be prevented. At present there is insufficient evidence to support the practice of restricting the maternal diet during pregnancy or breastfeeding or of delaying introduction of various allergenic foods to infants from atopic families (see Table 151-4). Exclusive breastfeeding for the first 4-6 mo of life may reduce allergic disorders in the first few years of life in infants at high risk for development of allergic disease. Potentially allergenic foods (eggs, milk, wheat, soy, peanut and tree nut products, fish) should be introduced after this period of exclusive breastfeeding and may prevent the development of allergies later in life. Use of partially hydrolyzed whey formulas may be beneficial if breast feeding cannot be continued for 4-6 mo or after weaning, especially to prevent eczema in high risk families, but his approach remains controversial. Probiotic supplements may also reduce the incidence and severity of eczema. Because some skin preparations contain peanut oil, which may sensitize young infants, especially those with cutaneous inflammation, such preparations should be avoided.

Bibliography is available at Expert Consult.

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**Table 151-8 ACIP and AAP Red Book Recommendations for Administering Vaccines to Patients with Egg Allergy**

<table>
<thead>
<tr>
<th>VACCINE</th>
<th>ACIP</th>
<th>AAP RED BOOK</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMR/MMRV</td>
<td>May be used</td>
<td>May be used</td>
</tr>
<tr>
<td>Influenza</td>
<td>Receive with some precautions*</td>
<td>Receive with some precautions*</td>
</tr>
<tr>
<td>Rabies</td>
<td>Use caution</td>
<td>No specific recommendation</td>
</tr>
<tr>
<td>Yellow fever</td>
<td>Contraindicated, but desensitization protocols may be followed to administer vaccine if necessary (citing PI)</td>
<td>Contraindicated, but desensitization protocols may be followed to administer vaccine if necessary (citing PI)</td>
</tr>
</tbody>
</table>

AAP, American Academy of Pediatrics; ACIP, Advisory Committee on Immunization Practices.


*In 2012, recommendations changed to suggest those with mild egg allergy receive the inactivated influenza vaccine in the primary care setting with a 30 minute observation and preparedness to treat anaphylaxis. Those with severe egg allergy are referred to an allergist.
Adverse drug reactions can be divided into predictable (type A) and unpredictable reactions (type B). Predictable drug reactions, including drug toxicity, drug interactions, and adverse effects, are dose dependent, can be related to known pharmacologic actions of the drug, and occur in patients without any unique susceptibility. Unpredictable drug reactions are dose independent, often are not related to the pharmacologic actions of the drug, and occur in patients who are genetically predisposed. These include idiosyncratic reactions, allergic (hypersensitivity) reactions, and pseudoallergic reactions. Allergic reactions require prior sensitization, manifest as signs or symptoms characteristic of an underlying allergic mechanism such as anaphylaxis or urticaria, and occur in genetically susceptible individuals. They can occur at doses significantly below the therapeutic range. Pseudoallergic reactions resemble allergic reactions but are caused by non–immunoglobulin (Ig) E-mediated release of mediators from mast cells and basophils. Drug-independent cross-reactive antigens can induce sensitization manifesting as drug allergy. Patients with cetuximab-induced anaphylaxis have IgE antibodies in pretreatment samples specific for galactose-\(\alpha\)-1,3-galactose. Galactose-\(\alpha\)-1,3-galactose is present on the antigen-binding portion of the cetuximab heavy chain and is similar to structures in the ABO blood group.
Table 152-1 | Heterogeneity of Drug-Induced Allergic Reactions

<table>
<thead>
<tr>
<th>ORGAN-SPECIFIC REACTIONS</th>
<th>CLINICAL FEATURES</th>
<th>EXAMPLES OF CAUSATIVE AGENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CUTANEOUS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exanthems</td>
<td>Diffuse fine macules and papules evolve over days after drug initiation</td>
<td>Allopurinol, aminopenicillins, cephalosporins, antiepileptic agents, and antibacterial sulfonamides</td>
</tr>
<tr>
<td></td>
<td>Delayed-type hypersensitivity</td>
<td></td>
</tr>
<tr>
<td>Urticaria, angioedema</td>
<td>Onset within minutes of drug initiation</td>
<td>IgE mediated: β-lactam antibiotics</td>
</tr>
<tr>
<td></td>
<td>Potential for anaphylaxis</td>
<td>Bradykinin mediated: ACEI</td>
</tr>
<tr>
<td>Fixed drug eruption</td>
<td>Often IgE mediated</td>
<td>Tetracycline, NSAIDs, and carbamazepine</td>
</tr>
<tr>
<td></td>
<td>Hyperpigmented plaques</td>
<td></td>
</tr>
<tr>
<td>Pustules</td>
<td>Acneform</td>
<td>Acneform: corticosteroids, sirolimus</td>
</tr>
<tr>
<td></td>
<td>Acute generalized eczematous pustulosis (AGEP)</td>
<td></td>
</tr>
<tr>
<td>Bullous</td>
<td>Tense blisters</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Flaccid blisters</td>
<td></td>
</tr>
<tr>
<td>SJS</td>
<td>Fever, erosive stomatitis, ocular involvement, purpuric macules on face and trunk with &lt;10% epidermal detachment</td>
<td>Antibacterial sulfonamides, anticonvulsants, oxicam NSAIDs, and allopurinol</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TEN</td>
<td>Similar features as SJS but &gt;30% epidermal detachment Mortality as high as 50%</td>
<td>Same as SJS</td>
</tr>
<tr>
<td>Cutaneous lupus</td>
<td>Erythematous/scaly plaques in photodistribution</td>
<td>Hydrochlorothiazide, calcium-channel blockers, ACEIs</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hematologic</td>
<td>Hemolytic anemia, thrombocytopenia, granulocytopenia</td>
<td></td>
</tr>
<tr>
<td>Hepatic</td>
<td>Hepatitis, cholestatic jaundice</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary</td>
<td>Pneumonitis, fibrosis</td>
<td></td>
</tr>
<tr>
<td>Renal</td>
<td>Interstitial nephritis, membranous glomerulonephritis</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>MULTIORGAN REACTIONS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anaphylaxis</td>
<td>Urticaria/angioedema, bronchospasm, gastrointestinal symptoms, hypotension IgE- and non–IgE-dependent reactions</td>
<td>β-Lactam antibiotics, monoclonal antibodies</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DRESS</td>
<td>Cutaneous eruption, fever, eosinophilia, hepatic dysfunction, lymphadenopathy</td>
<td>Anticonvulsants, sulfonamides, minocycline, allopurinol</td>
</tr>
<tr>
<td>Serum sickness</td>
<td>Urticaria, arthralgias, fever</td>
<td>Heterologous antibodies, infliximab</td>
</tr>
<tr>
<td>Systemic lupus erythematosus</td>
<td>Arthralgias, myalgias, fever, malaise</td>
<td>Hydralazine, procainamide, isoniazid</td>
</tr>
<tr>
<td>Vasculitis</td>
<td>Cutaneous or visceral vasculitis</td>
<td>Hydralazine, penicillamine, propylthiouracil</td>
</tr>
</tbody>
</table>

ACEI, angiotensin-converting enzyme inhibitor; DRESS, drug rash with eosinophilia and systemic symptoms; NSAID, nonsteroidal antiinflammatory drug (NSAID); SJS, Stevens-Johnson syndrome.

From Khan DA, Solensky R: Drug allergy, J Allergy Clin Immunol 125:S126–S137, 2010 (Table 1, p. S127).

EPIDEMIOLOGY

The incidence of adverse drug reactions in the general as well as pediatric populations remains unknown, although data from hospitalized patients show it to be 6.7%, with a 0.32% incidence of fatal adverse drug reactions. Databases such as the FDA MedWatch program (http://www.fda.gov/medwatch/index.html) likely suffer from underreporting. Cutaneous reactions are the most common form of adverse drug reactions, with ampicillin, amoxicillin, penicillin, and trimethoprim-sulfamethoxazole being the most commonly implicated drugs (Tables 152-1 and 152-2). Although the majority of adverse drug reactions do not appear to be allergic in nature, 6-10% can be attributed to an allergic or immunologic mechanism. Importantly, given the high probability of recurrence of allergic reactions, these reactions should be preventable, and information technology–based interventions may be especially useful to reduce risk of reexposure.

PATHOGENESIS AND CLINICAL MANIFESTATIONS

Immunologically mediated adverse drug reactions have been classified according to the Gell and Coombs classification: immediate hypersensitivity reactions (type I), cytotoxic antibody reactions (type II), immune complex reactions (type III), and delayed-type hypersensitivity reactions (type IV). Immediate hypersensitivity reactions occur when a drug or drug metabolite interacts with preformed drug-specific IgE antibodies that are bound to the surfaces of tissue mast cells and/or circulating basophils. The cross-linking of adjacent receptor-bound IgE by antigen causes the release of preformed and newly synthesized mediators, such as histamine and leukotrienes, that contribute to the clinical development of urticaria, bronchospasms, or anaphylaxis. Cytotoxic reactions involve IgG or IgM antibodies that recognize drug antigen on the cell membrane. In the presence of serum complement, the antibody-coated cell is either cleared by the monocyte–macrophage system or is destroyed. Examples are drug-induced hemolytic anemia and thrombocytopenia. Immune complex reactions are caused by soluble complexes of drug or metabolite in slight antigen excess with IgG or IgM antibodies. The immune complex is deposited in blood vessel walls and causes injury by activating the complement cascade, as seen in serum sickness. Clinical manifestations include fever, urticaria, rash, lymphadenopathy, and arthralgias. Symptoms typically appear 1-3 wk after the last dose of an offending drug and subside when the drug and/or its metabolite is cleared from the body. Delayed-type hypersensitivity reactions are mediated by drug-specific T lymphocytes. Sensitization usually occurs via the topical route of administration, resulting in allergic contact dermatitis. Commonly implicated drugs include neomycin and local anesthetics in topical formulations.

Certain adverse drug reactions, including drug fever and the morbilliform rash seen with use of ampicillin or amoxicillin in the setting of Epstein-Barr virus infection, are not easily classified. Studies point to the role of T cells and eosinophils in delayed maculopapular reactions to a number of antibiotics. The mechanisms of T-cell–mediated drug hypersensitivity are not well understood. A novel hypothesis, the p-i concept, suggests pharmacologic interactions of drugs with immune receptors as another class of drug hypersensitivity. In T-cell–mediated
### Table 152-2  Serious Non–IgE-Mediated Drug Eruptions

<table>
<thead>
<tr>
<th>DIAGNOSIS</th>
<th>MUCOSAL LESIONS</th>
<th>TYPICAL SKIN LESIONS</th>
<th>PRODROMAL SIGNS AND SYMPTOMS</th>
<th>DRUG ASSOCIATED (%)</th>
<th>DRUGS MOST OFTEN IMPLICATED</th>
<th>TYPICAL TIME TO ONSET (wk)</th>
<th>ALTERNATIVE CAUSES NOT RELATED TO DRUGS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug hypersensitivity syndrome (DHS) or drug rash with eosinophilia and</td>
<td>Infrequent</td>
<td>Severe exanthematous</td>
<td>30-50% involve fever,</td>
<td>≥90</td>
<td>Phenytoin, carbamazepine, phenobarbital, sulfonamides, allopurinol, minocycline, nitrofurantoin,</td>
<td>1-6</td>
<td>Cutaneous lymphoma</td>
</tr>
<tr>
<td>systemic symptoms (DRESS) syndrome</td>
<td>rash (could become edematous, pustular, purpuric), exfoliative dermatitis</td>
<td>rash</td>
<td>lymphadenopathy, hepatitis, nephritis, carditis, eosinophilia, atypical lymphocytes</td>
<td></td>
<td>terbinafine, vancomycin, dapsone, abacavir, nevirapine, nonsteroidal antiinflammatory drugs (NSAIDs)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stevens-Johnson syndrome (SJS)</td>
<td>Erosions at ≥2 sites</td>
<td>Crops of lesions on skin, conjunctivae, mouth, and genitalia; detachment of ≤10% of body surface area</td>
<td>High fever, sore throat, rhinorrhea, cough</td>
<td>48-64</td>
<td>Sulfonamides, phenytoin, carbamazepine, barbiturates, allopurinol, aminopenicillins, NSAIDs</td>
<td>1-3</td>
<td></td>
</tr>
<tr>
<td>Toxic epidermal necrolysis (TEN)</td>
<td>Erosions at ≥2 sites</td>
<td>Lesions similar to those with SJS; confluent epidermis separates readily with lateral pressure; detachment of ≥30% of body surface area</td>
<td>Fever, headache, sore throat; nearly all cases involve fever, “acute skin failure,” leukopenia, lesions of the respiratory and/or gastrointestinal tracts</td>
<td>43-65</td>
<td>Sulfonamides, phenytoin, carbamazepine, barbiturates, allopurinol, aminopenicillins, NSAIDs</td>
<td>1-3</td>
<td>Exanthematous stage of Kawasaki disease; staphylococcal scalded-skin syndrome</td>
</tr>
</tbody>
</table>

Drug Metabolism and Adverse Reactions

Most drugs and their metabolites are not immunologically detectable until they have become covalently attached to a macromolecule. This multivalent hapten–protein complex forms a new immunogenic epitope that can elicit T- and B-lymphocyte responses. The penicillins and related β-lactam antibiotics are highly reactive with proteins and can directly haptenate protein carriers, possibly accounting for the frequency of immune-mediated hypersensitivity reactions with this class of antibiotics.

Incomplete or delayed metabolism of some drugs can give rise to toxic metabolites. Hydroxylamine, a reactive metabolite produced by cytochrome P450 oxidative metabolism, may mediate adverse reactions to sulfonamides. Patients who are slow acetylators appear to be at increased risk (see Chapter 59). In addition, cutaneous reactions in patients with AIDS treated with trimethoprim-sulfamethoxazole, rifampin, or other drugs may be a result of glutathione deficiency resulting in toxic metabolites. Serum sickness–like reactions in which immune complexes have not been documented, which occur most commonly with cefaclor, may result from an inherited propensity for hepatic biotransformation of drugs into toxic or immunogenic metabolites.

Risk Factors for Hypersensitivity Reactions

Risk factors for adverse drug reactions include prior exposure, previous reactions, age (20-49 yr), route of administration (parenteral or topical), dose (high), and dosing schedule (intermittent), as well as genetic predisposition (slow acetylators). Atopy does not appear to predispose patients to allergic reactions to low-molecular-weight compounds, but atopic patients in whom an allergic reaction develops have a significantly increased risk of serious reaction. Atopic patients also appear to be at greater risk for pseudoallergic reactions induced by radiographic media. Pharmacogenomics has an important role in identifying individuals at risk for certain drug reactions (see Chapter 59).

DIAGNOSIS

An accurate medical history is an important first step in evaluating a patient with a possible adverse drug reaction. Suspected drugs need to be identified along with dosages, route of administration, previous exposures, and dates of administration. In addition, underlying hepatic or renal disease may influence drug metabolism. A detailed description of past reactions may yield clues to the nature of the adverse drug reaction. The propensity for a particular drug to cause the suspected reaction can be checked with information in Physicians' Desk Reference, Drug Eruption Reference Manual, or directly from the drug manufacturer. It is important to remember, however, that the history may be unreliable, and many patients are inappropriately labeled as being drug allergic. This label can result in inappropriate withholding of a needed drug or class of drugs. In addition, relying solely on the history can lead to overuse of drugs reserved for special indications, such as vancomycin in patients in whom penicillin allergy is suspected. Approximately 90% of patients with a clinical history of penicillin allergy do not have evidence of penicillin-specific IgE antibodies on testing.

Skin testing is the most rapid and sensitive method of demonstrating the presence of IgE antibodies to a specific allergen. It can be performed with high-molecular-weight compounds, such as foreign antisera, hormones, enzymes, and toxins. Reliable skin testing can also be performed with penicillin, but not with most other antibiotics. Most immunologically mediated adverse drug reactions are caused by metabolites rather than by parent compounds, and the metabolites for most drugs other than penicillin have not been defined. In addition, many metabolites are unstable or must combine with larger proteins to be useful for diagnosis. Testing with nonstandardized reagents requires caution in interpretation of both positive and negative results, because some drugs can induce nonspecific irritant reactions. Whereas a wheal-and-flare reaction is suggestive of drug-specific IgE antibodies, a negative skin test result does not exclude the presence of such antibodies because the relevant immunogen may not have been used as the testing reagent.

A positive skin test response to the major or minor determinants of penicillin has a 60% positive predictive value for an immediate hypersensitivity reaction to penicillin. In patients in whom skin test responses to the major and minor determinants of penicillin are negative, 97-99% (depending on the reagents used) tolerate the drug without an immediate reaction. At present, the major determinant of penicillin testing reagent PrePen (benzylpenicilloyl-polylysine) in the United States is available, but the minor determinant mixture has not been approved by the FDA as a testing reagent. Limited studies utilizing serum tests for IgE to β-lactams suggest high specificity (97-100%) but low sensitivity (29-68%). The positive and negative predictive values of skin testing for antibiotics other than penicillin are not well established. Nevertheless, positive immediate hypersensitivity skin test responses to nonirritant concentrations of nonpenicillin antibiotics may be interpreted as a presumptive risk of an immediate reaction to such agents.

Results of direct and indirect Coombs tests are often positive in drug-induced hemolytic anemia. Assays for specific IgG and IgM have been shown to correlate with a drug reaction in immune cytopenia, but, in most other reactions, such assays are not diagnostic. In general, many more patients express humoral or T-cell immune responses to drug determinants than express clinical disease. Serum tryptase is elevated with systemic mast cell degranulation and can be seen with drug-associated mast cell activation, although it is not pathognomonic for drug hypersensitivity, and nonelevated tryptase values can be seen in well-defined anaphylaxis.

TREATMENT

Specific desensitization, which involves the progressive administration of an allergen to render effector cells less reactive, is reserved for patients with IgE antibodies to a particular drug for whom an alternative drug is not available or appropriate. Specific protocols for many different drugs have been developed. Desensitization should be performed in a hospital setting, usually in consultation with an allergist and with resuscitation equipment available at all times. Although mild complications, such as pruritus and rash, are fairly common and often respond to adjustments in the drug dose or dosing intervals and medications to relieve symptoms, more severe systemic reactions can occur. Oral desensitization may be less likely to induce anaphylaxis than parenteral administration. Pretreatment with antihistamines or corticosteroids is not usually recommended. It is important to recognize that desensitization to a drug is effective only while the drug continues to be administered and that after a period of interruption or discontinuation, hypersensitivity can recur.

Graded challenges based on the administration of a drug in an incremental fashion until a therapeutic dose is achieved can be attempted with drugs causing non-IgE-mediated reactions, including trimethoprim-sulfamethoxazole. Graded challenges in aspirin- or nonsteroidal antiinflammatory drug (NSAID)–intolerant patients, particularly those with respiratory reactions, can also be performed. Patients with severe non–IgE-mediated hypersensitivity reactions should not receive the predisposing agents even in the small amounts used for skin testing (see Table 152-2).

β-Lactam Hypersensitivity

Penicillin is a frequent cause of anaphylaxis and is responsible for the majority of all drug-mediated anaphylactic deaths in the United States.
Although IgE-mediated reactions may occur after administration of penicillin by any route, parenteral administration is more likely to cause anaphylaxis. If a patient requires penicillin and has a previous history suggestive of penicillin allergy, it is necessary to perform skin tests on the patient for the presence of penicillin-specific IgE, ideally with both the major and minor determinants of penicillin. Skin tests for minor determinants of penicillin are important because approximately 20% of patients with documented anaphylaxis do not demonstrate skin reactivity to the major determinant. The major determinant is commercially available (Pre-Pen). The minor determinant mixture is currently not licensed and is synthesized as a nonstandardized testing reagent at select academic centers. Penicillin G is often used as a substitute for the minor determinant mixture, and may have negative predictive value similar to testing with major and minor determinants. Patients should be referred to an allergist capable of performing appropriate testing. If the skin test response is positive to either major or minor determinants of penicillin, the patient should receive an alternative non–cross-reacting antibiotic. If administration of penicillin is deemed necessary, desensitization can be performed by an allergist in an appropriate medical setting. Skin testing for penicillin–specific IgE is not predictive for delayed-onset cutaneous, bullous, or immune complex reactions. In addition, penicillin skin testing does not appear to desensitize the patient.

Other β-lactam antibiotics, including semisynthetic penicillins, cephapslorins, carbacephems, and carbapenems, share the β-lactam ring structure. Patients with late-onset morbilliform rashes with amoxicillin are not considered to be at risk for IgE-mediated reactions to penicillin and do not require skin testing before penicillin administration. Many patients with Epstein–Barr virus infections treated with ampicillin or amoxicillin can experience a nonurticarial rash. Similar reactions occur in patients who receive allopurinol as treatment for elevated uric acid or have chronic lymphocytic leukemia. If the rash to ampicillin or amoxicillin is urticarial or systemic or the history is unclear, the patient should undergo penicillin skin testing if a penicillin is needed. There have been reports of antibodies specific for semisynthetic penicillin side chains in the absence of β-lactam ring–specific antibodies, although the clinical significance of such side chain–specific antibodies is unclear.

Varying degrees of in vitro cross-reactivity have been documented between cephalosporins and penicillins. Although the risk of allergic reactions to cephalosporins in patients with positive skin test responses to penicillin appears to be low (<2%), anaphylactic reactions have occurred after administration of cephalosporins in patients with a history of penicillin anaphylaxis. If a patient has a history of penicillin allergy and requires a cephalosporin, skin testing for major and minor determinants of penicillin should preferably be performed to determine whether the patient has penicillin-specific IgE antibodies. If skin test results are negative, the patient can receive a cephalosporin with no greater risk than found in the general population. If skin test results are positive for penicillin, recommendations may include: administration of an alternative antibiotic; cautious graded challenge with appropriate monitoring, with the recognition that there is a 2% chance of inducing an anaphylactic reaction; and desensitization to the required cephalosporin. Cross-reactivity is most likely when the cephalosporin shares the same side chain as the penicillin (Table 152-3).

Conversely, patients who require penicillin and have a history of an IgE-mediated reaction to a cephalosporin should also undergo penicillin skin testing. Patients with a negative result can receive penicillin. Patients with a positive result should either receive an alternative medication or undergo desensitization to penicillin. In patients with a history of allergic reaction to one cephalosporin who require another cephalosporin, skin testing with the required cephalosporin can be performed, with the recognition that the negative predictive value of such testing is unknown. If the skin test response to the cephalosporin is positive, the significance of the test should be checked further in control subjects to determine whether the positive response is IgE-mediated or an irritant response. The drug can then be administered by graded challenge or desensitization.

Carbapenems (imipenem, meropenem) represent another class of β-lactam antibiotics with a bicyclic nucleus that demonstrate a high degree of cross-reactivity with penicillins, although prospective studies suggest incidence of cross-reactivity on skin testing of approximately 1%. In contrast to β-lactam antibiotics, monobactams (aztreonam) have a monocyclic ring structure. Aztreonam-specific antibodies have been shown to be predominantly side chain–specific; data suggest that aztreonam can be safely administered to most penicillin-allergic subjects. On the other hand, administration of aztreonam to a patient with cefazidime allergy may be associated with increased risk of allergic reaction owing to similarity of side chains.

### Sulfonamides

The most common type of reaction to sulfonamides is a maculopapular eruption often associated with fever that occurs after 7–12 days of therapy. Immediate reactions, including anaphylaxis, as well as other immunologic reactions, have also been suggested. Hypersensitivity reactions to sulfonamides occur with much greater frequency in HIV-infected individuals. For patients in whom maculopapular rashes develop after sulfonamide administration, both graded challenge and desensitization protocols have been shown to be effective. These regimens should not be used in individuals with a history of Stevens–Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN). Hyper-sensitivity reactions to sulfasalazine used for treatment of inflammatory bowel disease appear to result from the sulfapyridine moiety. Slow desensitization over ~1 mo permits tolerance of the drug in many patients. In addition, oral and enema forms of 5-aminosalicylic acid, thought to be the pharmacologically active agent in sulfasalazine, are effective alternative therapies.

### Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis

Blistering mucocutaneous disorders induced by drugs encompass a spectrum of reactions, including SJS and TEN (see Chapters 654.2 and 654.3). Epidermal detachment of <10% is suggestive of SJS, 30% detachment suggests TEN, and 10-30% detachment suggests overlap of the 2 syndromes. The features of SJS include confluent purpuric macules on face and trunk and severe, explosive mucosal erosions, usually at more than 1 mucosal surface, accompanied by fever and constitutional symptoms. Ocular involvement may be particularly severe, and the liver, kidneys, and lungs may also be involved. TEN, which appears to be related to keratinocyte apoptosis, manifests as

<table>
<thead>
<tr>
<th>Table 152-3</th>
<th>Groups of β-Lactam Antibiotics That Share Identical R1-Group Side Chains*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amoxicillin</td>
<td>Ampicillin, Ceftriaxone, Cefoxitin, Cefamandole, Ceftazidime</td>
</tr>
<tr>
<td>Cefadroxil</td>
<td>Cefaclor, Cefotaxime, Cephapslorin, Cefodroxime, Cefalothin</td>
</tr>
<tr>
<td>Cefprozil</td>
<td>Cephalexin, Cepodoxime, Ceftriaxone, Cefotaxime, Cefalothin</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>Cephapslorin, Cefotaxime, Cefotrizine, Ceftriaxone, Cefalothin</td>
</tr>
<tr>
<td>Loracarbef</td>
<td>Cephaloglycin, Cefditoren, Cefizoxime, Cefmenoxime</td>
</tr>
</tbody>
</table>

*Each column represents a group with identical R1 side chains.

widespread areas of confluent erythema followed by epidermal necrosis and detachment with severe mucosal involvement. The risk of infection and mortality are high. Skin biopsy differentiates subepidermal cleavage characteristic of TEN from intraepidermal cleavage characteristic of the scalded-skin syndrome induced by staphylococcal toxins. TEN must be treated in a burn unit. Corticosteroids are contraindicated because they can significantly increase the risk of infection. High intravenous doses of immunoglobulin have been shown to be beneficial in patients with TEN, likely because of inhibition of Fas-mediated keratinocyte cell death by naturally occurring Fas-blocking antibodies in the intravenous immunoglobulin preparation.

Hypersensitivity to Antiretroviral Agents
A growing number of adverse drug reactions have been observed with antiretroviral agents, including reverse transcriptase inhibitors, protease inhibitors, and fusion inhibitors. Hypersensitivity to abacavir is a well-recognized, multorgan, potentially life-threatening reaction that occurs in HIV-infected children. The reaction is independent of dose, with onset generally within 9–11 days of initiation of drug therapy. Rechallenge can be accompanied by significant hypotension and potential mortality (rate of 0.03%), and thus hypersensitivity to abacavir is an absolute contraindication for any subsequent use. Prophylaxis with prednisolone does not appear to prevent hypersensitivity reactions to abacavir. Importantly, genetic susceptibility appears to be conferred by the HLA-B*5701 allele, with a positive predictive value of >70% and a negative predictive value of 95–98%. Genetic screening would be cost-effective in white populations but not in populations of African or Asian descent, in which HLA-B*5701 allele frequency is <1%.

Chemotherapeutic Agents
Hypersensitivity reactions to chemotherapeutic drugs have been described, including to monoclonal antibodies. Rapid desensitization to a variety of unrelated agents, including carboplatin, paclitaxel, and rituximab, can be safely achieved in a 12-step protocol. Of note, this approach appears to be successful in both IgE-mediated and non–IgE-mediated reactions.

Biologics
An increasing number of biologic agents have become available for the treatment of autoimmune, allergic, cardiovascular, infectious, and neoplastic diseases. Their use may be associated with a variety of adverse reactions, including hypersensitivity reactions. Given the occurrence of anaphylaxis, including cases with delayed onset and protracted progression in spontaneous postmarketing adverse event reports, the FDA issued a boxed warning regarding risk of anaphylaxis and need for patient monitoring with use of omalizumab (see Chapter 144).

Vaccines
Measles-mumps-rubella vaccine has been shown to be safe in egg-allergic patients (although rare reactions to gelatin or neomycin can occur). The ovalbumin content in influenza vaccine is generally low and the majority of egg-allergic patients tolerate the vaccine. Skin testing with the influenza vaccine is not recommended for egg-allergic patients, but may be helpful if allergy to the vaccine itself is suspected. Egg-allergic patients should be given the injectable, not the live intranasal vaccine and be observed for 30 min after vaccination, in a setting prepared to treat anaphylaxis. For those with egg-allergic reactions resulting in more than urticaria, administration by an allergist is recommended.

Perioperative Agents
Anaphylactoid (non–IgE-mediated anaphylaxis) reactions occurring during general anesthesia may be caused by induction agents (thiopental) or muscle-relaxing agents (suxamethonium, pancuronium). Quaternary ammonium muscle relaxants (suxamethonium) can act as bivalent antigens in IgE-mediated reactions. Negative skin test results do not necessarily predict that a drug will be tolerated. Latex allergy should always be considered in the differential diagnosis of a perioperative reaction.

Local Anesthetics
Adverse drug reactions associated with local anesthetic agents are primarily toxic reactions resulting from rapid drug absorption, inadvertent intravenous injection, or overdose. Local anesthetics are classified as esters of benzoic acid (group I) or amides (group II). Group I includes benzocaine and procaine; group II includes lidocaine, bupivacaine, and mepivacaine. In suspected local anesthetic allergy, skin testing followed by a graded challenge can be performed or an anesthetic agent from a different group can be used.

Insulin
Insulin use has been associated with a spectrum of adverse drug reactions, including local and systemic IgE-mediated reactions, hemolytic anemia, serum sickness reactions, and delayed-type hypersensitivity. In general, human insulin is less allergic than porcine insulin, which is less allergic than bovine insulin, but for individual patients, porcine or bovine insulin may be the least allergic. Patients treated with nonhuman insulin have had systemic reactions to recombinant human insulin even on the first exposure. More than 50% of patients who receive insulin develop antibodies against the insulin preparation, although there may not be any clinical manifestations. Local cutaneous reactions usually do not require treatment and resolve with continued insulin administration, possibly owing to IgG-blocking antibodies. More severe local reactions can be treated with antihistamines or by splitting the insulin dose between separate administration sites. Local reactions to the protamine component of neutral protamine Hagedorn insulin may be avoided by switching to Lente insulin. Immediate-type reactions to insulin, including urticaria and anaphylactic shock, are unusual and almost always occur after reintroduction of insulin therapy in sensitized patients. Insulin therapy should not be interrupted if a systemic reaction to insulin occurs and continued insulin therapy is essential. Skin testing may identify a less-antigenic insulin preparation. The dose following a systemic reaction is usually reduced to one-third, and successive doses are increased in 2–5 unit increments until the dose resulting in glucose control is attained. Insulin skin testing and desensitization are required if insulin treatment is subsequently interrupted for more than 24-48 hr. Immunologic resistance usually occurs when high titters of predominately IgG antibodies to insulin develop. A rare form of insulin resistance caused by circulating antibodies to tissue insulin receptors is associated with acanthosis nigricans and lipodystrophy. Coexisting insulin allergy may be present in up to a third of patients with insulin resistance. Approximately half of affected patients benefit from substitution with a less-reactive insulin preparation, based on skin testing.

Drug-Induced Hypersensitivity Syndrome
Drug-induced hypersensitivity syndrome, also referred to as DRESS (drug rash with eosinophilia and systemic symptoms) syndrome, is a potentially life-threatening syndrome that has been described primarily with anticonvulsants, although many other medications have been implicated (see Tables 152-1 and 152-2). It is characterized by fever, maculopapular rash, facial edema, eosinophilia, generalized lymphadenopathy, and potentially life-threatening damage of 1 or more organs, usually renal or hepatic. Onset is delayed, usually weeks after initiation of the medication. It has been associated with reactivation of human herpesvirus 6. Treatment is withdrawal of the medication, systemic steroids, and supportive care, but symptoms can worsen or persist for weeks to months after the drug has been discontinued.

Red Man Syndrome
Red man syndrome is caused by nonspecific histamine release and is most commonly described with administration of intravenous vancomycin. It can be prevented by slowing the vancomycin infusion rate or by predimension of H1-blockers.

Radiocontrast Media
Anaphylactoid reactions to radiocontrast media or dye can occur after intravascular administration and during myelograms or retrograde pyelograms. No single pathogenic mechanism has been defined, but it
is likely that mast cell activation accounts for the majority of these reactions. Complement activation has also been described. There is no evidence that sensitivity to seafood or iodine predisposes to radiocontrast media reactions. Predictive tests are not available. Patients who have atopic profiles, who are using β-blockers, and who have had prior anaphylactoid reactions are at increased risk. Other diagnostic alternatives should be considered, or patients can be given low-osmolality radiocontrast media with a pretreatment regimen including oral prednisone, diphenhydramine, and albuterol, with or without cimetidine or ranitidine.

**Narcotic Analgesics**

Opiates such as morphine and related narcotics can induce direct mast cell degranulation. Patients may experience generalized pruritus, urticaria, and occasionally, wheezing. If there is a suggestive history and analgesia is required, a nonnarcotic medication should be considered.

If this intervention does not control pain, graded challenge with an alternative opiate is an option.

**Aspirin and Nonsteroidal Antiinflammatory Drugs**

Aspirin and NSAIDs can cause anaphylactoid reactions or urticaria and/or angioedema in children, and, rarely, asthma with or without rhinoconjunctivitis in adolescents. There is no skin or in vitro test to identify patients who may react to aspirin or other NSAIDs. Once aspirin or NSAID intolerance has been established, options include avoidance and pharmacologic desensitization and subsequent continued treatment with aspirin or NSAIDs, if indicated. A number of studies suggest that cyclooxygenase-2 inhibitors are tolerated by the majority of patients with NSAID-induced adverse reactions.

*Bibliography is available at Expert Consult.*
Bibliography
Joint Task Force on Practice Parameters; American Academy of Allergy, Asthma and Immunology; American College of Allergy, Asthma, and Immunology; Joint Council of Allergy, Asthma and Immunology: Drug allergy: an updated practice parameter, Ann Allergy Asthma Immunol 105:259–273, 2010.
Rheumatic diseases are defined by the constellation of results of the physical examination, autoimmune marker and other serologic tests, tissue pathology, and imaging. Defined diagnostic criteria exist for most rheumatic diseases. Recognition of clinical patterns remains essential for diagnosis because there is no single diagnostic test and results may be positive in the absence of disease. Further complicating the diagnosis, children sometimes present with partial criteria that evolve over time or with features of more than one rheumatic disease (overlap syndromes). The primary mimics of rheumatic diseases are infection and malignancy but also include metabolic, orthopedic, and chronic pain conditions. Exclusion of possible mimicking disorders is essential before initiation of treatment for a presumptive diagnosis, especially corticosteroids. After careful evaluation has excluded nonrheumatic causes, referral to a pediatric rheumatologist for confirmation of the diagnosis and treatment should be considered.

**SYMPTOMS SUGGESTIVE OF RHEUMATIC DISEASE**

There are no classic symptoms of a rheumatic disease, but common symptoms include joint pain, fever, fatigue, and rash. Presenting signs and symptoms help direct the evaluation and limit unnecessary testing. Once a differential diagnosis is developed on the basis of history and physical findings, a directed assessment assists in determining the diagnosis.

Arthralgias are common in childhood and are a frequent reason for referral to pediatric rheumatologists. Arthralgias without physical findings for arthritis suggest infection, malignancy, orthopedic conditions, benign syndromes, or pain syndromes such as fibromyalgia (Table 153-1). Although rheumatic diseases may manifest as arthralgias, arthritis is a stronger predictor of the presence of rheumatic disease and a reason for referral to a pediatric rheumatologist. The timing of joint pain along with associated symptoms including poor sleep and interference with normal activities provides important clues. Poor sleep, debilitating generalized joint pain that worsens with activity, school absences, and normal physical and laboratory findings in an adolescent suggest a pain syndrome (e.g., fibromyalgia). If arthralgia is accompanied by a history of dry skin, hair loss, fatigue, growth disturbance, and/or cold intolerance, testing for thyroid disease is merited. Nighttime awakenings because of severe pain along with decreased platelet count or white blood cell count or, alternatively, a very high white blood cell count, may lead to the diagnosis of malignancy, especially marrow-occupying lesions such as acute lymphocytic leukemia and neuroblastoma. Pain with physical activity suggests a mechanical problem such as an overuse syndrome or orthopedic condition. An adolescent girl presenting with knee pain aggravated by walking up stairs and on patellar distraction likely has patellofemoral syndrome. Children ages 3 to 10 yr who have a history of episodic pain that occurs at night after increased daytime physical activity that is relieved by rubbing, but who have no limp or complaints in the morning, likely have growing pains. There is often a positive family history for growing pains, which may aid in this diagnosis. Intermittent pain in a child, especially a girl age 3 to 10 yr, that is increased with activity and is associated with hyperextensible joints on exam is likely benign hypermobility syndrome. Many febrile illnesses cause arthralgias that improve when the temperature normalizes, and arthralgias are part of the diagnostic criteria for acute rheumatic fever (ARF; see Chapter 183.1).

Arthralgia may also be a presenting symptom of pediatric systemic lupus erythematosus (SLE) and chronic childhood arthritis such as juvenile idiopathic arthritis (JIA). Interestingly, many children with JIA do not complain of joint symptoms at presentation. Other symptoms more suggestive of arthritis include morning stiffness, joint swelling, limited range of motion, pain with joint motion, gait disturbance, fever, and fatigue and/or stiffness after physical inactivity (gelling phenomenon). A diagnosis of chronic juvenile arthritis cannot be made without the finding of arthritis on physical examination (see Chapters 155 and 156), and there are no laboratory tests diagnostic of juvenile rheumatoid arthritis or any other chronic inflammatory arthritis in childhood.

Fatigue is a nonspecific symptom that may point to the presence of a rheumatic disease but is also common in nonrheumatic causes such as viral infections, pain syndromes, depression, and malignancy. Fatigue, rather than the specific complaints of muscle weakness, is a common presenting complaint in juvenile dermatomyositis (JDM). It is also commonly present in SLE, vasculitis, and the chronic childhood arthritides. Overwhelming fatigue with inability to attend school is more suggestive of chronic fatigue syndrome, pediatric fibromyalgia, or other amplified pain syndrome.

**SIGNS SUGGESTIVE OF RHEUMATIC DISEASE**

A complete physical examination is mandated in any child in whom a rheumatic disease is suspected, because many rheumatic diseases have associated subtle physical findings that will further refine the differential diagnosis. In addition, many rheumatic diseases have multisystem effects, and a stepped assessment should focus on delineating the extent of organ system involvement (e.g., skin, joints, muscle, hepatic, renal, cardiopulmonary).

Presence of a photosensitive malar rash that spares the nasolabial folds is suggestive of SLE (Table 153-2; see Fig. 158-1A), especially in an adolescent girl. Diffuse facial rash is more indicative of JDM. A hyperkeratotic rash on the face or around the ears of an adolescent African-American girl may represent discoid lupus (see Fig. 158-1D). A palpable purpuric rash on the extensor surfaces of the lower extremities points to Henoch-Schönlein purpura (see Fig. 167-1A). Less localized purpuric rashes and petechiae are present in systemic vasculitis or blood dyscrasias including coagulopathies. Nonblanching erythematous papules on the palms are seen in vasculitis and SLE. Gottron papules (see Fig. 159-2) and heliotrope rashes (see Fig. 159-1) along with erythematous rashes on the elbows and knees are pathognomonic of JDM. Dilated capillary loops in the nail beds (periungual telangiectasias; see Fig. 159-3) are common in JDM, scleroderma, and secondary Raynaud phenomenon. An evanescent macular rash associated with fever is part of the diagnostic criteria for systemic onset arthritis (see Fig. 155-12). Sun sensitivity or photosensitive rashes are indicative of SLE or JDM but can also be caused by antibiotics.

Mouth ulcers are part of the diagnostic criteria for SLE and Behçet disease (see Fig. 158-1D); painful nasal ulcers and erythematous macules on the hard palate are also common in SLE. Cartilage loss in the nose, causing a saddle nose deformity, is classically present in granulomatosis with polyangiitis (formerly Wegener granulomatosis; see Fig. 167-4) but is also seen in relapsing polychondritis and syphilis.
Alopecia can be associated with SLE but is also found in localized scleroderma (see Fig. 160-4) and JDM. Raynaud phenomenon may be a primary benign idiopathic disorder or can be a presenting complaint in the child with scleroderma, lupus, mixed connective tissue disease (MCTD), or an overlap syndrome. Diffuse lymphadenopathy is present in many rheumatic diseases, including SLE, polyarticular JIA, and systemic JIA. Irregular pupils may represent the insidious and unrecognized onset of uveitis associated with juvenile arthritis. Erythematous conjunctivitis may be a result of uveitis or episcleritis associated with juvenile rheumatoid arthritis, SLE, sarcoidosis, spondyloarthropathies, or vasculitis.

A pericardial rub and orthopnea are suggestive of pericarditis, often seen in systemic JIA, SLE, and sarcoid. Coronary artery dilatation is strongly suggestive of Kawasaki disease but may also be a finding in systemic arthritis and other forms of systemic vasculitis. Intestinal lung disease, suggested by dyspnea on exertion or the finding of basal rales with decreased carbon monoxide diffusion capacity, occurs in SLE, MCTD, and systemic sclerosis. Signs consistent with pulmonary hemorrhage points to Wegener granulomatosis, microscopic angiitis, or SLE. Pulmonary vascular aneurysms are indicative of Behçet disease.

Arthritis is defined by the presence of intraarticular swelling or 2 or more of the following findings on joint examination: pain on motion, loss of motion, erythema, and heat. Arthritis is present in all of the chronic childhood arthritis syndromes, along with SLE, JDM, vasculitis, Behçet disease, sarcoidosis, Kawasaki disease, and Henoch-Schönlein purpura. Nonrheumatic causes of arthritis include malignancy, infections such as septic arthritis, Lyme disease, osteomyelitis, viral infections (such as rubella, hepatitis B, parvovirus B19), and postinfectious etiologies such as Epstein-Barr virus, ARF, and reactive arthritis. ARF typically involves a migratory (lasting hours to days), painful arthritis. Pain on palpation of long bones is suggestive of malignancy. Specific muscle testing for weakness should be performed in a child presenting with fatigue or difficulty with daily tasks, as both of these symptoms may be manifestations of muscle inflammation.

**LABORATORY TESTING**

There are no specific screening tests for rheumatologic disease. Once a differential diagnosis is determined, appropriate testing can be performed (Tables 153-3 and 153-4). Initial studies are generally performed in standard local laboratories. Screening for specific autoantibodies can be performed in commercial laboratories, but confirmation of results in a tertiary care center immunology laboratory is often necessary.

One essential laboratory test for rheumatic disease assessment is the complete blood count, as it yields many diagnostic clues. Elevated white blood cell count is compatible with malignancy, infection, systemic JIA, and vasculitis. Leukopenia can be caused by postinfectious, especially viral, etiologies, SLE, or malignancy. Lymphopenia is more specific for SLE than is leukopenia. Platelets are acute-phase reactants and are therefore elevated with inflammatory markers.

**Table 153-1 Symptoms Suggestive of Rheumatic Disease**

<table>
<thead>
<tr>
<th>SYMPTOM</th>
<th>RHEUMATIC DISEASE(S)</th>
<th>POSSIBLE NONRHEUMATIC DISEASES CAUSING SIMILAR SYMPTOMS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fevers</td>
<td>SLE, vasculitis, acute rheumatic fever, sarcoidosis, MCTD</td>
<td>Malignancies, infections and post-infectious syndromes, inflammatory bowel disease, periodic fever (autoinflammatory) syndromes, Kawasaki disease, HSP</td>
</tr>
<tr>
<td>Arthralgias</td>
<td>JIA, SLE, rheumatic fever, JDM, vasculitis, scleroderma, sarcoidosis</td>
<td>Hypothyroidism, trauma, endocarditis, other infections, pain syndromes, growing pains, malignancies, overdose syndromes</td>
</tr>
<tr>
<td>Weakness</td>
<td>JDM, myositis secondary to SLE, MCTD, and deep localized scleroderma</td>
<td>Muscular dystrophies, metabolic and other myopathies, hypothyroidism</td>
</tr>
<tr>
<td>Chest pain</td>
<td>Juvenile rheumatoid arthritis, SLE (with associated pericarditis or costochondritis)</td>
<td>Costochondritis (isolated), rib fracture, viral pericarditis, panic attack, hyperventilation</td>
</tr>
<tr>
<td>Back pain</td>
<td>Spondylitis</td>
<td>Vertebral compression fracture, diskitis, intraspinal tumor, spondylolysis, spondylolisthesis, bone marrow–occupying malignancy, pain syndromes, osteomyelitis, muscle spasm, injury</td>
</tr>
</tbody>
</table>

**Table 153-2 Signs Suggestive of Rheumatic Disease**

<table>
<thead>
<tr>
<th>SIGN</th>
<th>RHEUMATIC DISEASES</th>
<th>COMMENTS</th>
<th>NONRHEUMATIC CAUSES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malar rash</td>
<td>SLE, JDM</td>
<td>SLE classically spares nasolabial folds</td>
<td>Sunburn, parvovirus B19 (fifth disease), Kawasaki disease</td>
</tr>
<tr>
<td>Oral ulcers</td>
<td>SLE, Behçet disease</td>
<td>Behçet disease also associated with genital ulcers</td>
<td>HSV infection, PFAPA syndrome</td>
</tr>
<tr>
<td>Purpuric rash</td>
<td>Vasculitis, e.g., ANCA-associated vasculitis, HSP</td>
<td>HSP typically starts as small lesions on lower extremities and buttocks that coalesce</td>
<td>Meningococcemia, thrombocytopenia, clotting disorders</td>
</tr>
<tr>
<td>Gottron papules</td>
<td>JDM</td>
<td>Look for associated heliotrope rash, periungual telangiectasias</td>
<td>Psoriasis, eczema</td>
</tr>
<tr>
<td>Arthritis</td>
<td>Juvenile idiopathic arthritis, SLE, vasculitis, HSP, MCTD, scleroderma, acute rheumatic fever, reactive arthritis</td>
<td>Chronic joint swelling (&gt;6 wk) required for diagnosis of chronic arthritis of childhood; MCTD associated with diffuse puffiness of hands</td>
<td>Postviral arthritis, reactive arthritis, trauma, infection, Lyme disease, Kawasaki disease, malignancy, overuse syndromes</td>
</tr>
</tbody>
</table>

HSP, Henoch-Schönlein purpura; JDM, juvenile dermatomyositis; JIA, juvenile idiopathic arthritis; MCTD, mixed connective tissue disease; SLE, systemic lupus erythematosus.
be caused by any chronic illness, but hemolytic anemia (positive Coombs test result) may point to SLE or MCTD. Rheumatoid factor is present in less than 10% of children with JIA and thus has poor sensitivity as a diagnostic tool; it may be elevated by infections such as endocarditis, tuberculosis, syphilis, viral infections (parvovirus B19, hepatitides B and C, mycoplasma) as well as primary biliary cirrhosis and malignancies. In a child with chronic arthritis, rheumatoid factor serves as a prognostic indicator.

Inflammatory markers (erythrocyte sedimentation rate, C-reactive protein level) are nonspecific and are elevated in infections and malignancies as well as rheumatic diseases. Their levels may also be normal in rheumatic diseases such as arthritis, scleroderma, and dermatomyositis. Inflammatory marker measurements are more useful in rheumatic diseases such as arthritis, scleroderma, and dermatomyositis. Inflammatory marker measurements are more useful in rheumatic diseases such as arthritis, scleroderma, and dermatomyositis.

Table 153-3

<table>
<thead>
<tr>
<th>Autoantibody Specificity and Disease Associations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ANTIBODY</strong></td>
</tr>
<tr>
<td>-----------------------------------------------</td>
</tr>
<tr>
<td>Antinuclear antibody (ANA)</td>
</tr>
<tr>
<td>Double-stranded DNA (dsDNA)</td>
</tr>
<tr>
<td>Smith (Sm)</td>
</tr>
<tr>
<td>Smooth muscle (Sm)</td>
</tr>
<tr>
<td>PM-Scl (polymyositis-scleroderma)</td>
</tr>
<tr>
<td>SSA (Ro)</td>
</tr>
<tr>
<td>SSB (La)</td>
</tr>
<tr>
<td>Ribonuclease protein (RNP)</td>
</tr>
<tr>
<td>Histone</td>
</tr>
<tr>
<td>Centromere</td>
</tr>
<tr>
<td>Topoisomerase I (Scl-70)</td>
</tr>
<tr>
<td>Antineutrophil cytoplasmic antibodies (ANCAs)</td>
</tr>
<tr>
<td>Cytoplasmic (cANCAs)/ PR3-ANCA</td>
</tr>
<tr>
<td>Perinuclear (pANCAs)/ MPO-ANCA</td>
</tr>
<tr>
<td>Anticitrullinated protein (ACPAs) also called anti-cyclic citrullinated protein (anti-CCP)</td>
</tr>
</tbody>
</table>

MCTD, mixed connective tissue disease; MPO-ANCA, antimielyperoxidase; PR3-ANCA, antiproteinase 3; RF, rheumatoid factor; SLE, systemic lupus erythematosus. Modified from Aggerwal A: Clinical application of tests used in rheumatology, Indian J Pediatr 69:889–892, 2002.

**IMAGING STUDIES**

Plain radiographs are useful in evaluation of arthralgias and arthritis, as they offer reassurance in benign pain syndromes and their findings are often normal in malignancies, osteomyelitis, and long-standing chronic juvenile arthritis. Radionuclide bone scans help localize areas of abnormality in the patient with diffuse pains caused by osteomyelitis, neuroblastoma, chronic multifocal osteomyelitis, and systemic arthritis. MRI findings are abnormal in inflammatory myositis and suggest the optimal site for biopsy. MRI is more sensitive than plain radiographs in detecting the presence of early erosive arthritis and demonstrates increased joint fluid, synovial enhancement, and sequela of trauma with internal joint derangement. Cardiopulmonary evaluation is suggested for diseases commonly affecting the heart and infection, endocarditis, and parvovirus B19 infection. The ANA test result is also positive in up to 30% of normal children and the level of ANA is increased in those with a 1st-degree relative with a known rheumatic disease. In the majority of children with a positive ANA test result without signs of a rheumatic disease on initial evaluation, autoimmune disease does not develop disease over time, so this finding does not necessitate referral to a pediatric rheumatologist. A positive ANA test result is found in many rheumatic diseases, including IIA, in which it serves as a predictor of the risk for inflammatory eye disease. Once a positive ANA test result is discovered in a child, the need for specific autoantibody testing is directed by the presence of clinical signs and symptoms (see Table 153-3).
lung, including SLE, systemic scleroderma, MCTD, JDM, and sarcoid, as clinical manifestations may be subtle. This evaluation, which may include echocardiogram, pulmonary function tests, and high-resolution CT of the lungs along with consideration of bronchoalveolar lavage, is generally performed by a pediatric rheumatologist to whom the patient is referred (see Table 153-4).

Bibliography is available at Expert Consult.
Bibliography
Nonpharmacologic as well as pharmacologic interventions are often necessary to meet the desired goals of disease management. Optimal disease management requires family-centered care delivered by a multidisciplinary team of healthcare professionals providing medical, psychological, social, and school support. Rheumatologic conditions most often follow a course marked by flares and periods of remission, although some children have unremitting disease. The goals of treatment are to control disease, relieve discomfort, avoid or limit drug toxicity, prevent or reduce organ damage, and maximize the physical function and quality of life of affected children. Nonpharmacologic therapy is an important adjunct to medical management of rheumatic diseases. A key predictor of long-term outcome consists of early recognition and referral to a rheumatology team experienced in the specialized care of children with rheumatic diseases. Significant differences in outcome are seen 10 yr after disease onset in patients with juvenile idiopathic arthritis (JIA) depending on whether referral to a pediatric rheumatology center was accomplished within 6 mo of onset.

PEDIATRIC RHEUMATOLOGY TEAMS AND PRIMARY CARE PHYSICIANS

The multidisciplinary pediatric rheumatology team (Table 154-1) offers coordinated services for children and their families. General principles of treatment include: early recognition of signs and symptoms of rheumatic disease with timely referral to rheumatology for prompt initiation of treatment; monitoring for disease complications and adverse effects of treatment; coordination of subspecialty care and rehabilitation services with communication of clinical information; and child- and family-centered chronic illness care, including self-management support, alliance with community resources, partnership with schools, resources for dealing with the financial burdens of disease, and connection with advocacy groups. Planning for transition to adult care providers needs to start in adolescence. Central to effective care is partnership with the primary care provider, who helps coordinate care, monitor compliance with treatment plans, ensure appropriate immunization, monitor for medication toxicities, and

Chapter 154

Treatment of Rheumatic Diseases

Jeffrey A. Dvergsten, Esi Morgan-DeWitt, and C. Egla Rabinovich
identify disease exacerbations and concomitant infections. Communication between the primary care provider and subspecialty team permits timely intervention when needed.

**THERAPEUTICS**

A key principle of pharmacologic management of rheumatic diseases is that early disease control, striving for induction of remission, leads to less tissue and organ damage with improved short- and long-term outcomes. Medications are chosen from broad therapeutic classes on the basis of diagnosis, disease severity, anthropometrics, and adverse effect profile. Many drug therapies used do not have U.S. Food and Drug Administration (FDA) indications for pediatric rheumatic diseases, and their arthritis with NSAID therapy. Patients may try several different NSAIDs for 6-wk trials before finding one that demonstrates clinical benefit. NSAIDs with longer half-lives or sustained-release formulations allow for once- or twice-daily dosing and improve compliance. Laboratory monitoring for toxicity includes a complete blood count (CBC), serum creatinine, liver function tests (LFTs), and urinalysis every 6-12 mo, though guidelines for frequency of testing are not established.

**Nonbiologic Disease-Modifying Antirheumatic Drugs**

Methotrexate (MTX), an antimetabolite, is a cornerstone of therapy in pediatric rheumatology because of its sustained effectiveness and relative low toxicity over prolonged periods of treatment. The mechanism of action low-dose MTX in arthritis is complex but is believed...
Table 154-2 | Therapeutics for Childhood Rheumatic Diseases*  

<table>
<thead>
<tr>
<th>CLASSIFICATION</th>
<th>THERAPEUTIC†</th>
<th>DOSE</th>
<th>INDICATION†</th>
<th>ADVERSE REACTIONS</th>
<th>MONITORING</th>
</tr>
</thead>
</table>
| Nonsteroidal antiinflammatory drugs (NSAIDs)‡ | Etodolac* | PO once-daily dose:  
20-30 kg: 400 mg  
31-45 kg: 600 mg  
46-60 kg: 800 mg  
>60 kg: 1,000 mg | JIA  
Spondyloarthropathy  
Pain  
Serositis  
Cutaneous vasculitis  
Uveitis | GI intolerance  
(abdominal pain, nausea),  
gastritis, hepatitis,  
tinnitus, anemia,  
pseudoporphyria,  
aseptic meningitis,  
headache, renal disease | CBC, LFTs, BUN/creatinine,  
urinalysis at baseline, then  
every 6-12 mo |
| | Ibuprofena | 40 mg/kg/day PO  
divided 3 times daily  
Max 2400 mg per day | JIA  
Spondyloarthropathy  
Pain  
Serositis  
Cutaneous vasculitis  
Uveitis | GI intolerance  
(abdominal pain, nausea),  
gastritis, hepatitis,  
tinnitus, anemia,  
pseudoporphyria,  
aseptic meningitis,  
headache, renal disease | CBC, LFTs, BUN/creatinine,  
urinalysis at baseline, then  
every 6-12 mo |
| | Naproxena | 15 mg/kg/day PO in 2  
divided doses  
Maximum 1,000 mg per day | JIA  
Spondyloarthropathy  
Pain  
Serositis  
Cutaneous vasculitis  
Uveitis | GI intolerance  
(abdominal pain, nausea),  
gastritis, hepatitis,  
tinnitus, anemia,  
pseudoporphyria,  
aseptic meningitis,  
headache, renal disease | CBC, LFTs, BUN/creatinine,  
urinalysis at baseline, then  
every 6-12 mo |
| | Celecoxiba | 10-25 kg: 50 mg PO  
twice daily  
>25 kg: 100 mg PO  
twice daily | JIA  
Spondyloarthropathy  
Pain  
Serositis  
Cutaneous vasculitis  
Uveitis | GI intolerance  
(abdominal pain, nausea),  
gastritis, hepatitis,  
tinnitus, anemia,  
pseudoporphyria,  
aseptic meningitis,  
headache, renal disease | CBC, LFTs, BUN/creatinine,  
urinalysis at baseline, then  
every 6-12 mo |
| | Meloxicama | 0.125 mg/kg,  
maximum 7.5 mg,  
PO once daily | JIA  
Spondyloarthropathy  
Pain  
Serositis  
Cutaneous vasculitis  
Uveitis | GI intolerance  
(abdominal pain, nausea),  
gastritis, hepatitis,  
tinnitus, anemia,  
pseudoporphyria,  
aseptic meningitis,  
headache, renal disease | CBC, LFTs, BUN/creatinine,  
urinalysis at baseline, then  
every 6-12 mo |
| Disease modifying antirheumatic drugs (DMARDs) | Methotrexate* | 10-20 mg/m²/wk (0.35-0.65 mg/kg/wk) PO  
20-30 mg/m²/wk  
(0.65-1 mg/kg/wk)  
SC; higher doses  
better absorbed by  
SC injection | JIA  
Uveitis | GI intolerance (nausea,  
vomiting), hepatitis,  
myelosuppression,  
mucositis, teratogenesis,  
lymphoma, interstitial  
pneumonitis | CBC, LFTs at baseline,  
monthly × 3, then every  
8-12 wk |
| | Leflunomide | PO once daily:  
10 to <20 kg: 10 mg  
20-40 kg: 15 mg  
>40 kg: 20 mg | JIA | GI intolerance, rash,  
skin discoloration,  
anemia, cytopenias,  
myopathy, CNS  
stimulation, death  
(overdose) | CBC, LFTs, at baseline,  
monthly × 6, then every  
8-12 wk |
| | Hydroxychloroquine | 5-6 mg/kg PO once daily; do not exceed  
6.5 mg/kg daily  
Maximum dose  
400 mg daily | SLE  
JDMS  
Antiphospholipid antibody syndrome | Retinal toxicity, GI  
intolerance, rash,  
skin discoloration,  
anemia, cytopenias,  
myopathy, CNS  
stimulation, death  
(overdose) | Ophthalmologic screening every 6-12 mo |
| | Sulfasalazine* | 30-50 mg/kg/day divided in twice-daily doses  
Adult maximum 3 g/day | Spondyloarthropathy,  
JIA | GI intolerance, rash,  
hypersensitivity reactions, Stevens-Johnson syndrome,  
cytopenias, hepatitis,  
headache | CBC, LFTs, BUN/creatinine,  
urinalysis at baseline, every  
other wk × 3 mo, monthly × 3,  
then every 3 mo |
| Tumor necrosis factor α (TNF-α) antagonists | Adalimumab* | SC once every other wk:  
15 to <30 kg: 20 mg  
≥30 kg: 40 mg | JIA, spondyloarthropathy, psoriatic arthritis, uveitis | Injection site reaction, infection, rash,  
cytopenias, lupus-like syndrome, potential increased malignancy risk | TB test; anti-dsDNA, CBC |
| | Etanercept* | 0.8 mg/kg SC once weekly (maximum 50 mg/dose) or  
0.4 mg/kg SC twice weekly (maximum 25 mg/dose) | JIA | Injection site reactions, infections, rash,  
demyelinating disorders, cytopenias, potential increased malignancy risk | TB test; CBC |
| | Infliximab | 5-10 mg/kg IV q4-8wk | JIA  
Spondyloarthropathy  
Uveitis  
Sarcoidosis | Infusion reactions, hepatitis, potential increased malignancy risk | TB test; anti-dsDNA, LFTs |

*Consult a clinical pharmacology reference for current dosing and monitoring guidelines, and complete list of known adverse effects.
<table>
<thead>
<tr>
<th>CLASSIFICATION</th>
<th>THERAPEUTIC†</th>
<th>DOSE</th>
<th>INDICATION†</th>
<th>ADVERSE REACTIONS</th>
<th>MONITORING</th>
</tr>
</thead>
<tbody>
<tr>
<td>Modulate T-cell activation</td>
<td>Abatacept</td>
<td>IV every 2 wk × 3 doses, then monthly for ≥6 yr of age:</td>
<td>JIA</td>
<td>Infusion, headache, potential increased malignancy risk</td>
<td>CBC, BMP; consider monitoring quantitative IgG</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt;75 kg: 10 mg/kg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>75-100 kg: 750 mg</td>
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<tr>
<td></td>
<td></td>
<td>&gt;100 kg: 1,000 mg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-CD20 (B cell) antibody</td>
<td>Rituximab</td>
<td>575 mg/m², maximum 1,000 mg, IV on days 1 and 15</td>
<td>SLE</td>
<td>Infusion reactions, lymphopenia, reactivation hepatitis B, rash, serum sickness, arthritis, PML</td>
<td>CBC, BMP; consider monitoring quantitative IgG</td>
</tr>
<tr>
<td>Anti-BLyS antibody</td>
<td>Belimumab</td>
<td>10 mg/kg IV every 2 wk × 3 doses, then every 4 wk</td>
<td>SLE</td>
<td>Infusion reactions, infection, depression</td>
<td></td>
</tr>
<tr>
<td>Interleukin 1 antagonist</td>
<td>Anakinra</td>
<td>1-2 mg/kg/daily</td>
<td>Systemic JIA</td>
<td>Injection site reactions, infection</td>
<td>CBC</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Adult maximum 100 mg</td>
<td>CAPS</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Given SC every 8 wk (CAPS) every 4 wk (Systemic JIA):</td>
<td>CAPS</td>
<td>Injection site reaction, infection</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>15-40 kg: 2 mg/kg (up to 3 mg/kg if needed)</td>
<td>Systemic JIA</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;40 kg: 150 mg</td>
<td></td>
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</tr>
<tr>
<td>Interleukin-6 antagonist</td>
<td>Tocilizumab</td>
<td>≥2 yr and ≥30 kg, 8 mg/kg/dose every 2 wk; ≥2 yr and ≤30 kg, 12 mg/kg/dose every 2 wk</td>
<td>Systemic JIA</td>
<td>Infusion reactions, elevated LFTs, elevated lipids, thrombocytopenia, infections</td>
<td>CBC, LFTs, platelet count, serum lipid profile</td>
</tr>
<tr>
<td>Intravenous immunoglobulin</td>
<td>IVIG</td>
<td>1,000-2,000 mg/kg IV infusion</td>
<td>Kawasaki disease</td>
<td>Infusion reaction, aseptic meningitis, renal failure</td>
<td>Serum creatinine, BUN, IgG level</td>
</tr>
<tr>
<td>Cytotoxic</td>
<td>Cyclophosphamide</td>
<td>0.5-1 g/m² IV (maximum 1.5 g) monthly for 6-mo induction, then every 2-3 mo for oral regimen: 1-2 mg/kg/daily; maximum 150 mg/daily</td>
<td>SLE</td>
<td>Nausea, vomiting, myelosuppression, mucositis, hyponatremia, alopecia, hemorrhagic cystitis, gonadal failure, teratogenesis, secondary malignancy</td>
<td>CBC</td>
</tr>
<tr>
<td>Immunosuppressive</td>
<td>Mycophenolate mofetil</td>
<td>Oral suspension: maximum 1,200 mg/m²/day PO (up to 2 g/day) divided twice daily</td>
<td>SLE</td>
<td>GI intolerance (diarrhea, nausea, vomiting), renal impairment, neutropenia, teratogenesis, secondary malignancy, PML</td>
<td>CBC, BMP</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Capsules: maximum 1,500 mg/day PO for BSA 1.25-1.5 m², 2 g/day PO for BSA &gt;1.5 m² divided twice daily</td>
<td>Uveitis</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
to result from the inhibition of folate-dependent processes by MTX polyglutamates, primarily their effect on the enzyme 5-aminomimidazole-4-carboxamide ribonucleotide (AICAR) transformylase leading to an increase of extracellular adenosine and consequently, cyclic adenosine monophosphate, which inhibits the production of proinflammatory cytokines including tumor necrosis factor (TNF)-α and interleukin (IL)-1β and their downstream effects on lymphocyte activation and proliferation.

MTX has a central role in the treatment of arthritis, especially in children with polyarticular JIA. The response to oral MTX (10 mg/m² once a week) is better than the response to placebo (63% vs. 36%). Children who show no response to standard doses of MTX often do show response to higher doses (15 or 30 mg/m²/wk). Subcutaneous administration of MTX is similar in absorption and pharmacokinetic properties to intramuscular injection, with less pain. MTX is commonly used in treatment of juvenile dermatomyositis as a steroid-sparing agent, with efficacy in 70% of patients. It has also been used successfully at a dosage of 10-20 mg/m²/wk in patients with systemic lupus erythematosus (SLE) to treat arthritis, serositis, and rash.

Because of the lower dose used in treating rheumatic diseases, MTX is well tolerated by children with toxicity being milder and qualitatively different from that observed with treatment of neoplasms. In 8 published studies including 288 patients with JIA taking MTX, adverse effects included elevated liver enzyme values (15%), GI toxicity (13%), leukopenia, interstitial pneumonitis, rash, and alopecia (<1%). Hepatotoxicity observed among adults with rheumatoid arthritis treated with MTX has raised concern about similar problems in children. Analysis of liver biopsy specimens in children with JIA undergoing long-term MTX treatment has revealed occasional mild fibrosis and no evidence of even moderate liver damage. Children receiving MTX should be counseled to avoid alcohol, smoking, and pregnancy. Folic acid 1 mg daily is given as an adjunct to minimize adverse effects. Lymphoproliferative disorders have been reported in adults treated with MTX, primarily in association with Epstein-Barr virus infection. Regression of lymphoma may follow withdrawal of MTX.

Monitoring laboratory tests for MTX toxicity include CBC and LFTs at regular intervals, initially every 4 wk for the 1st 3 mo of treatment, then every 8-12 wk, with more frequent intervals after dosing adjustments or in response to abnormal values.

**Hydroxychloroquine**

Hydroxychloroquine sulfate is an antimalarial drug important in the treatment of SLE and dermatomyositis, particularly cutaneous manifestations of disease and to reduce lupus flares. It is not indicated to treat JIA because of lack of efficacy. The most significant potential adverse effect is retinal toxicity, which occurs rarely but results in irreversible color blindness or loss of central vision. Children receiving MTX should be monitored for ophthalmologic examinations, including assessment of peripheral vision and color fields, are conducted at baseline and every 6-12 mo to screen for retinal toxicity. Retinal toxicity is rare (1/3,000 patients) and is associated with weight-based dosing exceeding 6.5 mg/kg/day; therefore, recommended dosing is <6.5 mg/kg/day not to exceed 400 mg/day.

Other potential adverse effects include rash, skin discoloration, gastric irritation, bone marrow suppression, central nervous system stimulation, and myositis.
Leflunomide
Leflunomide is a DMARD approved for treatment of rheumatoid arthritis that offers an alternative to MTX for treatment of JIA. MTX outperformed leflunomide for treatment of JIA in a randomized trial (at 16 wk, 89% of patients receiving MTX achieved a 30% response rate vs. 68% of those receiving leflunomide), although both drugs were effective. Dosing is oral, once daily, and weight based: 10 mg for children 10 to <20 kg, 15 mg for children 20-40 kg, and 20 mg for children >40 kg. Adverse reactions include paresthesias and peripheral neuropathy, GI intolerance, elevated liver transaminases and hepatic failure, cytopenias, alopecia, and teratogenesis. Leflunomide has a long half-life, and in cases in which discontinuation of the agent is required, a drug elimination protocol with cholestyramine may be indicated. Avoidance of pregnancy is essential. Monitoring laboratory tests include CBC, LFTs, every 4 wk for the 1st 6 mo of treatment, then every 8-12 wk.

Sulfasalazine
Sulfasalazine is used to treat children with polyarticular JIA oligoarticular JIA, and the peripheral arthritis and enthesitis associated with juvenile ankylosing spondylitis. In JIA, sulfasalazine 50 mg/kg/day (adult maximum: 3,000 mg/day) achieves greater improvement in joint inflammation, global assessment parameters, and laboratory parameters than placebo. More than 30% of sulfasalazine-treated patients withdraw from the treatment because of adverse effects, primarily GI irritation and skin rashes. Sulfasalazine is associated with severe systemic hypersensitivity reactions, including Stevens-Johnson syndrome. Sulfasalazine is generally considered contraindicated in children with active systemic JIA because of increased hypersensitivity reactions. Sulfasalazine should not be used in patients with sulfa or salicylate hypersensitivity or porphyria.

Monitoring laboratory tests for sulfasalazine toxicity include CBC, LFTs, serum creatinine/blood urea nitrogen (BUN), and urinalysis, every other week for the 1st 3 mo of treatment, monthly for 3 mo, every 3 mo for 1 yr, then every 6 mo.

Mycophenolate Mofetil
Mycophenolate mofetil (MMF) is an immunosuppressive drug approved by the FDA for organ transplant rejection. In rheumatology, MMF is used primarily for treatment of lupus, uveitis, and autoimmune skin manifestations. In adult clinical trials, MMF was noninferior to cyclophosphamide for induction therapy of lupus nephritis, with a potential for less-adverse effects (infection, gonadal toxicity). Dosing is based on body surface area: 600 mg/m² orally twice daily, with maximum dosage limits varying by formulation and body surface area. The most common adverse reaction is GI intolerance. Infections, cytopenias, and secondary malignancies are among other adverse reactions reported.

Glucocorticoids
Glucocorticoids are given through oral, intravenous, ocular, topical, and intraarticular administration as part of treatment of rheumatic disease. Oral steroids are foundational treatment for moderate to severe lupus, dermatomyositis, and most forms of vasculitis; their long-term use is associated with a long list of well-described, dose-dependent complications, including linear growth suppression, Cushingoïd features, osteoporosis, avascular necrosis, hypertension, impaired glucose tolerance, mood disturbance, and increased infection risk. Glucocorticoids should be tapered to the lowest effective dose over time, and DMARDS introduced as steroid-sparing agents.

Intravenous steroids have been used to treat severe, acute manifestations of systemic rheumatic diseases such as SLE, dermatomyositis, and vasculitis. The intravenous route allows for higher doses to obtain an immediate, profound antiinflammatory effect. Methylprednisolone, 10-30 mg/kg/dose up to a maximum of 1 g, given over 1 hr daily for 1-5 days, is the intravenous preparation of choice. Although generally associated with fewer adverse effects than oral steroids, intravenously administered steroids are associated with significant and occasionally life-threatening toxicities, such as cardiac arrhythmia, acute hypertension, hypotension, hyperglycemia, shock, pancreatitis, and avascular necrosis.

Ocular steroids are prescribed by ophthalmologists as ophthalmologic drops or injections into the soft tissue surrounding the globe (sub–Tenon capsule injection) for active uveitis. Long-term ocular steroid use leads to cataract formation and glaucoma. Current ophthalmologic management has significantly decreased the frequency of blindness as a complication of JIA-associated uveitis.

Intraarticular steroids are being used with increasing frequency as initial therapy for children with oligoarticular JIA or as bridge therapy while awaiting efficacy of a DMARD in polyarticular disease. Most patients have significant clinical improvement within 3 days. Duration of response depends on steroid preparation used, joint affected, and arthritis subtype, with the anticipated response rate to knee injection being between 60% and 80% at 6 mo. Intraarticular administration may result in subcutaneous atrophy and hypopigmentation of the skin at the injection site, as well as subcutaneous calcifications along the needle track.

Biologic Agents
Biologic agents are proteins that have been engineered to target and modulate specific components of the immune system with the goal of decreasing the inflammatory response. Antibodies have been developed to target specific cytokines such as IL-1 and IL-6 or to interfere with specific immune cell function through depletion of B cells or suppression of T-cell activation (Table 154-3). The availability of these agents has dramatically increased the therapeutic options for treating rheumatic disease recalcitrant to nonbiologic therapies and they are, in some instances, becoming first-line interventions. A primary concern regarding biologic therapy is that when use is combined with other immunosuppressants, risk of malignancy may be increased.

Tumor Necrosis Factor-α Antagonists
Currently, 2 TNF antagonists have an FDA indication for treatment of children with moderate to severe polyarticular JIA (etanercept and adalimumab). Etanercept is a genetically engineered fusion protein consisting of 2 identical chains of the recombinant extracellular TNF receptor monomer fused with the Fc domain of human immunoglobulin G. Etanercept binds both TNF-α and lymphotoxin-α (formerly CTLa, cytotoxic T lymphocyte–associated antigen; Ig, immunoglobulin; IL, interleukin; TNF, tumor necrosis factor.


<table>
<thead>
<tr>
<th>Table 154-3</th>
<th>Summary of Biologic Therapies Studied in Juvenile Idiopathic Arthritis and Their Method of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DRUG</strong></td>
<td><strong>METHOD OF ACTION</strong></td>
</tr>
<tr>
<td>Etanercept</td>
<td>Soluble TNF p75 receptor fusion protein that binds to and inactivates TNF-α</td>
</tr>
<tr>
<td>Infliximab</td>
<td>Chimeric human/mouse monoclonal antibody that binds to soluble TNF-α and its membrane-bound precursor, neutralizing its action</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>A humanized IgG1 monoclonal antibody that binds to TNF-α</td>
</tr>
<tr>
<td>Abatacept</td>
<td>Soluble, fully human fusion protein of the extracellular domain of (CTLA-4, linked to a modified Fc portion of the human IgG1. It acts as a costimulatory signal inhibitor by binding competitively to CD80 or CD86, where it selectively inhibits T-cell activation</td>
</tr>
<tr>
<td>Tocilizumab</td>
<td>A humanized anti–human IL-6 receptor monoclonal antibody</td>
</tr>
<tr>
<td>Anakinra</td>
<td>An IL-1 receptor antagonist (IL-1RA)</td>
</tr>
</tbody>
</table>

**Method of Action**

- **Etanercept**: Soluble TNF p75 receptor fusion protein that binds to and inactivates TNF-α
- **Infliximab**: Chimeric human/mouse monoclonal antibody that binds to soluble TNF-α and its membrane-bound precursor, neutralizing its action
- **Adalimumab**: A humanized IgG1 monoclonal antibody that binds to TNF-α
- **Abatacept**: Soluble, fully human fusion protein of the extracellular domain of (CTLA-4, linked to a modified Fc portion of the human IgG1. It acts as a costimulatory signal inhibitor by binding competitively to CD80 or CD86, where it selectively inhibits T-cell activation
- **Tocilizumab**: A humanized anti–human IL-6 receptor monoclonal antibody
- **Anakinra**: An IL-1 receptor antagonist (IL-1RA)
called TNF-β) and inhibits their activity. Three fourths of children with active polyarticular JIA that fails to respond to MTX demonstrate response to etanercept after 3 mo of therapy. Dosing is 0.8 mg/kg subcutaneous weekly (maximum 50 mg/dose) or 0.4 mg/kg subcutaneously twice a week (maximum 25 mg/dose). Adalimumab is a fully human anti-TNF monoclonal antibody used alone or in combination with MTX. In a placebo-controlled withdrawal-design study, a children continuing to receive adalimumab were less likely to experience disease flares (43% vs. 71%) even if they were also taking MTX (37% vs. 65%). Adalimumab is administered subcutaneously every other week at a dose of 20 mg for children weighing 15-30 kg and 40 mg for those weighing >30 kg.

Infliximab, a chimeric mouse-human monoclonal antibody, was tested in a randomized controlled clinical trial for use in JIA but did not achieve study end points. However, it is FDA approved for pediatric inflammatory bowel disease and has been used "off label" for treatment of polyarticular JIA, uveitis, Behçet syndrome, and sarcoidosis. Two additional anti-TNF agents—golimumab, a human monoclonal antibody against TNF, and certolizumab pegol, a pegylated humanized antibody against TNF—have been approved by the FDA for rheumatoid arthritis in adults and are currently in pediatric trials.

The most common adverse reactions are injection-site reactions that diminish over time. TNF blockade is associated with an increased frequency of serious systemic infections, including sepsis, dissemination of latent tuberculosis, and invasive fungal infections in endemic areas. TNF blockade should not be initiated in subjects with history of chronic or frequent recurrent infections. Tuberculosis should be tested for prior to initiation of therapy with TNF antagonists. If test results are positive, antitubercular treatment must be administered before anti-TNF treatment can be started. There is a theoretically increased risk of malignancy with TNF-α antagonists, and there have been reports of development of lupus-like syndromes, leukocytoclastic vasculitis, interstitial lung disease, demyelinating syndromes, antibody formation to the drug, rashes, cytopenias, anaphylaxis, serum sickness, and other reactions. The benefit: risk profile appears favorable after a decade of experience with this therapeutic class; the safety of longer-term suppression of TNF function is unknown.

Modulator of T-Cell Activation
Abatacept is a selective inhibitor of T-cell costimulation resulting in T-cell anergy. It is FDA approved for treatment of moderate to severe polyarticular JIA. In a double-blind, randomized controlled withdrawal trial in children whose disease had not responded to DMARDs, 53% of placebo-treated patients, compared with 20% of abatacept-treated patients, experienced disease flares during the double-blind withdrawal period. The frequency of adverse events did not differ between the groups. Abatacept is administered IV every other week for 3 doses (<75 kg; 10 mg/kg/dose; 75-100 kg; 750 mg/dose; >100 kg; 1,000 mg/dose; maximum 1,000 mg/dose at 0, 2, and 4 wk) and then monthly thereafter.

B-Cell Depletion
Rituximab is a chimeric monoclonal antibody to the antigen CD20, a transmembrane protein on the surface of B-cell precursors and mature B lymphocytes. This antibody induces B-cell apoptosis and causes depletion of circulating and tissue-based B cells. Antibody production is not completely abrogated as plasma cells are not removed. Rituximab is licensed for treatment of B-cell non-Hodgkin lymphoma and is FDA approved for use in adult rheumatoid arthritis and idiopathic thrombocytopenic purpura but does not have a pediatric indication. Rituximab may also have a role in treatment of SLE, particularly its hematologic manifestations. Adverse events include serious infusion reactions, cytopenias, hepatitis B virus reactivation, hypogammaglobulinemia, infections, serum sickness, vasculitis, and a rare but fatal side effect, progressive multifocal leukoencephalopathy. Resistance to rituximab may develop over time in patients being treated for lymphoma.

Belimumab is a human monoclonal antibody to B-lymphocyte stimulator that negatively affects B-cell proliferation, differentiation, and long-term survival. It was FDA-approved in March 2011 for treatment of SLE in adults and studies of long-term safety and efficacy are ongoing. Currently, belimumab is not FDA approved for use in pediatric SLE.

Interleukin-1 Antagonists
Anakinra, a recombinant form of the human IL-1 receptor antagonist, competitively inhibits binding of IL-1α and IL-1β to the natural receptor, interrupting the cytokine proinflammatory cascade. Anakinra has been approved for rheumatoid arthritis in adults. In meta-analyses of treatments for rheumatoid arthritis, anakinra was outperformed by TNF-α antagonists but has a special niche in pediatric rheumatology for treatment of systemic JIA (SoJIA) and other autoinflammatory syndromes, such as cryopyrin-associated periodic syndromes. The medication is dosed subcutaneously, 1-2 mg/kg, once daily. An IL-1β monoclonal antibody, canakinumab is FDA approved for use in cryopyrin-associated periodic syndromes dosed subcutaneously every 8 wk and SoJIA dosed subcutaneously every 4 wk. Adverse reactions include significant injection site reactions and increased bacterial infections.

Interleukin-6 Receptor Antagonist
Tocilizumab, is an anti-IL-6 receptor antibody binding to both soluble as well as membrane-associated receptors. Tocilizumab has FDA approval for treatment of SoJIA and polyarticular JIA. Adverse reactions include transaminase and lipid elevations. Tocilizumab is given as an IV infusion every 2 (SoJIA) to 4 (polyarticular JIA) wk.

Intravenous Immunoglobulin
Intravenous immunoglobulin (IVIG) is thought to be beneficial in various clinical conditions. IVIG significantly improves the short- and long-term natural history of Kawasaki disease. Open studies have supported benefit for juvenile dermatomyositis, lupus-associated thrombocytopenia, and polyarticular JIA. IVIG is given as an IV infusion every 2 (SoJIA) to 4 (polyarticular JIA) wk.

Cytotoxics
Cyclophosphamide
Cyclophosphamide requires metabolic conversion in the liver to its active metabolites, which alkylate the guanine in DNA, leading to immunosuppression by the inhibition of the S2 phase of mitosis. The subsequent decrease in numbers of T and B lymphocytes results in diminished humoral and cellular immune responses. Cyclophosphamide infusions (500-1,000 mg/m²) given monthly for 6 mo, and then every 3 mo for 12-18 mo, have been shown to reduce the frequency of renal failure in patients with lupus and diffuse proliferative glomerulonephritis. Open trials suggest efficacy in severe central nervous system lupus. Oral cyclophosphamide (1-2 mg/kg/day) is effective as induction treatment of severe antineutrophilic cytoplasmic antibody-associated vasculitis and other forms of systemic vasculitis as well as interstitial lung disease or pulmonary hemorrhage associated with rheumatic disease. Cyclophosphamide is a potent cytotoxic drug associated with significant toxicities. Potential short-term adverse effects include nausea, vomiting, anorexia, alopecia, mucositis, hemorrhagic cystitis, and bone marrow suppression. Long-term complications include an increased risk for sterility and cancer, especially leukemia, lymphoma, and bladder cancer. Thirty percent to 40% of adult women with lupus treated with intravenous cyclophosphamide become infertile; the risk of ovarian failure appears to be significantly lower in adolescent and premenarchal girls. Ovarian suppression with an inhibitor of gonadotropin-releasing hormone to preserve fertility is currently being studied.

Other Drugs
Azathioprine is sometimes used to treat antineutrophilic cytoplasmic antibody-associated vasculitis following induction therapy or to treat SLE. Cyclosporine has been used occasionally in the treatment of dermatomyositis on the basis of uncontrolled studies and is helpful in the
treatment of macrophage activation syndrome complicating SoJIA (see Chapter 155). There are case reports describing the successful use of thalidomide, or its analog lenalidomide, as treatment for SoJIA, inflammatory skin disorders, and Behçet disease. Several drugs commonly used in the past to treat arthritis are no longer part of standard treatment, including salicylates, gold compounds, and d-penicillamine.

Bibliography is available at Expert Consult.
Bibliography


Juvenile idiopathic arthritis (JIA) is the most common rheumatic disease in children and one of the more common chronic illnesses of childhood. JIA represents a heterogeneous group of disorders all sharing the clinical manifestation of arthritis. The etiology and pathogenesis of JIA are largely unknown, and the genetic component is complex, making clear distinction among various subtypes difficult. As a result, several classification schemas exist, each with its own limitations. The former classification scheme of the American College of Rheumatology uses the term juvenile rheumatoid arthritis and categorizes the disease into 3 onset types (Table 155-1). Attempting to standardize nomenclature, The International League of Associations for Rheumatology (ILAR) proposed a different classification using the term JIA (Table 155-2), inclusive of all subtypes of chronic juvenile arthritis. We refer to the ILAR classification criteria; see Chapter 156 for enthesitis-related arthritis (ERA) and psoriatic JIA (Tables 155-3 and 155-4).

**EPIDEMIOLOGY**

The worldwide incidence of JIA ranges from 0.8-22.6/100,000 children per year, with prevalence ranges from 7-401/100,000. These wide-ranging numbers reflect population differences, particularly environmental exposure and immunogenetic susceptibility, along with variations in diagnostic criteria, difficulty in case ascertainment, and lack of population-based data. It is estimated that 300,000 children in the United States have arthritis, including 100,000 with a form of JIA. Oligoarthritis is the most common subtype (40-50%), followed by polyarthritis (25-30%) and systemic JIA (5-15%) (see Table 155-4). There is no sex predominance in systemic JIA (sJIA), but more girls than boys are affected in both oligoarticular (3:1) and polyarticular (5:1) JIA. The peak age at onset is between 2 and 4 yr for oligoarticular disease. Age of onset has a bimodal distribution in polyarthritis, with peaks at 2-4 yr and 10-14 yr. sJIA occurs throughout childhood with a peak between 1 and 5 yr.

**ETIOLOGY**

The etiology and pathogenesis of JIA are not completely understood, though both immunogenetic susceptibility and an external trigger are considered necessary. JIA is a complex genetic trait in which multiple genes may affect disease susceptibility. Variants in major histocompatibility complex (MHC) class I and class II regions have indubitably been associated with different JIA subtypes. Non-HLA candidate loci are also associated with JIA, including polymorphisms in the genes encoding protein tyrosine phosphatase nonreceptor 22 (PTPN22), tumor necrosis factor (TNF)-α, macrophage inhibitory factor, interleukin (IL)-6, and IL-10. There is evidence that the IL-6 gene confers susceptibility to sJIA, with increased transmission of the −174G allele in patients older than 5 yr. Possible nongenetic triggers include bacterial and viral infections, enhanced immune responses to bacterial or mycobacterial heat shock proteins, abnormal reproductive hormone levels, and joint trauma.

**PATHOGENESIS**

JIA is an autoimmune disease associated with alterations in both humoral and cell-mediated immunity. T lymphocytes have a central role, releasing proinflammatory cytokines favoring a type 1 helper T-lymphocyte response. Studies of T-cell receptor expression confirm recruitment of T lymphocytes specific for synovial non–self antigens. B-cell activation, immune complex formation, and complement activation also promote inflammation. Inheritance of specific cytokine alleles may predispose to upregulation of inflammatory networks, resulting in systemic disease or more severe arthritic disease.

sJIA is characterized by dysregulation of the innate immune system with a lack of autoreactive T cells and autoantibodies. It therefore may be more accurately classified as an autoinflammatory disorder, more like familial Mediterranean fever, than the other subtypes of JIA. This theory is also supported by work demonstrating similar expression patterns of a phagocytic protein (S100A12) in sJIA and familial Mediterranean fever, as well as the same marked responsiveness to IL-1 inhibitors.

All these immunologic abnormalities cause inflammatory synovitis, characterized pathologically by villous hypertrophy and hyperplasia with hyperemia and edema of the synovial tissue. Vascular endothelial hyperplasia is prominent and is characterized by infiltration of mononuclear and plasma cells with a predominance of T lymphocytes (Fig. 155-1). Advanced and uncontrolled disease leads to pannus formation and progressive erosion of articular cartilage and contiguous bone (Figs. 155-2 and 155-3).

**CLINICAL MANIFESTATIONS**

Arthritis must be present to make a diagnosis of any JIA subtype. Arthritis is defined by intraarticular swelling or the presence of 2 or more of the following signs: limitation of range of motion, tenderness or pain on motion, increased heat in ≥1 joint. Duration of disease: ≥6 wk. Onset type defined by type of articular involvement in the 1st 6 mo after onset:

- Polyarthritis: ≥5 inflamed joints
- Oligoarthritis: ≤4 inflamed joints
- Systemic-onset disease: arthritis with rash and a characteristic quotidian fever
- Exclusion of other forms of juvenile arthritis

*Table 155-1*

<table>
<thead>
<tr>
<th>Criteria for the Classification of Juvenile Rheumatoid Arthritis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at onset: &lt;16 yr</td>
</tr>
<tr>
<td>Arthritis (swelling or effusion, or the presence of 2 or more of the following signs: limitation of range of motion, tenderness or pain on motion, increased heat) in ≥1 joint</td>
</tr>
<tr>
<td>Duration of disease: ≥6 wk</td>
</tr>
<tr>
<td>Onset type defined by type of articular involvement in the 1st 6 mo after onset:</td>
</tr>
<tr>
<td>Polyarthritis: ≥5 inflamed joints</td>
</tr>
<tr>
<td>Oligoarthritis: ≤4 inflamed joints</td>
</tr>
<tr>
<td>Systemic-onset disease: arthritis with rash and a characteristic quotidian fever</td>
</tr>
<tr>
<td>Exclusion of other forms of juvenile arthritis</td>
</tr>
</tbody>
</table>

### Table 155-2: International League of Associations for Rheumatology Classification of Juvenile Idiopathic Arthritis (JIA)

<table>
<thead>
<tr>
<th>CATEGORY</th>
<th>DEFINITION</th>
<th>EXCLUSIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic</td>
<td>Arthritis in ≥1 joint with, or preceded by, fever of at least 2 wk in duration that is documented to be daily (&quot;quotidian&quot;) for at least 3 days and accompanied by ≥1 of the following: 1. Evanescent (nonfixed) erythematous rash 2. Generalized lymph node enlargement 3. Hepatomegaly or splenomegaly or both 4. Serositis†</td>
<td>a. Psoriasis or a history of psoriasis in the patient or a 1st-degree relative b. Arthritis in an HLA-B27–positive boy beginning after the 6th birthday c. Ankylosing spondylitis, enthesitis-related arthritis, sacroiliitis with inflammatory bowel disease, Reiter syndrome, or acute anterior uveitis, or a history of one of these disorders in a 1st-degree relative d. Presence of immunoglobulin M RF on at least 2 occasions at least 3 mo apart</td>
</tr>
<tr>
<td>Oligoarthritis</td>
<td>Arthritis affecting 1-4 joints during the 1st 6 mo of disease. Two subcategories are recognized: 1. Persistent oligoarthritis—ffecting ≤4 joints throughout the disease course 2. Extended oligoarthritis—ffecting &gt;4 joints after the 1st 6 mo of disease a, b, c, d (above) plus e. Presence of systemic JIA in the patient</td>
<td>a, b, c, d (above)</td>
</tr>
<tr>
<td>Polyarthritis (RF-negative)</td>
<td>Arthritis affecting ≥5 joints during the 1st 6 mo of disease; a test for RF is negative</td>
<td>a, b, c, d</td>
</tr>
<tr>
<td>Polyarthritis (RF-positive)</td>
<td>Arthritis affecting ≥5 joints during the 1st 6 mo of disease; ≥2 tests for RF at least 3 mo apart during the 1st 6 mo of disease are positive</td>
<td>a, b, c, d</td>
</tr>
<tr>
<td>Psoriatic arthritis</td>
<td>Arthritis and psoriasis, or arthritis and at least 2 of the following: 1. Dactylitis‡ 2. Nail pitting§ and onycholysis 3. Psoriasis in a 1st-degree relative</td>
<td>b, c, d, e</td>
</tr>
<tr>
<td>Enthesitis-related arthritis</td>
<td>Arthritis and enthesitis, or arthritis or enthesitis with at least 2 of the following: 1. Presence of or a history of sacroiliac joint tenderness or inflammatory lumbosacral pain or both¶ 2. Presence of HLA-B27 antigen 3. Onset of arthritis in a male &gt;6 yr old 4. Acute (symptomatic) anterior uveitis 5. History of ankylosing spondylitis, enthesitis-related arthritis, sacroiliitis with inflammatory bowel disease, Reiter syndrome, or acute anterior uveitis in a 1st-degree relative</td>
<td>a, d, e</td>
</tr>
<tr>
<td>Undifferentiated arthritis</td>
<td>Arthritis that fulfills criteria in no category or in ≥2 of the above categories.</td>
<td></td>
</tr>
</tbody>
</table>

RF, rheumatoid factor.

*Quotidian* fever is defined as a fever that rises to 39°C (102.2°F) once a day and returns to 37°C (98.6°F) between fever peaks.

†Serositis refers to pericarditis, pleuritis, or peritonitis, or some combination of the 3.

‡Dactylitis is swelling of ≥1 digits, usually in an asymmetric distribution, that extends beyond the joint margin.

§A minimum of 2 pits on any 1 or more nails at any time.

¶Enthesitis is defined as tenderness at the insertion of a tendon, ligament, joint capsule, or fascia to bone.

*Inflammatory lumbosacral pain refers to lumbosacral pain at rest with morning stiffness that improves on movement.*


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### Table 155-3: Characteristics of the American College of Rheumatology (ACR) and International League of Associations for Rheumatology (ILAR) Classifications of Childhood Chronic Arthritis

<table>
<thead>
<tr>
<th>PARAMETER</th>
<th>ACR (1977)</th>
<th>ILAR (1997)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Term</td>
<td>Juvenile rheumatoid arthritis (JRA)</td>
<td>Juvenile idiopathic arthritis (JIA)</td>
</tr>
<tr>
<td>Minimum duration</td>
<td>≥6 wk</td>
<td>≥6 wk</td>
</tr>
<tr>
<td>Age at onset</td>
<td>&lt;16 yr</td>
<td>&lt;16 yr</td>
</tr>
<tr>
<td>≤4 joints in 1st 6 mo after presentation</td>
<td>Pauciarticular</td>
<td>Pauciarticular</td>
</tr>
<tr>
<td>&gt;4 joints in 1st 6 mo after presentation</td>
<td>Polyarticular</td>
<td>Polyarthritis rheumatoid factor–negative</td>
</tr>
<tr>
<td>Fever, rash, arthritis</td>
<td>Systemic-onset</td>
<td>Systemic</td>
</tr>
<tr>
<td>Other categories included</td>
<td>Exclusion of other forms</td>
<td>Psoriatic arthritis</td>
</tr>
<tr>
<td>Inclusion of psoriatic arthritis, inflammatory bowel disease, ankylosing spondylitis</td>
<td>No (see Chapter 156)</td>
<td>Yes</td>
</tr>
<tr>
<td>INTERNATIONAL LEAGUE OF ASSOCIATIONS FOR RHEUMATOLOGY SUBTYPE</td>
<td>PEAK AGE OF ONSET (Yr)</td>
<td>FEMALE:MALE RATIO</td>
</tr>
<tr>
<td>---------------------------------------------------------------</td>
<td>------------------------</td>
<td>-------------------</td>
</tr>
<tr>
<td>Systemic arthritis</td>
<td>1-5</td>
<td>1:1</td>
</tr>
<tr>
<td>Oligoarthritis</td>
<td>2-4</td>
<td>3:1</td>
</tr>
<tr>
<td>Polyarthritis:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RF-negative</td>
<td>2-4 and 10-14</td>
<td>3:1 and 10:1</td>
</tr>
<tr>
<td>RF-positive</td>
<td>9-12</td>
<td>9:1</td>
</tr>
<tr>
<td>Psoriatic arthritis</td>
<td>2-4 and 9-11</td>
<td>2:1</td>
</tr>
<tr>
<td>Enthesitis-related arthritis</td>
<td>9-12</td>
<td>1:7</td>
</tr>
</tbody>
</table>

ANA, antinuclear antibody; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; JIA, juvenile idiopathic arthritis; MAS, macrophage activation syndrome; MTX, methotrexate; NSAID, nonsteroidal antiinflammatory drug; RF, rheumatoid factor; TNF, tumor necrosis factor; WBC, white blood cell count.

Oligoarthritis is defined as involving \( \leq 4 \) joints within the 1st 6 mo of disease onset, and often only a single joint is involved (see Table 155-4). It predominantly affects the large joints of the lower extremities, such as the knees and ankles (Fig. 155-4). Isolated involvement of upper extremity large joints is less common. Those in whom disease never develops in more than 4 joints are regarded as having persistent oligoarticular JIA, whereas evolution of disease in more than 4 joints after 6 mo changes the classification to extended oligoarticular JIA and is associated with a worse prognosis. Isolated involvement of the hip is almost never a presenting sign and suggests ERA (see Chapter 156) or a nonrheumatic cause. The presence of a positive antinuclear antibody (ANA) confers increased risk for asymptomatic anterior uveitis, requiring periodic slit-lamp examination (Table 155-5). ANA positivity may also be correlated with younger age at disease onset, female sex, asymmetric arthritis, and lower number of involved joints over time.

Polyarthritis is characterized by inflammation of \( \geq 5 \) joints in both upper and lower extremities (Figs. 155-5 and 155-6). Rheumatoid factor (RF)-positive polyarthritis resembles the characteristic symmetric presentation of adult rheumatoid arthritis. Rheumatoid nodules on the extensor surfaces of the elbows, spine, and over the Achilles tendons, although unusual, are associated with a more severe course and almost exclusively occur in RF-positive individuals (Fig. 155-7). Micrognathia reflects chronic temporomandibular joint disease.
Macrophage activation syndrome (MAS) is a rare but potentially fatal complication of sJIA that can occur at any time (onset, medication change, active or remission) during the disease course. It is also referred to as secondary hemophagocytic syndrome or hemophagocytic lymphohistiocytosis (HLH) (see Chapter 507). There is increasing evidence that sJIA/MAS and HLH share similar functional defects in granule-dependent cytotoxic lymphocyte activity. MAS classically manifests as acute onset of high spiking fevers, lymphadenopathy, hepatosplenomegaly, and encephalopathy. Laboratory evaluation shows thrombocytopenia and leukopenia with elevated liver enzymes, lactate dehydrogenase, ferritin, and triglycerides. Patients may have purpura and mucosal bleeding, as well as elevated fibrin split product values and prolonged prothrombin and partial prothromboplastin times. The erythrocyte sedimentation rate (ESR) falls because of hypofibrinogenemia and hepatic dysfunction, a feature useful in distinguishing MAS from a flare of systemic disease (Table 155-6). Although finalized diagnostic criteria for MAS do not currently exist, the features that were decided by an international consensus panel as the most important indicators of MAS include a falling platelet count, extreme hyperferritinemia, evidence of macrophage hemophagocytosis in the bone marrow, increased liver enzymes, falling leukocyte count, persistent, continuous fever ≥38°C (100.4°F), falling ESR, hypofibrinogenemia, and hypertriglyceridemia. A relative change in laboratory values is likely more relevant in making an early diagnosis than are absolute normal values. The diagnosis is suggested by clinical criteria and is confirmed by bone marrow biopsy demonstrating hemophagocytosis (Table 155-6).

Emergency treatment with high-dose intravenous methylprednisolone, cyclosporine, or anakinra may be effective. Severe cases may require therapy similar to that for primary HLH (see Chapter 507). Bone mineral metabolism and skeletal maturation are adversely affected in children with JIA, regardless of subtype. Children with JIA have decreased bone mass (osteopenia), which appears to be associated with increased disease activity. Increased levels of cytokines such as TNF-α and IL-6, both key regulators in bone metabolism, have deleterious effects on bone within the joint as well as systemically in the axial and appendicular bones. Abnormalities of skeletal maturation become most prominent during the pubertal growth spurt.

**DIAGNOSIS**

JIA is a clinical diagnosis without any diagnostic laboratory tests. The meticulous clinical exclusion of other diseases and many mimics is therefore essential. Laboratory studies, including tests for ANA and RF, are only supportive or prognostic, and their results may be normal in patients with JIA (see Tables 155-1 to 155-4).

**DIFFERENTIAL DIAGNOSIS**

The differential diagnosis for arthritis is broad and a careful, thorough investigation for other underlying etiology is imperative (Table 155-7). History, physical exam, laboratory tests, and radiography may help exclude other possible causes. Arthritis can be a presenting manifestation for any of the multisystem rheumatic diseases of childhood, including systemic lupus erythematosus (see Chapter 158), juvenile dermatomyositis (see Chapter 159), sarcoidosis (see Chapter 165), and
Figure 155-6 Progression of joint destruction in a girl with polyarticular juvenile idiopathic arthritis, rheumatoid factor–positive, despite doses of corticosteroids sufficient to suppress symptoms in the interval between the radiographs shown in A and B. A, Radiograph of the hand at onset. B, Radiograph taken 4 yr later, showing a loss of articular cartilage and destructive changes in the distal and proximal interphalangeal and metacarpophalangeal joints as well as destruction and fusion of wrist bones.

Figure 155-7 Rheumatoid nodules overlying bony prominences in an adolescent with rheumatoid factor–positive polyarthritis. (From Rosenberg AM, Oen KG: Polyarthritis. In Cassiday JT, Petty RE, Laxer RM, et al, editors: Textbook of pediatric rheumatology, ed 6, Philadelphia, 2011, Saunders Elsevier, Fig. 15-5, p. 257.)

Figure 155-8 CT scan of the temporomandibular joint of a patient with juvenile idiopathic arthritis exhibiting destruction on the right.

the vasculitic syndromes (see Chapter 167). In scleroderma (see Chapter 160), limited range of motion as a consequence of sclerotic skin overlying a joint may be confused with sequelae from chronic inflammatory arthritis. Acute rheumatic fever is characterized by exquisite joint pain and tenderness, a remittent fever, and a migratory polyarthritis. Autoimmune hepatitis can also be associated with an acute arthritis.

Many infections are associated with arthritis, and a recent history of infectious symptoms may help make a distinction. Viruses, including parvovirus B19, rubella, Epstein-Barr virus, hepatitis B virus, and HIV,
Figure 155-9 Radiograph of the cervical spine of a patient with active juvenile idiopathic arthritis, showing fusion of the neural arch between joints C2 and C3, narrowing and erosion of the remaining neural arch joints, obliteration of the apophyseal space, and loss of the normal lordosis.

Figure 155-10 Severe hip disease in a 13 yr old boy with active systemic juvenile idiopathic arthritis. Radiograph shows destruction of the femoral head and acetabula, joint space narrowing, and subluxation of left hip. The patient had received corticosteroids systemically for 9 yr.

Figure 155-11 High-spiking intermittent fever in a 3 yr old patient with systemic juvenile idiopathic arthritis. (From Ravelli A, Martini A: Juvenile idiopathic arthritis, Lancet 369:767–778, 2007.)

Figure 155-12 The rash of systemic juvenile idiopathic arthritis. The rash is salmon-colored, macular, and nonpruritic. Individual lesions are transient and occur in crops over the trunk and extremities. (Reprinted from the American College of Rheumatology: Clinical slide collection on the rheumatic diseases, Atlanta, copyright 1991, 1995, 1997, ACR. Used with permission of the American College of Rheumatology.)

Table 155-6 Main Clinical, Laboratory, and Pathologic Features of Macrophage Activation Syndrome

<table>
<thead>
<tr>
<th>LABORATORY CRITERIA</th>
<th>CLINICAL CRITERIA</th>
<th>HISTOPATHOLOGIC CRITERIA</th>
</tr>
</thead>
<tbody>
<tr>
<td>2. Abnormal liver function tests</td>
<td>2. Hepatomegaly</td>
<td>2. Increased CD163 staining of the bone marrow</td>
</tr>
<tr>
<td>3. Coagulopathy (hypofibrinogenemia)</td>
<td>3. Splenomegaly</td>
<td></td>
</tr>
<tr>
<td>4. Decreased erythrocyte sedimentation rate</td>
<td>4. Lymphadenopathy</td>
<td></td>
</tr>
<tr>
<td>5. Hypertiglyceridemia</td>
<td>5. Hemorrhages</td>
<td></td>
</tr>
<tr>
<td>6. Hyponatremia</td>
<td>6. Central nervous system dysfunction (headache, seizures, lethargy, coma, disorientation)</td>
<td></td>
</tr>
<tr>
<td>7. Hypoalbuminemia</td>
<td>7. Increased sCD25 and sCD163</td>
<td></td>
</tr>
<tr>
<td>8. Hypoferritinemia</td>
<td>8. Macrophage hemophagocytosis in the bone marrow</td>
<td></td>
</tr>
<tr>
<td>9. Elevated sCD25 and sCD163</td>
<td>9. Increased CD163 staining of the bone marrow</td>
<td></td>
</tr>
</tbody>
</table>


Can induce a transient arthritis. Arthritis may follow enteric infections (see Chapter 157). Lyme disease (see Chapter 222) should be considered in children with oligoarthritis living in or visiting endemic areas. Although a history of tick exposure, preceding flu-like illness, and subsequent rash should be sought, they are not always present. Monoarticular arthritis unresponsive to antiinflammatory treatment may be the result of chronic mycobacterial or other infection such as Kingella kingae, and the diagnosis is established by synovial fluid analysis or biopsy. Acute onset of fever and a painful, erythematous, hot joint suggests septic arthritis. Isolated hip pain with limited motion raises the possibility of suppurative arthritis (see Chapter 685), osteomyelitis (see Chapter 684), toxic synovitis, Legg-Calvé-Perthes disease, slipped capital femoral epiphysis, and chondrolysis of the hip (see Chapter 678). Lower-extremity arthritis and tenderness over insertion of ligaments and tendons, especially in a boy, raises the possibility of ERA (see Chapter 156). Psoriatic arthritis can manifest as limited joint involvement in an unusual distribution (e.g., small joints of the hand and
Inflammatory bowel disease may manifest as oligoarthritis, usually affecting joints in the lower extremities, as well as gastrointestinal symptoms, elevations in ESR, and microcytic anemia. Many conditions present solely with arthralgias (i.e., joint pain). Hypermobility may cause joint pain, especially in the lower extremities. Growing pains should be suspected in a child between the ages of 4-12 yr complaining of leg pain in the evenings with normal investigative studies and no morning symptoms. Nocturnal pain also alerts to the possibility of a malignancy. An adolescent with missed school days may suggest a diagnosis of fibromyalgia (see Chapter 168). Children with leukemia or neuroblastoma may have joint or bone pain resulting from malignant infiltration of the bone, synovium, or, more often, the bone marrow, sometimes mo before demonstrating lymphoblasts on peripheral blood smear. Physical examination may reveal no tenderness, a deeper pain with palpation of the bone, or pain out of proportion to exam findings. Malignant pain often awakens the child from sleep and may cause cytopenias. Because platelets are an acute-phase reactant, a high ESR with leukopenia and a low normal platelet count may also be a clue to underlying leukemia. In addition, the characteristic quotidian fever of sJIA is absent in malignancy. Bone marrow examination is necessary for diagnosis. Some diseases, such as cystic fibrosis, diabetes mellitus, and the glycogen storage diseases, have associated arthropathies (see Chapter 169). Swelling that extends beyond the joint can be a sign of lymphedema or Henoch-Schönlein purpura (see Chapter 515). A peripheral arthritis indistinguishable from JIA occurs in the humoral immunodeficiencies (see Chapter 124), such as common variable immunodeficiency and
X-linked agammaglobulinemia. Skeletal dysplasias associated with a degenerative arthropathy are diagnosed from their characteristic radiologic abnormalities.

Systemic onset of JIA often presents as an fever of unknown origin (see Chapter 177). Important considerations in the differential diagnosis include infections (endocarditis, brucellosis, cat scratch disease, Q fever, mononucleosis), autoinflammatory disease (see Chapter 163) malignancy (leukemia, lymphoma, neuroblastoma) and HLH (see Chapter 507.2).

**LABORATORY FINDINGS**

Hematologic abnormalities often reflect the degree of systemic or articular inflammation, with elevated white blood cell and platelet counts and a microcytic anemia. Inflammation may also cause elevations in ESR and C-reactive protein, although it is not unusual for both to be normal in children with JIA.

Elevated ANA titers are present in 40-85% of children with oligoarticular or polyarticular JIA, but are rare with sJIA. ANA seropositivity is associated with increased risk of chronic uveitis in JIA. Approximately 5-15% of patients with polyarticular JIA are seropositive for RF. Anti–cyclic citrullinated peptide antibody, like RF, is a marker of more aggressive disease. Both ANA and RF seropositivity can occur in association with transient events, such as viral infection.

Children with sJIA usually have striking elevations in inflammatory markers and white blood cell and platelet counts. Hemoglobin levels are low, typically in the range of 7-10 g/dL, with indices consistent with anemia of chronic disease. The ESR is usually high, except in MAS. Although immunoglobulin levels tend to be high, ANA and RF are uncommon. Ferritin values are typically elevated and can be markedly increased in MAS (>10,000 ng/mL). In the setting of MAS, all cell lines have the potential to decline precipitously owing to the consumptive process. A low or normal white blood cell count and/or platelet count in a child with active sJIA should raise concerns for MAS.

Early radiographic changes of arthritis include soft tissue swelling, periarticular osteopenia, and periosteal new-bone apposition around affected joints (Fig. 155-13). Continued active disease may lead to subchondral erosions, loss of cartilage, with varying degrees of bony destruction, and fusion. Characteristic radiographic changes in cervical spine, most frequently in the neural arch joints at C2-C3 (see Fig. 155-9) may progress to atlantoaxial subluxation. MRI is more sensitive than radiography to detect early changes (Fig. 155-14).

**TREATMENT**

The goals of treatment are to achieve disease remission, prevent or halt joint damage, and foster normal growth and development. All children with JIA need individualized treatment plans, and management is tailored according to disease subtype and severity, presence of poor

![Figure 155-13](imageURL) Early (6 mo duration) radiographic changes of juvenile idiopathic arthritis. Soft-tissue swelling and periosteal new bone formation appear adjacent to the 2nd and 4th proximal interphalangeal joints.

![Figure 155-14](imageURL) MRI of the wrist in a child with wrist arthritis. Image on the left shows multiple erosions of carpal bones. Image on the right, obtained after administration of gadolinium contrast agent, reveals uptake consistent with active synovitis.
Pharmacologic Treatment of Juvenile Idiopathic Arthritis (JIA)

**TYPICAL MEDICATIONS** | **TYPICAL DOSES** | **JIA SUBTYPE** | **SIDE EFFECT(S)**
--- | --- | --- | ---
**NONSTEROIDAL ANTIINFLAMMATORY DRUGS**
Naproxen | 15 mg/kg/day PO divided bid (maximum dose 500 mg bid) | Polyarthritis | Gastritis, renal and hepatic toxicity, pseudoporphyria
Ibuprofen | 40 mg/kg/day PO divided tid (maximum dose 800 mg tid) | Systemic Oligoarthritis | Same as above
Meloxicam | 0.125 mg/kg PO once daily (maximum dose 15 mg daily) | Same as above | Same as above
**DISEASE-MODIFYING ANTIRHEUMATIC DRUGS**
Methotrexate | 0.5-1 mg/kg PO or SC weekly (maximum dose 25 mg/wk) | Polyarthritis | Nausea, vomiting, oral ulcerations, hepatic toxicity, blood count dyscrasias, immunosuppression, teratogenicity
Sulfasalazine | Initial 12.5 mg/kg PO daily; increase by 10 mg/kg/day | Persistent or extended oligoarthritis | GI upset, allergic reaction, pancytopenia, renal and hepatic toxicity, Stevens-Johnson syndrome
Leflunomide* | 10-20 mg PO daily | Polyarthritis | GI upset, hepatic toxicity, allergic rash, alopecia (reversible), teratogenicity (needs washout with cholestyramine)
**BIOLOGIC AGENTS**
Anti-Tumor Necrosis Factor-α
Etanercept | 0.8 mg/kg SC weekly or 0.4 mg/kg SC twice weekly (maximum dose 50 mg/wk) | Polyarthritis Systemic | Immunosuppressant, concern for malignancy, demyelinating disease, lupus-like reaction, injection site reaction
Infliximab* | 3-10 mg/kg IV q4-8wk | Persistent or extended oligoarthritis | Same as above, infusion reaction
Adalimumab | <30 kg: 20 mg SC every other week; >30 kg: 40 mg SC every other week | Same as above | Same as above
Anti-CD20
Rituximab* | 750 mg/m² IV 2 wk x 2 (maximum dose 1,000 mg) | Polyarthritis | Immunosuppressant, infusion reaction, progressive multifocal encephalopathy
**Interleukin-1 Inhibitors**
Anakinra* | 1-2 mg/kg SC daily (maximum dose 100 mg/day) | Polyarthritis | Immunosuppressant, GI upset, injection site reaction
Canakinumab | 15-40 kg: 2 mg/kg/dose SC q8wk; >40 kg: 150 mg SC q8wk | Systemic | Immunosuppressant, headache, GI upset, injection site reaction
Rilonacept* | 2.2 mg/kg/dose SC weekly (maximum dose 160 mg) | Systemic | Immunosuppressant, allergic reaction, dyslipidemia, injection site reaction
**Interleukin-6 Receptor Antagonist**
Tocilizumab | <30 kg: 12 mg/kg/dose q2wk; >30 kg: 8 mg/kg/dose q2wk (maximum dose 800 mg) | Polyarthritis | Immunosuppressant, hepatic toxicity, dyslipidemia, cytopenias, GI upset, infusion reaction

*bid, Twice daily; GI, gastrointestinal; IV, intravenous; PO, oral; SC, subcutaneous; tid, 3 times daily.

*Not indicated by the U.S. Food and Drug Administration for use in JIA.

prognostic indicators, and response to medications. Disease management also requires monitoring for potential medication toxicities (see Chapter 154).

Children with oligoarthritis often show partial response to nonsteroidal antiinflammatory drugs (NSAIDs), with improvement in inflammation and pain (Table 155-8). Those who have no or partial response after 4-6 wk of treatment with NSAIDs or who have functional limitations, such as joint contracture or leg-length discrepancy, benefit from injection of intraarticular corticosteroids. Triamcinolone hexacetonide is a long-lasting preparation that provides a prolonged response. A minority of patients with oligoarthritis show no response to NSAIDs and injections, and therefore require treatment with disease-modifying antirheumatic drugs (DMARDs), methotrexate, and, if no response, TNF inhibitors. NSAIDs alone rarely induce remission in children with polyarthritis or sJIA. Methotrexate is the oldest and least toxic of the DMARDs available for adjunctive therapy. It may take 6-12 wk to see the effects of methotrexate. Failure of methotrexate monotherapy warrants the addition of a biologic DMARD. Biologic medications that inhibit proinflammatory cytokines, such as TNF-α, IL-1, and IL-6, demonstrated excellent disease control. TNF-α antagonists (e.g., etanercept, adalimumab) are used to treat children with an inadequate response to methotrexate, with poor prognostic factors, or with severe disease onset. Early aggressive therapy with a combination of methotrexate and a TNF-α antagonist may result in earlier achievement of clinically inactive disease.

TNF inhibition is not as effective for the systemic symptoms found in sJIA. When systemic symptoms dominate systemic steroids are started followed by the initiation of IL-1 or IL-6 antagonist therapy, which often induces a dramatic and rapid response. Patients with severe disease activity may go directly to anakinra. Canakinumab, an IL-1β inhibitor, and tocilizumab, an IL-6 receptor antagonist, are
FDA-approved treatments for sJIA in children older than 2 yr. Standardized consensus treatment plans have been published to guide therapy for sJIA. These outline 4 treatment plans based on glucocorticoids, methotrexate, anakinra, or tocilizumab with optional glucocorticoid use in the latter 3 plans as clinically indicated. With the advent of newer DMARDs, the use of systemic corticosteroids can often be avoided or minimized. Systemic steroids are recommended only for management of severe systemic illness, for bridge therapy during the wait for therapeutic response to a DMARD, and for control of uveitis. Steroids impose risks of severe toxicities, including Cushing syndrome, growth retardation, and osteopenia, and they do not prevent joint destruction.

Oral Janus kinase (JAK) inhibitors (tofacitinib, ruxolitinib) inhibit JAK signaling pathways involved in immune activation and inflammation. Tofacitinib is FDA approved for adults with rheumatoid arthritis.

Management of JIA must include periodic slit-lamp ophthalmologic examinations to monitor for asymptomatic uveitis (see Table 155-5; Figs. 155-15 and 155-16). Optimal treatment of uveitis requires collaboration between the ophthalmologist and rheumatologist. Initial management of uveitis may include mydriatics and corticosteroids used topically, systemically, or through periocular injection. DMARDs allow for a decrease in exposure to steroids, and methotrexate and antibodies to TNF-α (adalimumab and infliximab) are effective in treating severe uveitis.

Dietary evaluation and counseling to ensure appropriate calcium, vitamin D, protein, and caloric intake are important for children with JIA. Physical therapy and occupational therapy are invaluable adjuncts to any treatment program. A social worker and nurse clinician can be important resources for families, to recognize stresses imposed by a chronic illness, to identify appropriate community resources, and to aid compliance with the treatment protocol.

**PROGNOSIS**

Although the course of JIA in an individual child is unpredictable, some prognostic generalizations can be made on the basis of disease type and course. Studies analyzing management of JIA in the pre-TNF-α era indicate that up to 50% of patients with JIA have active disease persisting into early adulthood, often with severe limitations of physical function.

Children with persistent oligoarticular disease fare well, with a majority achieving disease remission. Those with extended oligoarticular disease have a poorer prognosis. Children with oligoarthritis, particularly girls who are ANA-positive and with onset of arthritis earlier than 6 yr of age, are at greatest risk for development of chronic uveitis. There is no association between the activity or severity of arthritis and uveitis. Persistent, uncontrolled anterior uveitis (see Fig. 155-15) can cause posterior synechiae, cataracts, glaucoma, and band keratopathy, with resultant blindness. Morbidity can be averted with early diagnosis and implementation of systemic therapy.

The child with polyarticular JIA often has a more prolonged course of active joint inflammation and requires early and aggressive therapy. Predictors of severe and persistent disease include young age at onset, RF seropositivity or rheumatoid nodules, the presence of anti–cyclic citrullinated peptide antibodies, and large numbers of affected joints. Disease involving the hip and hand and wrist is also associated with a poorer prognosis and may lead to significant functional impairment.

sJIA is often the most difficult to control in terms of both articular inflammation and systemic manifestations. Poorer prognosis is related to polyarticular distribution of arthritis, fever lasting >3 mo, and increased inflammatory markers, such as platelet count and ESR, for >6 mo. IL-1 and IL-6 inhibitors, have changed the management and improved the outcomes for children with severe and prolonged systemic disease.

Orthopedic complications include leg length discrepancy and flexion contractures, particularly of the knees, hips, and wrists. Discrepancies in leg length can be managed with a shoe lift on the shorter side to prevent secondary scoliosis. Joint contractures require aggressive medical control of arthritis, often in conjunction with intraarticular corticosteroid injections, appropriate splinting, and stretching of the affected tendons. Popliteal cysts may require no treatment if they are small or respond to intraarticular corticosteroid injection in the anterior knee.

Psychosocial adaptation may be affected by JIA. Studies indicate that, compared with control subjects, a significant number of children with JIA have problems with lifetime adjustment and employment. Disability not directly associated with arthritis may continue into young adulthood in as many as 20% of patients, together with continuing chronic pain syndromes at a similar frequency. Psychological complications, including problems with school attendance and socialization, may respond to counseling by mental health professionals.

*Bibliography is available at Expert Consult.*
Bibliography


Chapter 156
Ankylosing Spondylitis and Other Spondyloarthritides
Pamela F. Weiss and Robert A. Colbert

The diseases collectively referred to as spondyloarthritides include ankylosing spondylitis (AS), arthritis associated with inflammatory bowel disease (IBD) and psoriasis, and reactive arthritis following gastrointestinal or genitourinary infections (Tables 156-1 and 156-2). Many children with spondyloarthritis are classified in the juvenile idiopathic arthritis (JIA) category of enthesitis-related arthritis (ERA). Children and adolescents with spondyloarthritis, who may not meet ERA criteria, include arthritis associated with psoriasis or IBD, juvenile AS (JAS), and reactive arthritis.

EPIDEMIOLOGY
JIA is diagnosed in 90 per 100,000 children in the United States every year (see Chapter 155). ERA accounts for 10-20% of JIA, and has a mean age of onset of 12 yr. Unlike other JIA categories, males are affected more often than females, accounting for 60% of ERA cases. AS occurs in 0.2-0.5% of adults, with approximately 15% of cases beginning in childhood. These disorders can be familial, largely as a result of the influence of HLA-B27, which is found in 90% of JAS and 50% of ERA compared to 7% of healthy individuals. Approximately 20% of children with ERA have a family history of HLA-B27–associated disease, such as reactive arthritis, AS, or IBD with sacroiliitis.

ETIOLOGY AND PATHOGENESIS
Spondyloarthritides are complex diseases in which susceptibility is largely genetically determined. HLA-B27 is responsible for 23.3% of AS heritability, with genes encoding the interleukin (IL)-23 receptor (IL23R), ERAP1 (endoplasmic reticulum aminopeptidase-1), IL-12p40 (IL12B), and others having important roles, but together accounting for only approximately 2% of heritability. Infection with certain gastrointestinal or genital pathogens can trigger reactive arthritis (see Chapter 157 and Table 156-2); environmental triggers for other forms of spondyloarthritis have not been identified. Unusual properties of HLA-B27, such as its tendency to misfold and form unusual cell surface structures, may have a role. Inflamed joints and entheses in spondyloarthritides contain T cells, B cells, macrophages, osteoclasts, proliferating fibroblasts and osteoblasts. Bone loss and osteoproliferation in and around vertebral bodies and facet joints in long-standing AS contribute to significant morbidity.

CLINICAL MANIFESTATIONS AND DIAGNOSIS
Clinical manifestations that help distinguish spondyloarthritides from other forms of juvenile arthritis include arthritis of the axial skeleton (sacroiliac joints) and hips, enthesitis (inflammation at the site of tendon, ligament, or joint capsule attachment to bone), symptomatic eye inflammation (acute anterior uveitis), and gastrointestinal inflammation (even in the absence of IBD) (see Table 156-1).

Enthesitis-Related Arthritis
Children have ERA if they have either arthritis and enthesitis or arthritis or enthesitis, with at least 2 of the following characteristics: (1) sacroiliac joint tenderness or inflammatory lumbosacral pain, (2) the presence of HLA-B27, (3) onset of arthritis in a male older than 6 yr,

| Table 156-1 | Overlapping Characteristics of the Spondyloarthritides |
| --- | --- | --- | --- | --- |
| CHARACTERISTIC | JUVENILE ANKYLOSING SPONDYLITIS | JUVENILE PSORIATIC ARTHRITIS | INFLAMMATORY BOWEL DISEASE | REACTIVE ARTHRITIS |
| Enthesis | +++ | + | + | ++ |
| Axial arthritis | +++ | ++ | ++ | + |
| Peripheral arthritis | +++ | +++ | +++ | +++ |
| HLA-B27 positive | +++ | + | +++ | +++ |
| Antinuclear antibody positive | – | + | – | – |
| Rheumatoid factor positive | – | – | – | – |
| Systemic disease: | | | | |
| Eyes | + | + | + | + |
| Skin | – | ++ | + | + |
| Mucous membranes | – | – | + | + |
| Gastrointestinal tract | – | – | +++ | +++ |

Frequency of characteristics: –, absent; +, <25%; ++, 25-50%; ++++, 50-75%; ++++, 75% or more

Table 156-2 | Etiologic Microorganisms of Reactive Arthritis |
<table>
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<tr>
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<tbody>
<tr>
<td>PROBABLE</td>
<td>POSSIBLE</td>
</tr>
<tr>
<td>Chlamydia trachomatis</td>
<td>Neisseria gonorrhoeae</td>
</tr>
<tr>
<td>Shigella flexneri</td>
<td>Mycoplasma fermentans</td>
</tr>
<tr>
<td>Salmonella enteritidis</td>
<td>Mycoplasma genitalium</td>
</tr>
<tr>
<td>Salmonella typhimurium</td>
<td>Ureaplasma urealyticum</td>
</tr>
<tr>
<td>Yersinia enterocolitica</td>
<td>Escherichia coli</td>
</tr>
<tr>
<td>Yersinia pseudotuberculosis</td>
<td>Cryptosporidium</td>
</tr>
<tr>
<td>Campylobacter jejuni</td>
<td>Entamoeba histolytica</td>
</tr>
<tr>
<td>Giardia lamblia</td>
<td>Clostridi um difficile</td>
</tr>
<tr>
<td>Brucella abortus</td>
<td>Streptococcus pyogenes</td>
</tr>
<tr>
<td>Chlamydia pneumoniae</td>
<td>Chlamydia psittaci</td>
</tr>
</tbody>
</table>

Psoriatic Arthritis

Psoriatic arthritis accounts for approximately 10% of JIA. Common clinical features of psoriatic arthritis are nail pitting (Fig. 156-1), onycholysis, and dactylitis (sausage-like swelling of the fingers or toes).

Children have psoriatic arthritis if they have arthritis and psoriasis or arthritis and at least 2 of the following: (1) dactylitis, (2) nail pitting or onycholysis, or (3) psoriasis in a 1st-degree relative. The presence of psoriasis aids in diagnosis but is not required. Disease onset peaks during the preschool and early adolescent years. Children with onset during the preschool years are more often female, antinuclear antibody–positive, and at risk for asymptomatic ocular inflammation.

Table 156-3

<table>
<thead>
<tr>
<th>Symptoms Characteristic of Inflammatory Back Pain</th>
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<tbody>
<tr>
<td>Pain at night with morning stiffness (and improvement upon arising)</td>
</tr>
<tr>
<td>No improvement with rest</td>
</tr>
<tr>
<td>Improvement with exercise</td>
</tr>
<tr>
<td>Insidious onset</td>
</tr>
<tr>
<td>Good response to nonsteroidal antiinflammatory drugs</td>
</tr>
</tbody>
</table>

Disease onset during adolescence is equally common among males and females. In the majority of children, the arthritis is asymmetric and affects 4 or fewer joints at presentation. Large (knees and ankles) and small (fingers and toes) joints may be involved. Although distal interphalangeal joint involvement is uncommon, it is highly suggestive of the diagnosis. Enthesitis is detectable in 20-60% of patients and seems to be more frequent in those who present at an older age. Axial (sacroiliac) and root (hip) joints may be affected in up to 30% of children; the risk of axial arthritis is highest in those who are HLA-B27-positive.

Juvenile Ankylosing Spondylitis

JAS frequently begins with oligoarthritis and enthesitis. The arthritis occurs predominantly in the lower extremities and often involves the hips. In comparison to adult-onset AS, axial disease and inflammatory back pain are less frequent at disease onset, while enthesitis and peripheral arthritis are more common. AS is diagnosed according to the modified NY criteria if there is sufficient radiographic evidence of sacroiliitis (sacroiliitis of grade 2 or greater bilaterally or at least grade 3 unilaterally) and if the patient meets at least one clinical criterion involving inflammatory back pain, limitation of motion in the lumbar spine (Fig. 156-2), or limitation of chest expansion. JAS is present if the patient is <16 yr old. Juvenile onset AS is frequently used to describe adult AS when the symptoms began before 16 yr of age, but full criteria were not met until later.

To fulfill the modified New York criteria for AS, patients must have radiographic changes in the sacroiliac joints as well as clinical sequelae of axial disease. Because radiographic sacroiliitis can take many years to develop in adults and even longer in children, and clinical sequelae may lag further behind, criteria to identify pre-radiographic axial spondyloarthritis have been developed by the Assessment of SpondyloArthritis International Society. To meet criteria for axial spondyloarthritis patients must have at least 3 mo of back pain and sacroiliitis on imaging (acute inflammation on MRI or definite radiographic sacroiliitis by the New York criteria) plus 1 feature of spondyloarthritis (i.e., inflammatory back pain, arthritis, enthesitis [heel], uveitis, dactylitis, psoriasis, Crohn disease/ulcerative colitis, good response to nonsteroidal antiinflammatory drugs [NSAIDs], family history for spondyloarthritis, HLA-B27, or elevated C-reactive protein). Alternatively, patients can fulfill axial spondyloarthritis criteria if
they are HLA-B27–positive and have at least 2 features of spondyloarthritis. These criteria have not been validated in the pediatric population but may be useful as a guide to evaluating preradiographic spondyloarthritis.

**Arthritis with Inflammatory Bowel Disease**
The presence of erythema nodosum, pyoderma gangrenosum, fever, weight loss, or anorexia in a child with chronic arthritis should raise suspicion of IBD. Two patterns of arthritis complicate IBD. Polyarthritis affecting large and small joints is most common and often reflects the activity of the intestinal inflammation. Less frequently, arthritis of the axial skeleton, including the sacroiliac joints, occurs, resulting in AS. As with psoriatic arthritis, the presence of HLA-B27 is a risk factor for the development of axial disease. The severity of axial involvement is independent of the activity of the gastrointestinal inflammation.

**Laboratory Findings**
Laboratory evidence of systemic inflammation with elevation of the erythrocyte sedimentation rate and/or C-reactive protein value is variable in most spondyloarthritides and may or may not be present at the onset of disease. Rheumatoid factor and antinuclear antibodies are absent, except in patients with psoriatic arthritis, of which as many as 50% are antinuclear antibody–positive. HLA-B27 is present in ≈90% of children with JAS, compared with ≈7% of healthy individuals but is less frequent in ERA and other types of spondyloarthritis.

**Imaging**
Conventional radiographs detect chronic bony changes and damage but not active inflammation. Early radiographic changes in the sacroiliac joints include indistinct margins and erosions that can result in joint space widening. Sclerosis typically starts on the iliac side of the joint (Fig. 156-3). Peripheral joints may exhibit periarthritis osteoporosis, with loss of sharp cortical margins in areas of enthesis, which may eventually show erosions or bony spurs (entheses osteophytes). Squaring of the corners of the vertebral bodies and syndesmophyte formation resulting in the classic “bamboo spine” characteristic of advanced AS is rare in early disease, particularly in childhood. CT, like radiographs, can detect chronic bony changes but not active inflammation and has the disadvantage of more radiation exposure. The gold standard for early visualization of sacroiliitis is evidence of bone marrow edema adjacent to the joint on MRI with short T1 inversion recovery (STIR) sequences. Gadolinium does not add value to the study if STIR is used. MRI will reveal abnormalities before the plain radiograph. Whole body MRI is also used to evaluate the axial skeleton in adults with early disease as it can detect vertebral lesions in addition to sacroiliac changes.

**DIFFERENTIAL DIAGNOSIS**
The onset of arthritis following a recent history of diarrhea or symptoms of urethritis or conjunctivitis may suggest reactive arthritis (see Chapter 157). Lower back pain can be caused by suppurrative arthritis of the sacroiliac joint, osteomyelitis of the pelvis or spine, osteoid osteoma of the posterior elements of the spine, pelvic muscle pyomyositis, or malignancies. In addition, mechanical conditions such as spondylolysis, spondylolisthesis, and Scheuermann disease should be considered. Back pain secondary to fibromyalgia usually affects the soft tissues of the upper back in a symmetric pattern and is associated with well-localized tender points and sleep disturbance (see Chapter 168.1). Legg-Calvé-Perthes disease (avascular necrosis of the femoral head), slipped capital femoral epiphysis, and chondrolysis may also manifest as pain over the inguinal ligament and loss of internal rotation of the hip joint, but without other features of spondyloarthritis, such as involvement of other entheses and/or joints. Radiography or MRI is critical for distinguishing these conditions.

**TREATMENT**
The goals of therapy are to control inflammation, minimize pain, preserve function, and prevent ankylosis (fusion of adjacent bones) using a combination of antiinflammatory medications, physical therapy, and education. Treatment regimens for spondyloarthritis include monotherapy or combination therapy with NSAIDs, disease-modifying antirheumatic drugs, or biologic agents. NSAIDs, such as naproxen (15–20 mg/kg/day), are frequently used initially and may reduce structural damage (syndesmophyte formation and growth) if used continuously. With relatively mild disease, intraarticular corticosteroids (e.g., triamcinolone hexacetonide) may also help to control peripheral joint inflammation. However, for moderate disease and JAS, it is typically necessary to add a second-line agent. Disease-modifying antirheumatic drugs such as sulfasalazine (up to 50 mg/kg/day; maximum 3 g/day) or methotrexate (10 mg/m²) may be beneficial for peripheral arthritis, but these medications have not been shown to improve axial disease in adults. Tumor necrosis factor-α inhibitors (e.g., etanercept, infliximab, adalimumab) have been efficacious in reducing symptoms and improving function in adults with AS, and there is evidence that similar responses are seen in children. It remains unclear whether tumor necrosis factor inhibitors have an impact on structural damage in established AS, underscoring the need for earlier recognition and better therapies.

Physical therapy and low-impact exercise should be included in the treatment program for all children with spondyloarthritis. Exercise to maintain range of motion in the back, thorax, and affected joints should be instituted early in the disease course. Custom-fitted insoles are particularly useful in management of painful entheses around the feet, and the use of pillows to position the lower extremities while the child is in bed can be helpful.

**Prognosis**
Observational studies suggest that ongoing disease activity for greater than 5 yr in juvenile spondyloarthritis predicts disability. Disease remission occurs in less than 20% of children with spondyloarthritis 5 yr after diagnosis. Factors associated with disease progression include tarstitis, HLA-B27 positivity, hip arthritis within the 1st 6 mo, and disease onset after age 8. Important questions, such as which patients with ERA will go on to have JAS/AS, have yet to be addressed. Outcomes for JAS compared with adult-onset AS suggest that hip disease requiring replacement is more common in children but axial disease is more severe in adults.

_Bibliography is available at Expert Consult._
Bibliography
Reactive and Postinfectious Arthritis

Chapter 157

Pamela F. Weiss and Robert A. Colbert

In addition to causing arthritis by means of direct microbial infection (i.e., septic arthritis; see Chapter 685), infection can lead to the generation and deposition of immune complexes as well as antibody or T cell–mediated cross-reactivity with self. Microbes may influence the immune response in ways that indirectly affect susceptibility to immune-mediated inflammatory diseases such as systemic lupus erythematosus, inflammatory bowel disease, juvenile idiopathic arthritis, and spondyloarthritis. Reactive and postinfectious arthritides are defined as joint inflammation caused by a sterile inflammatory reaction following a recent infection. We use reactive arthritis to refer to arthritis that occurs following enteropathogenic or urogenital infections and postinfectious arthritis to describe arthritis that occurs after infectious illnesses not classically considered in the reactive arthritis group, such as infection with group A streptococcus or viruses. In some instances, nonviable components of the initiating organism have been demonstrated in affected joints, and the presence of viable, yet nonculturable, bacteria within the joint remains an area of investigation.

The course of reactive arthritis is variable and may remit or progress to a chronic spondyloarthritis including ankylosing spondylitis (see Chapter 156). In postinfectious arthritis, the pain or joint swelling is usually transient, lasting less than 6 wk, and does not necessarily share the typical spondyloarthritis pattern of joint involvement. The distinction between postinfectious arthritis and reactive arthritis is not always clear, either clinically or in terms of pathophysiology.

PATHOGENESIS

Reactive arthritis typically follows enteric infection with Salmonella sp., Shigella flexneri, Yersinia enterocolitica, Campylobacter jejuni, or genitourinary tract infection with Chlamydia trachomatis. Escherichia coli and Clostridium difficile are also causative enteric agents, although less common (see Table 156-2 in Chapter 156). Although similar in some respects to reactive arthritis, acute rheumatic fever caused by group A streptococcus (see Chapters 183.1 and 438), arthritis associated with infective endocarditis (see Chapter 437), and the tenosynovitis associated with Neisseria gonorrhoeae are considered in later chapters.

Approximately 75% of patients with reactive arthritis are HLA-B27–positive. Incomplete elimination of bacteria and bacterial products, such as DNA, has been proposed as a factor in reactive arthritis. A relationship with clinical characteristics of specific infectious disorders is not present. In postinfectious arthritis, several viruses (rubella, varicella-zoster, herpes simplex, cytomegalovirus) have been isolated from the joints of patients. Antigens from other viruses (e.g., hepatitis B, adenovirus) have been identified in immune complexes from joint tissue.

Patients with reactive arthritis who are HLA-B27–positive have an increased frequency of acute and symptomatic uveitis and other extraarticular features. In addition, HLA-B27 is a risk factor for persistent gastrointestinal inflammation following enteric infections, even after resolution of the initial infection, and significantly increases the risk that the individual will develop chronic spondyloarthritis. Nevertheless, reactive arthritis also occurs in HLA-B27–negative patients, emphasizing the importance of other genes in disease susceptibility.
Viruses Associated with Arthritis

<table>
<thead>
<tr>
<th>TOGAVIRUSES</th>
<th>ADENOVIRUSES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rubella</td>
<td>Adenovirus 7</td>
</tr>
<tr>
<td>ALPHAVIRUSES</td>
<td></td>
</tr>
<tr>
<td>Ross River</td>
<td></td>
</tr>
<tr>
<td>Chikungunya</td>
<td></td>
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<tr>
<td>O’nyong-nyong</td>
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<tr>
<td>Mayaro</td>
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</tr>
<tr>
<td>Sindbis</td>
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<tr>
<td>Ockelbo</td>
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<tr>
<td>Pogosta</td>
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</tr>
<tr>
<td>ORTHOPOXVIRUSES</td>
<td></td>
</tr>
<tr>
<td>Variola virus (smallpox)</td>
<td></td>
</tr>
<tr>
<td>Vaccinia virus</td>
<td></td>
</tr>
<tr>
<td>Paroviruses</td>
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</table>


Specific treatment is unnecessary for most cases of reactive or postinfectious arthritis. Nonsteroidal antiinflammatory agents are often needed for management of pain and functional limitation. Unless ongoing *Chlamydia* infection is suspected, attempts to treat the offending organism are not warranted. If swelling or arthralgia recurs, further evaluation may be necessary to exclude active infection or evolving rheumatic disease. Intraarticular steroid injections may be utilized for refractory or severely involved joints once acute infection has been ruled out. Systemic steroids or disease-modifying anti-rheumatic drugs are rarely indicated but may be considered for chronic disease. Participation in physical activity should be encouraged, and physical therapy may be needed to maintain normal function and prevent muscle atrophy. For postinfectious arthritis due to streptococcal disease, current recommendations include penicillin prophylaxis for at least 1 yr. Long-term prophylaxis is often recommended, but the duration is controversial and may need to be individualized.

**Complications and Prognosis**

Postinfectious arthritis following viral infections usually resolves without complications unless it is associated with involvement of other organs, such as encephalomyelitis. Children with reactive arthritis after enteric infections occasionally experience inflammatory bowel disease months to years after onset. Both uveitis and carditis have been reported in children diagnosed with reactive arthritis. Reactive arthritis, especially after bacterial enteric infection or genitourinary tract infection with *C. trachomatis*, has the potential for evolving to chronic arthritis, particularly spondylarthrits (see Chapter 156). The presence of HLA-B27 or significant systemic features increases the risk of chronic disease.

Bibliography is available at Expert Consult.
Bibliography
Systemic lupus erythematosus (SLE) is a chronic autoimmune disease characterized by multisystem inflammation and the presence of circulating autoantibodies directed against self-antigens. SLE occurs in both children and adults, disproportionately affecting females of reproductive age. Although nearly every organ may be affected, most commonly involved are the skin, joints, kidneys, blood-forming cells, blood vessels, and the central nervous system. Compared with adults, children and adolescents with SLE have more severe disease and more widespread organ involvement.

ETIOLOGY
The pathogenesis of SLE remains largely unelucidated, but several factors likely influence risk and severity of disease, including genetics, hormonal milieu, and environmental exposures.

A genetic predisposition to SLE is suggested by the association with specific genetic abnormalities, including congenital deficiencies of C1q, C2, and C4, as well as several polymorphisms (e.g., interferon regulatory factor 5 and protein tyrosine phosphatase N22), and familial clustering of SLE or other autoimmune disease. In addition, certain human leukocyte antigen (HLA) types (including HLA-B8, HLA-DR2, and HLA-DR3) occur with increased frequency in patients with SLE. Although SLE clearly has a genetic component, its occurrence is sporadic in families and its concordance is incomplete (estimated at 2-5% among dizygotic twins and 25-60% among monozygotic twins), suggesting that multiple genes are involved and that epigenetic and non-genetic factors are also important in disease expression.

Because SLE preferentially affects females, especially during their reproductive years, it is suspected that hormonal factors are important in pathogenesis. Of individuals with SLE, 90% are female, making gender the strongest risk factor for SLE. Estrogens are likely to play a role in SLE, and both in vitro and animal model studies suggest that estrogen exposure promotes B-cell autoreactivity. Estrogen-containing oral contraceptives do not appear to induce flares in quiescent SLE, whereas estrogen exposure promotes B-cell autoreactivity. Estrogen-containing oral contraceptives do not appear to induce flares in quiescent SLE, but their risk of flares may be increased in postmenopausal women receiving hormone replacement.

Environmental exposures that may trigger the development of SLE remain largely unknown; certain viral infections (including Epstein-Barr virus) may play a role in susceptible individuals, and ultraviolet light exposure is known to aggravate SLE disease activity. Environmental influences also may induce epigenetic modifications to DNA, which increase the risk of SLE and drug-induced lupus; in mouse models, drugs such as procainamide and hydralazine can promote lymphocyte hypomethylation causing a lupus-like syndrome.

EPIDEMIOLOGY
The reported prevalence of SLE in children and adolescents (1-6/100,000) is lower than that in adults (20-70/100,000). Prevalence of SLE is highest among African-Americans, Asians, Hispanics, Native Americans, and Pacific Islanders for both adult and pediatric populations. SLE predominantly affects females, with reported 2.5:1 ratio prior to puberty, 9:1 ratio during reproductive years, and return to near prepubertal ratios in the postmenopausal period. Childhood SLE is rare before 5 yr of age and is usually diagnosed in adolescence, with a median age at diagnosis of 11-12 yr. Up to 20% of all individuals with SLE are diagnosed prior to age 16 yr.

PATHOLOGY
Histologic features most suggestive of SLE include findings in the kidney and skin, especially the discoid rash. Renal manifestations of SLE are classified histologically according to the criteria of the International Society of Nephrology (see Chapter 514). The finding of diffuse proliferative glomerulonephritis (class IV) significantly increases risk for renal morbidity. Renal biopsies are helpful to establish the diagnosis of SLE and to stage disease. Immune complexes are commonly found with “full house” deposition of immunoglobulin and complement. The characteristic discoid rash depicted in Figure 158-1D is characterized on biopsy by hyperkeratosis, follicular plugging, and infiltration of mononuclear cells into the dermal-epidermal junction. The histopathology of photosensitive rashes can be nonspecific, but immunofluorescence examination of both affected and nonaffected skin may reveal deposition of immune complexes within the dermal–epidermal junction. This finding is called the lupus band test, which is specific for SLE.

PATHOGENESIS
A hallmark of SLE is the generation of autoantibodies directed against self-antigens, particularly nucleic acids. These intracellular antigens are ubiquitously expressed but are usually inaccessible and cloistered within the cell. During cell necrosis or apoptosis, the antigens are released. SLE skin cells are highly susceptible to damage from ultraviolet light, and the resulting cell death leads to release of cell contents, including nucleic antigens. Individuals with SLE may have markedly increased levels of apoptosis or significantly impaired ability to clear cell debris, causing prolonged exposure to nucleic antigens in the bloodstream and increased opportunity for recognition by immune cells, leading to B cell autoantibody production. Circulating autoantibodies form immune complexes and deposit in tissues, leading to local complement activation, initiation of a proinflammatory cascade, and,
ultimately, tissue damage. Antibodies to double-stranded DNA can form immune complexes, deposit in glomeruli, and initiate inflammation leading to glomerulonephritis. However, many individuals with SLE have circulating antibodies to double-stranded DNA yet do not have nephritis, suggesting that autoantibodies are not the only pathway leading to end organ damage in SLE. Both the innate and adaptive arms of the immune system have been implicated in the dysregulation of the immune system seen in SLE. High levels of interferon-α production by plasmacytoid dendritic cells promote expression of other proinflammatory cytokines and chemokines, maturation of monocytes into myeloid dendritic cells, promotion of autoreactive B and T cells, and loss of self-tolerance. Many, but not all, patients with SLE exhibit this cytokine profile, known as the **type I interferon signature**. Other cytokines with increased expression in SLE include interleukin (IL)-1, IL-2, IL-6, IL-10, IL-12, IL-17, IL-21, interferon-γ, B-lymphocyte stimulator (BLyS), and anti–tumor necrosis factor-α.

Both B and T cells demonstrate functional impairments in SLE. In active SLE, B-cell populations have impaired tolerance and increased autoreactivity, enhancing B cells’ ability to produce autoantibodies following exposure to self-antigen. In addition, cytokines such as BLyS may promote abnormal B-cell number and function. T-cell abnormalities in SLE include increased numbers of memory T cells and decreased number and function of T-regulatory cells. SLE T cells display aberrant signaling and increased autoreactivity. As a result, they are resistant to attrition by normal apoptosis pathways.

**CLINICAL MANIFESTATIONS**

Any organ system can be involved in SLE, so the potential clinical manifestations are myriad (Table 158-1). The presentation of SLE in childhood or adolescence differs from that in adults. The most common presenting complaints of children with SLE include fever, fatigue, hematologic abnormalities, arthralgia, and arthritis. Arthritis is usually present in the 1st yr of diagnosis, may be asymptomatic (morning stiffness, painless swelling) but is often a symmetric polyarthritis affecting large and small joints. Tenosynovitis is often present, but radiologic joint changes are very rare. Pediatric lupus may develop in patients previously diagnosed with polyarticular or systemic juvenile idiopathic arthritis (see Chapter 155).

Renal disease in SLE is often asymptomatic, underscoring the need for careful monitoring of blood pressure and urinalyses; in adolescents, SLE often presents with nephrotic syndrome and/or renal failure with the predominant symptoms being edema, fatigue, changes in urine color, and nausea/vomiting. Because SLE symptoms and findings may develop serially over several years and not be present at one time, the diagnosis may require longitudinal follow up. SLE is often characterized by periods of flare and disease quiescence or may follow a more smoldering disease course. The neuropsychiatric complications of SLE may occur with or without apparently active SLE, posing a particularly difficult diagnostic challenge in adolescents, who are already at high risk for mood disorders (Fig. 158-2). Long-term complications of SLE and its therapy, including accelerated atherosclerosis and osteoporosis, become clinically evident in young to middle adulthood. SLE is a disease that evolves over time in each affected individual, and new manifestations may arise even many years after diagnosis.

**DIAGNOSIS**

The diagnosis of SLE requires a comprehensive clinical and laboratory assessment revealing characteristic multisystem disease and excluding other etiologies, including infection and malignancy. Presence of 4 of the **11 American College of Rheumatology (ACR) 1997 Revised Classification Criteria for SLE** (Table 158-2) simultaneously or cumulatively over time establishes the diagnosis of SLE. Of note, although a positive antinuclear antibody (ANA) test result is not required for the diagnosis of SLE, ANA-negative lupus is extremely rare. Although ANA is very sensitive for SLE (95-99%), it is not very specific (~50%). Antibodies against double-stranded DNA and anti-Smith are specific for SLE (~98%) but not as sensitive (40-65%). Hypocomplementemia, although common in SLE, is not represented among the ACR classification criteria; hypocomplementemia has been added to updated criteria validated by the Systemic Lupus International Collaborating Clinics (SLICC) in 2012 (Table 158-3). Other differences in the SLICC criteria include addition of nonscarring alopecia, additional cutaneous and neurologic manifestations of lupus, and a positive direct Coombs test in the absence of hemolytic anemia.

**DIFFERENTIAL DIAGNOSIS**

Multiorgan disease is the hallmark of SLE, and given its wide array of potential clinical manifestations, SLE is in the differential diagnosis of many clinical scenarios, including unexplained fevers, joint pain, arthritis, rash, cytopenias, neurologic or cardiopulmonary abnormalities, nephritis, and nephrotic syndrome. For patients ultimately diagnosed with pediatric SLE, the initial differential diagnosis often includes infections (sepsis, Epstein-Barr virus, parvovirus B19, endocarditis), malignancies (leukemia and lymphoma), poststreptococcal glomerulonephritis, other rheumatologic conditions (systemic onset juvenile idiopathic arthritis, vasculitides), and drug-induced lupus.

**Drug-induced lupus** refers to the presence of SLE manifestations triggered by exposure to specific medications, including minocycline, many anticonvulsants, sulfonamides, antiarrhythmic agents, and other drugs (Table 158-4). In individuals prone to SLE, these agents may act as a trigger for true SLE. In others, these agents provoke a reversible lupus-like syndrome. Unlike SLE, drug-induced lupus affects males and females equally. A genetic predisposition toward slow drug acetylation may increase the risk of drug-induced lupus. Circulating antihistone

<table>
<thead>
<tr>
<th>Table 158-1</th>
<th>Potential Clinical Manifestations of Systemic Lupus Erythematosus</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TARGET ORGAN</strong></td>
<td><strong>POTENTIAL CLINICAL MANIFESTATIONS</strong></td>
</tr>
<tr>
<td>Constitutional</td>
<td>Fatigue, anorexia, weight loss, fever, lymphadenopathy</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>Arthritis, myositis, tendinosis, arthralgias, myalgias, avascular necrosis, osteoporosis</td>
</tr>
<tr>
<td>Skin</td>
<td>Malar rash, discoid (annular) rash, photosensitive rash, cutaneous vasculitis (petechiae, palpable purpura, digit ulcers, gangrene, urticaria), livedo reticularis, periungal capillary abnormalities, Raynaud phenomenon, alopecia, oral and nasal ulcers, panniculitis, chilblains, alopecia</td>
</tr>
<tr>
<td>Renal</td>
<td>Hypertension, proteinuria, hematuria, edema, nephrotic syndrome, renal failure</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Pericarditis, myocarditis, conduction system abnormalities, Libman-Sacks endocarditis</td>
</tr>
<tr>
<td>Neurologic</td>
<td>Seizures, psychosis, cerebritis, stroke, transverse myelitis, depression, cognitive impairment, headaches, migraines, pseudotumor, peripheral neuropathy (mononeuritis multiplex), chorea, optic neuritis, cranial nerve palsies, acute confusional states, dural sinus thrombosis</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>Pleuritis, interstitial lung disease, pulmonary hemorrhage, pulmonary hypertension, pulmonary embolism</td>
</tr>
<tr>
<td>Hematologic</td>
<td>Immune-mediated cytopenias (hemolytic anemia, thrombocytopenia or leukopenia), anemia of chronic inflammation, hypercoagulability, thrombocytopenic thrombotic microangiopathy</td>
</tr>
<tr>
<td>Gastroenterology</td>
<td>Hepatosplenomegaly, pancreatitis, vasculitis affecting bowel, protein-losing enteropathy, pentonitidis</td>
</tr>
<tr>
<td>Ocular</td>
<td>Retinal vasculitis, scleritis, episcleritis, papilledema, dry eyes, optic neuritis</td>
</tr>
</tbody>
</table>
Figure 158-2 Overlapping neuropsychiatric symptoms in pediatric SLE. Patients with pediatric SLE most commonly have more than 1 neuropsychiatric symptom—in particular for seizures. (From Silverman E, Eddy A: Systemic lupus erythematosus. In Cassidy JT, Petty RE, Laxer RM, et al, editors, Textbook of pediatric rheumatology, ed 6, Philadelphia, 2011, Saunders/Elsevier, Fig. 21-17, p. 329.)

Table 158-2 American College of Rheumatology 1997 Revised Classification Criteria for Systemic Lupus Erythematosus

<table>
<thead>
<tr>
<th>Clinical Criterion</th>
<th>Immunologic Criterion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malar rash</td>
<td>Positive antinuclear antibody</td>
</tr>
<tr>
<td>Discoid rash</td>
<td>Positive double-stranded DNA antibody</td>
</tr>
<tr>
<td>Photosensitivity</td>
<td>Positive anti-Smith antibody</td>
</tr>
<tr>
<td>Oral or nasal ulcers</td>
<td>Antiphospholipid antibody positivity</td>
</tr>
<tr>
<td>Arthritis</td>
<td>Positive lupus anticoagulant, false-positive test for rapid plasma regain, medium to high titer anticardiolipin antibody level (IgA, IgG, IgM), or positive anti-β2-glycoprotein I antibody (IgA, IgG, IgM)</td>
</tr>
<tr>
<td>Serositis</td>
<td>Low complement</td>
</tr>
<tr>
<td></td>
<td>Low C3, C4, or Ch50 level</td>
</tr>
<tr>
<td></td>
<td>Positive direct Coombs test (in the absence of hemolytic anemia)</td>
</tr>
</tbody>
</table>

*The presence of 4 of 11 criteria establishes the diagnosis of SLE. These criteria were not developed for clinical diagnosis.*

Table 158-3 Systemic Lupus International Collaborating Clinics (SLICC) Classification Criteria for Systemic Lupus Erythematosus

<table>
<thead>
<tr>
<th>Clinical Criterion</th>
<th>Immunologic Criterion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute cutaneous lupus</td>
<td>Positive antinuclear antibody</td>
</tr>
<tr>
<td>Malar rash, bullous lupus, toxic epidermal necrolysis variant of SLE, maculopapular lupus rash, photosensitive lupus rash, or subacute cutaneous lupus</td>
<td></td>
</tr>
<tr>
<td>Chronic cutaneous lupus</td>
<td>Positive double-stranded DNA antibody</td>
</tr>
<tr>
<td>Classic discoid rash, lupus panniculitis, mucosal lupus, lupus erythematosus tumidus, chilblains lupus, discoid lupus/lichen planus overlap</td>
<td></td>
</tr>
<tr>
<td>Oral or nasal ulcers</td>
<td>Positive anti-Smith antibody</td>
</tr>
<tr>
<td>Nonscarring alopecia</td>
<td>Antiphospholipid antibody positivity</td>
</tr>
<tr>
<td>Synovitis (≥2 joints)</td>
<td>Positive lupus anticoagulant, false-positive test for rapid plasma regain, medium to high titer anticardiolipin antibody level (IgA, IgG, IgM), or positive anti-β2-glycoprotein I antibody (IgA, IgG, IgM)</td>
</tr>
<tr>
<td>Serositis</td>
<td>Low complement</td>
</tr>
<tr>
<td>Pleursy or pericardial pain ≥1 day, pleural effusion or rub, pericardial effusion or rub, ECG evidence of pericarditis</td>
<td></td>
</tr>
<tr>
<td>Renal</td>
<td>Low C3, C4, or Ch50 level</td>
</tr>
<tr>
<td>Presence of red blood cell casts or urine protein/creatinine ratio representing &gt;500 mg protein/24 hours</td>
<td></td>
</tr>
<tr>
<td>Neurologic</td>
<td>Positive direct Coombs test (in the absence of hemolytic anemia)</td>
</tr>
<tr>
<td>Seizures, psychosis, mononeuritis multiplex, myelitis, peripheral or cranial neuropathy, or acute confusional state</td>
<td></td>
</tr>
<tr>
<td>Hemolytic anemia</td>
<td></td>
</tr>
<tr>
<td>Leukopenia (&lt;4,000/mm³) or lymphopenia (&lt;1,000/mm³)</td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia (&lt;100,000/mm³)</td>
<td></td>
</tr>
</tbody>
</table>

*The presence of 4 criteria (including at least 1 clinical and 1 immunologic criterion) establishes the diagnosis of SLE. Biopsy-proven lupus nephritis with positive ANA or anti–double-stranded DNA also satisfies the diagnosis of SLE. These criteria were developed for classification in clinical trials and not for clinical diagnosis.*

antibodies are often present in drug-induced SLE; these antibodies are only detected in up to 20% of individuals with SLE. Hepatitis, which is rare in SLE, is more common in drug-induced lupus. Individuals with drug-induced lupus are less likely to demonstrate antibodies to double-stranded DNA, hypocomplementemia, and significant renal or neurologic disease. In contrast to SLE, manifestations of drug-induced lupus typically resolve after withdrawal of the offending medication; however, complete recovery may take several months to years.

**LABORATORY FINDINGS**

A positive ANA test result is present in 95-99% of individuals with SLE. This test has poor specificity for SLE, as up to 20% of healthy individuals also have a positive ANA test result, making the ANA a poor screening test for SLE. ANA titers are not reflective of disease activity; therefore, repeating ANA titers is not helpful in disease management. Antibodies to double-stranded DNA are more specific for SLE, and in some individuals, anti–double-stranded DNA levels correlate with disease activity, particularly those with significant nephritis. Anti-Smith antibody, although found specifically in patients with SLE, does not correlate with disease activity. Serum levels of total hemolytic complement (CH₅₀), C3, and C4 are typically decreased in active disease and often improve with treatment; although hypocomplementemia is not included in the ACR classification criteria, it has been added to 2012 SLICC criteria, along with direct Coombs positivity. Table 158-5 lists autoantibodies found in SLE along with their clinical associations.

Hypergammaglobulinemia is a common but nonspecific finding. Inflammatory markers, particularly erythrocyte sedimentation rate, are often elevated in active disease. C-reactive protein (CRP) correlates less well with disease activity and acutely elevated CRP values may reflect disease activity. Serum levels of total hemolytic complement (CH₅₀), C3, and C4 are typically decreased in active disease and often improve with treatment; although hypocomplementemia is not included in the ACR classification criteria, it has been added to 2012 SLICC criteria, along with direct Coombs positivity.

**TREATMENT**

Treatment of SLE is tailored to the individual and is based on specific disease manifestations and medication tolerability. For all patients, sunscreen and avoidance of prolonged direct sun exposure and other ultraviolet light may help control disease and should be reinforced at every visit with the patient. Hydroxychloroquine (5-7 mg/kg/day up to 400 mg/day) is recommended for all individuals with SLE if tolerated. In addition to treating mild SLE manifestations such as rash and mild arthritis, hydroxychloroquine prevents SLE flares, improves lipid profiles, and may have a beneficial impact on mortality and renal outcomes. Potential toxicities include retinal pigmentation and color vision impairment; therefore, ophthalmology exams every 6-12 mo are recommended for patients taking hydroxychloroquine. Nonsteroidal antiinflammatory agents can be useful for management of arthralgias and arthritis; it is important to keep in mind their potential hepatic, renal, and cardiovascular toxicities.

Corticosteroids are a mainstay for treatment of significant manifestations of SLE and work quickly to improve acute deterioration; side effects often limit patient compliance, especially in adolescence, and potential toxicities are worrisome. It is important to limit dose and length of exposure to corticosteroids whenever possible. Potential consequences of corticosteroid therapy include growth disturbance, weight gain, striae, acne, hyperglycemia, hypertension, cataracts, avascular necrosis, and osteoporosis. The optimal dosing of corticosteroids in children and adolescents with SLE remains unknown; severe disease is often treated with high doses of intravenous methylprednisolone (e.g., 30 mg/kg/day for 3 days, followed by weekly pulses) or high doses of oral prednisone (1-2 mg/kg/day). As disease manifestations improve, corticosteroid dosages are gradually tapered over months. It often becomes necessary to introduce steroid-sparing immunosuppressive medications in order to limit cumulative steroid exposure.

**Steroid-sparing immunosuppressive agents** often used in the treatment of pediatric SLE include methotrexate, leflunomide, azathioprine, mycophenolate mofetil, cyclophosphamide, and belimumab. Methotrexate, leflunomide, and azathioprine are often used to treat persistent moderate disease, including arthritis, significant cutaneous or hematologic involvement, and pleural disease. Intravenous or oral cyclophosphamide is reserved for the most severe, potentially life-threatening SLE manifestations, such as renal, neurologic, and cardiopulmonary disease. Although cyclophosphamide is highly effective in controlling disease, the potential toxicities are significant, including cytopenias, infection, hemorrhagic cystitis, premature gonadal failure, and increased risk of future malignancy. Attention to adequate hydration can attenuate the risk of hemorrhagic cystitis. Fortunately, young girls are at much lower risk of gonadal failure than older women, and the use of gonadotropin-releasing hormone agonists, such as leuprolide acetate, may help prevent gonadal failure. Clinical trial data on the...
use of rituximab in SLE with treatment-resistant glomerulonephritis has been largely disappointing, but results from the LUNAR study suggest there may be benefit for subpopulations of SLE patients. The FDA has approved the use of belimumab (a monoclonal antibody against BLYs, also called B-cell activating factor); when added to standard SLE therapy, belimumab improves multiple markers of disease severity. BLYs levels are elevated in SLE and relate to disease activity. Treatment reduces the number of SLE flares and decreases the dose of prednisone. Side effects include fever, nausea, and diarrhea.

The Childhood Arthritis Rheumatology Research Alliance has developed a consensus treatment plan induction therapy of newly-diagnosed proliferative lupus nephritis that is specific to the pediatric SLE population; these guidelines advise 6 mo of therapy with either cyclophosphamide or mycophenolate mofetil, used in combination with a standardized glucocorticoid regimen. For patients who fail to achieve a partial response in 6 mo it is appropriate to switch agents. Consensus statements for maintenance therapy of lupus nephritis recommend use of mycophenolate mofetil, every 3 mo IV cyclophosphamide or azathioprine for 12 mo after completing induction therapy.

Given the lifelong nature of SLE, optimal care of children and adolescents with this disease also involves preventive practices. Owing to the enhanced risk of atherosclerosis in SLE, attention to cholesterol levels, smoking status, body mass index, blood pressure, and other traditional cardiovascular risk factors is warranted. Even though the Atherosclerosis Prevention in Pediatric Lupus Erythematosus (APPLE) study failed to support placing all children with SLE on a statin, ad hoc analyses suggest that statins may be considered for primary prevention of atherosclerotic disease in certain clinical circumstances, particularly pubertal patients with an elevated CRP. For all SLE patients, adequate intake of calcium and vitamin D is necessary to prevent future osteoporosis. Infections commonly complicate SLE, so routine immunization is recommended, as well as annual influenza vaccination and administration of the 23-valent pneumococcal vaccine. Prompt attention to febrile episodes should include an evaluation for serious infections. It should be remembered that pregnancy can worsen SLE, and obstetric complications are more common in SLE. In addition, many of the medications used to treat SLE are teratogenic. As a consequence, it is important to counsel adolescent girls about these risks and appropriate contraceptive options. SLE patients with antiphospholipid antibodies syndrome are treated with long-term anticoagulation to prevent thrombotic events.

**COMPLICATIONS**

Within the 1st several yr of diagnosis, the most common causes of death in individuals with SLE include infection and complications of glomerulonephritis and neuropsychiatric disease (Table 158-6). Over the long-term, the most common causes of mortality also include complications of atherosclerosis and malignancy. The increased risk of premature atherosclerosis in SLE is not explained by traditional risk factors and is partly a result of the chronic immune dysregulation and inflammation associated with SLE. Increased malignancy rates may be caused by immune dysregulation as well as exposure to medications with carcinogenic potential.

**PROGNOSIS**

The severity of disease in pediatric SLE is notably worse than the typical course for most adult-onset SLE. However, owing to advances in the diagnosis and treatment of SLE, survival has improved dramatically over the past 50 yr. Currently, the 5 yr survival rate for pediatric SLE is ~95%, though the 10 yr survival rate remains ~80-90%. Given their long burden of disease, children and adolescents with SLE face a high risk of future morbidity and mortality from the disease and its complications, especially atherosclerosis and malignancy (see Table 158-6). Given the complex and chronic nature of SLE, it is optimal for children and adolescents with SLE to be treated by pediatric rheumatologists in a multidisciplinary clinic.

Bibliography is available at Expert Consult.

### Table 158-6 Morbidity in Childhood Lupus

<table>
<thead>
<tr>
<th>System</th>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal</td>
<td>Hypertension, dialysis, transplantation</td>
</tr>
<tr>
<td>Central nervous system</td>
<td>Organic brain syndrome, seizures, psychosis, neurocognitive dysfunction</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Atherosclerosis, myocardial infarction, cardiomyopathy, valvular disease</td>
</tr>
<tr>
<td>Immune</td>
<td>Recurrent infection, functional asplenia, malignancy</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>Osteopenia, compression fractures, avascular necrosis</td>
</tr>
<tr>
<td>Ocular</td>
<td>Cataracts, glaucoma, retinal detachment, blindness</td>
</tr>
<tr>
<td>Endocrine</td>
<td>Diabetes, obesity, growth failure, infertility, fetal wastage</td>
</tr>
</tbody>
</table>


**158.1 Neonatal Lupus**

Deborah Friedman, Rebecca E. Sadun, Stacy P. Ardoin, and Laura E. Schanberg

Neonatal lupus, an entity distinct from SLE, is one of the few rheumatic disorders manifesting in the neonate. Clinical manifestations of neonatal lupus include a characteristic annular or macular rash typically affecting the face (especially the periorbital area), trunk, and scalp (Fig. 158-3). The rash typically appears within the 1st 6 wk of life after exposure to ultraviolet light and lasts 3-4 mo; however, it can be present at birth. Infants may also have cytopenias and hepatitis, but the most feared complication is congenital heart block. Conduction system abnormalities range from prolongation of the PR interval to complete heart block, with development of progressive...
Bibliography
Because maternal autoantibodies gain access to the fetus via the placenta at the 16th wk of gestation, all pregnant women with circulating anti-Ro or anti-La antibody (or those with a history of offspring with neonatal lupus or congenital heart block) are monitored by a pediatric cardiologist with regular fetal electrocardiography from 16 wk of gestation until delivery. If fetal bradycardia is found unexpectedly during in utero monitoring, screening for maternal anti-Ro and anti-La antibodies is warranted.

In contrast to SLE, neonatal lupus is not characterized by ongoing immune dysregulation, although infants with neonatal lupus may be at some increased risk for development of future autoimmune disease. A mother who has borne a child with congenital heart block caused by neonatal lupus has an approximately 17% risk of recurrence with future pregnancies. With cardiac pacing, children with conduction system disease in the absence of cardiomyopathy have an excellent prognosis. If the conduction defect is not addressed, affected children are at risk for exercise intolerance, arrhythmias, and death. A proposed management algorithm is presented in Figure 158-4.

Bibliography is available at Expert Consult.
Bibliography
Juvenile dermatomyositis (JDM) is the most common inflammatory myositis in children, distinguished by proximal muscle weakness and a characteristic rash. Inflammatory cell infiltrates result in vascular inflammation, the underlying pathology in this disorder.

ETIOLOGY
Evidence suggests that the etiology of JDM is multifactorial, based on genetic predisposition and an unknown environmental trigger. Human
leukocyte antigen (HLA) alleles such as B8, DRB1*0301, DQA1*0501, and DQA1*0501 are associated with increased susceptibility to JDM in selected populations. Maternal microchimerism may play a part in the etiology of JDM by causing graft-versus-host disease or autoimmune phenomena. Persistent maternal cells have been found in blood and tissue samples of children with JDM. An increased number of these maternal cells are positive for HLA-DQA1*0501, which may assist with transfer or persistence of chimeric cells. Specific cytokine polymorphisms in tumor necrosis factor-α promoter and variable number tandem repeats of the interleukin-1 receptor antagonist may increase genetic susceptibility. These polymorphisms are common in the general population. A history of infection in the 3 mo prior to disease onset is commonly reported; multiple studies have failed to produce a causative organism. Constitutional signs and upper respiratory symptoms predominate, but one-third of patients report preceding gastrointestinal (GI) symptoms. Group A streptococcus, upper respiratory infections, GI infections, coxsackievirus B, toxoplasma, enteroviruses, parvovirus B19, and multiple other organisms have been postulated as possible pathogens in the etiology of JDM. Despite these concerns, results of serum antibody testing and polymerase chain reaction amplification of the blood and muscle tissue for multiple infectious diseases have not been revealing. Environmental factors may also play a contributing role, with geographic and seasonal clustering reported; however, no clear theory of etiology has emerged.

**Epidemiology**

The incidence of JDM is approximately 3 cases/1 million children/yr without racial predilection. Peak age of onset is between 4 and 10 yr. There is a second peak of dermatomyositis onset in late adulthood (45-64 yr), but adult-onset dermatomyositis appears to be a distinctly separate entity in prognosis and etiology. In the United States, the ratio of girls to boys with JDM is 2:1. Multiple cases of myositis in a single family are rare, but familial autoimmune disease may be increased in families with children who have JDM than in families of healthy children. Reports of seasonal association have not been confirmed, although clusters of cases may occur.

**Pathogenesis**

Interferon upregulates genes critical in immunoregulation and major histocompatibility complex (MHC) class I expression, activates natural killer cells, and supports dendritic cell maturation. Upregulation of gene products controlled by type I interferons occurs in patients with dermatomyositis, potentially correlating with disease activity and holding promise as clinical biomarkers.

It appears that children with genetic susceptibility to JDM (HLA-DQA1*0501, HLA-DRB1*0301) may have prolonged exposure to maternal chimeric cells and/or an unknown environmental trigger. Once triggered, an inflammatory cascade with type I interferon response leads to upregulation of MHC class I expression and maturation of dendritic cells. Overexpression of MHC class I upregulates adhesion molecules, which influence migration of lymphocytes, leading to inflammatory infiltration of muscle. In an autoregulatory feedback loop, muscle inflammation increases the type I interferon response, regenerating the cycle of inflammation. Cells involved in the inflammatory cascade include natural killer cells (CD56), T-cell subsets (CD4, CD8, Th17), monocytes/macrophages (CD14), and plasmacytoid dendritic cells. Neopterin, interferon-inducible protein 10, monocyte chemotactant protein, myxovirus resistance protein, and von Willebrand factor products, as well as other markers of vascular inflammation may be elevated in patients with JDM who have active inflammation.

**Clinical Manifestations**

Children with JDM present with either rash, insidious onset of weakness, or both. Fevers, dysphagia or dysphonia, arthritis, muscle tenderness, and fatigue are also commonly reported at diagnosis (Tables 159-1 and 159-2).

Rash develops as the first symptom in 50% of cases and appears concomitant with weakness only 25% of the time. Children often exhibit extreme photosensitivity to ultraviolet light exposure with generalized erythema in sun-exposed areas. If seen over the chest and neck, this erythema is known as the *shawl sign*. Erythema is also commonly seen over the knees and elbows. The characteristic *heliotrope rash* (Fig. 159-1) is a blue-violet discoloration of the eyelids that may be associated with periorbital edema. Facial erythema crossing the

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**Table 159-1**

<table>
<thead>
<tr>
<th>Diagnostic Criteria for Juvenile Dermatomyositis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Classic rash</strong></td>
</tr>
<tr>
<td><strong>Heliotrope rash of the eyelids</strong></td>
</tr>
<tr>
<td><strong>Gottron papules</strong></td>
</tr>
<tr>
<td><strong>Plus 3 of the following:</strong></td>
</tr>
<tr>
<td><strong>Weakness</strong></td>
</tr>
<tr>
<td><strong>Symmetric</strong></td>
</tr>
<tr>
<td><strong>Proximal</strong></td>
</tr>
<tr>
<td><strong>Muscle enzyme elevation (≥1)</strong></td>
</tr>
<tr>
<td><strong>Creatine kinase</strong></td>
</tr>
<tr>
<td><strong>Aspartate aminotransferase</strong></td>
</tr>
<tr>
<td><strong>Lactate dehydrogenase</strong></td>
</tr>
<tr>
<td><strong>Aldolase</strong></td>
</tr>
<tr>
<td><strong>Electromyographic changes</strong></td>
</tr>
<tr>
<td><strong>Short, small polyphasic motor unit potentials</strong></td>
</tr>
<tr>
<td><strong>Fibrillations</strong></td>
</tr>
<tr>
<td><strong>Positive sharp waves</strong></td>
</tr>
<tr>
<td><strong>Insertional irritability</strong></td>
</tr>
<tr>
<td><strong>Bizarre, high-frequency repetitive discharges</strong></td>
</tr>
<tr>
<td><strong>Necrosis</strong></td>
</tr>
<tr>
<td><strong>Inflammation</strong></td>
</tr>
</tbody>
</table>

**Table 159-2**

<table>
<thead>
<tr>
<th>Clinical Features of Juvenile Dermatomyositis During the Course of the Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Feature</strong></td>
</tr>
<tr>
<td>-------------</td>
</tr>
<tr>
<td>Muscle weakness</td>
</tr>
<tr>
<td>Dysphagia or dysphonia</td>
</tr>
<tr>
<td>Muscle atrophy</td>
</tr>
<tr>
<td>Muscle pain and tenderness</td>
</tr>
<tr>
<td>Skin lesions</td>
</tr>
<tr>
<td>Heliotrope rash of eyelids</td>
</tr>
<tr>
<td>Gottron papules</td>
</tr>
<tr>
<td>Erythematos rash of malar/facial area</td>
</tr>
<tr>
<td>Periungual capillary changes</td>
</tr>
<tr>
<td>Photosensitive rash</td>
</tr>
<tr>
<td>Ulcerations</td>
</tr>
<tr>
<td>Calcinosis</td>
</tr>
<tr>
<td>Lipodystrophy</td>
</tr>
<tr>
<td>Raynaud phenomenon</td>
</tr>
<tr>
<td>Arthritis and arthralgia</td>
</tr>
<tr>
<td>Joint contractures</td>
</tr>
<tr>
<td>Fever</td>
</tr>
<tr>
<td>Gastrointestinal signs and symptoms</td>
</tr>
<tr>
<td>Restrictive pulmonary disease</td>
</tr>
<tr>
<td>Interstitial lung disease</td>
</tr>
<tr>
<td>Cardiac involvement</td>
</tr>
</tbody>
</table>


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Chapter 159  
Juvenile Dermatomyositis

Juvenile Dermatomyositis

Patients with JDM may roll to the side rather than sit straight up from lying to compensate for truncal weakness. Approximately half of children exhibit muscle tenderness as a result of muscle inflammation.

Esophageal and respiratory muscles are also affected, resulting in aspiration or respiratory failure. It is essential to assess for dysphonia or nasal speech, palatal elevation with gag, dysphagia, and gastroesophageal reflux by means of history, physical exam, and swallow study, if symptoms are present. Respiratory muscle weakness can be a medical emergency and lead to respiratory failure. Children with respiratory muscle weakness do not manifest typical symptoms of impending respiratory failure with increased work of breathing, instead demonstrating hypercarbia rather than hypoxemia.

Lipodystrophy and calcinosis (Fig. 159-4) are thought to be associated with long-standing or undertreated disease. Dystrophic deposition of calcium phosphate, hydroxyapatite, or fluoroapatite crystals occurs in subcutaneous plaques or nodules, resulting in painful ulceration of the skin with extrusion of crystals or calcific liquid. Calcinosis is reported in up to 40% of children with JDM, but the prevalence is thought to be lower in children who are treated early and aggressively. In rare instances, an “exoskeleton” of calcium deposition forms, greatly limiting mobility. Lipodystrophy results in progressive loss of subcutaneous and visceral fat, typically over the face and upper body, and may be associated with a metabolic syndrome similar to polycystic ovarian syndrome with insulin resistance, hirsutism, acanthosis, and nasolabial folds is also common, in contrast to the malar rash without nasolabial involvement typical of systemic lupus erythematosus.

Classic Gottron papules (Fig. 159-2) are bright pink or pale, shiny, thickened or atrophic plaques over the proximal interphalangeal joints and distal interphalangeal joints and occasionally on the knees, elbows, small joints of the toes, and ankle malleoli. The rash of JDM is sometimes mistaken for eczema or psoriasis. Rarely, a thickened erythematous and scaly rash develops in children over the palms (known as mechanic’s hands) and soles along the flexor tendons, which is associated with anti–Jo-1 antibodies.

Evidence of small vessel inflammation is often visible in the nailfolds and gums as individual capillary loops that are thickened, tortuous, or absent (Fig. 159-3). Telangiectasias may be visible to the naked eye but are more easily visualized under capillaroscopy or with use of a magnifier such as an ophthalmoscope. Severe vascular inflammation causes cutaneous ulcers on toes, fingers, axillae, or epicanthal folds.

Weakness associated with JDM is often insidious and difficult to differentiate from fatigue at onset. It is typically symmetric, affecting proximal muscles such as the neck flexors, shoulder girdle, and hip flexors. Parents may report difficulty climbing stairs, combing hair, and getting out of bed. Examination reveals inability to perform a sit-up, head lag in a child after infancy, and Gower sign (use of hands on thighs to stand from a sitting position).
sient rhabdomyolysis with myoglobinuria. Myositis in children may include trichinosis, infections associated with prominent muscular symptoms. In adults, myositis is observed in adults with dermatomyositis but very rarely in children.

**DIAGNOSIS**

Diagnosis of dermatomyositis requires the presence of characteristic rash as well as at least three signs of muscle inflammation and weakness (see Table 159-1). Diagnostic criteria developed in 1975 predate the use of MRI and have not been validated in children. Diagnosis is often delayed because of the insidious nature of disease onset.

Electromyography shows signs of myopathy (increased insertional activity, fibrillations, and sharp waves) as well as muscle fiber necrosis (decreased action potential amplitude and duration). Nerve conduction studies are typically normal unless severe muscle necrosis and atrophy are present. It is important that electromyography (EMG) be performed in a center with experience in pediatric EMG and its interpretation. Muscle biopsy is typically indicated when diagnosis is in doubt or for grading disease severity. Biopsy of involved muscle reveals focal necrosis and phagocytosis of muscle fibers, fiber regeneration, endomysial proliferation, inflammatory cell infiltrates and vasculitis, and tubuloreticular inclusion bodies within endothelial cells. Findings of lymphoid structures and vasculopathy may portend more severe disease.

Some children present with classic rash but no apparent muscle weakness or inflammation; this variation is called myopathic JDM or dermatomyositis sine myositis. It is unclear whether these children have isolated skin disease or mild undetected muscle inflammation, risking progression to more severe muscle involvement with long-term sequelae such as calcinosis and lipodystrophy if untreated.

Differential diagnosis depends on the presenting symptoms. If the presenting complaint is solely weakness without rash or atypical disease, other causes of myopathy should be considered, including polymyositis, infection-related myositis (influenza A and B, coxsackievirus B, and other viral illnesses), muscular dystrophies (Duchenne and Becker as well as others), myasthenia gravis, Guillain-Barré syndrome, endocrinopathies (hyperthyroidism, hypothyroidism, Cushing syndrome, Addison disease, parathyroid disorders), mitochondrial myopathies, and metabolic disorders (glycogen and lipid storage diseases). Infections associated with prominent muscular symptoms include trichinosis, *Bartonella* infection, toxoplasmosis, and staphylococcal pyomyositis. Blunt trauma and crush injuries may lead to transient rhabdomyolysis with myoglobinuria. Myositis in children may also be associated with vaccinations, drugs, growth hormone, and graft-versus-host disease. The rash of JDM may be confused with eczema, dyshidrosis, psoriasis, malar rash from systemic lupus erythematosus, capillary telangiectasias from Raynaud phenomenon, and other rheumatic diseases. Muscle inflammation is also seen in children with systemic lupus erythematosus, juvenile idiopathic arthritis, mixed connective tissue disease, inflammatory bowel disease, and antineutrophil cytoplasmic antibody–positive vasculitides. Table 159-3 compares other juvenile inflammatory myositis disorders.

**LABORATORY FINDINGS**

Elevated serum levels of muscle-derived enzymes (creatine kinase, aldolase, aspartate aminotransferase, alanine aminotransferase, and lactate dehydrogenase) reflect muscle inflammation. Not all enzyme levels rise with inflammation in a specific individual; alanine aminotransferase is most commonly elevated on initial presentation, whereas the creatine kinase level may be normal. The erythrocyte sedimentation rate is often normal, and the rheumatoid factor test result is typically negative. There may be anemia consistent with chronic disease. Antinuclear antibody is present in >80% of children with JDM. Results of tests for antibodies to SSA, SSB, Sm, ribonucleoprotein, and double-stranded DNA are generally negative. Antibodies to Pm/ScI identify a small, distinct subgroup of myopathies with a protracted disease course, often complicated by pulmonary interstitial fibrosis and/or cardiac involvement. Similar to what is seen in adults, the presence of myositis-specific autoantibodies in JDM such as anti–Jo-1, anti–Mi-2, anti–p155/140, anti–NXp2, and other myositis-specific autoantibodies help define distinct clinical subsets and may predict the development of complications, although differences remain in certain aspects such as malignancy between adults and children.

Radiographic studies aid both diagnosis and medical management. MRI using T2-weighted images and fat suppression (Fig. 159-5) identifies active sites of disease, reducing sampling error and increasing the sensitivity of muscle biopsy and EMG, results of which are nondiagnostic in 20% of instances if the procedures are not directed by MRI. Extensive rash and abnormal MRI findings may be found despite normal serum levels of muscle-derived enzymes. Muscle biopsy often demonstrates evidence of disease activity and chronicity that is not suspected from the levels of the serum enzymes alone.

A contrast swallow study may document palatal dysfunction and risk of aspiration. Pulmonary function testing detects a restrictive defect consistent with respiratory weakness and reduced diffusion capacity of carbon monoxide from alveolar fibrosis associated with other connective tissue diseases. Serial measurement of vital capacity or negative inspiratory force can document changes in respiratory weakness, especially in an inpatient setting. Calcinosis is seen easily on radiographs, along the fascial planes and within muscles.
Table 159-3  Phenotypic Characteristics of the Clinical Subgroups of Juvenile Myositis*

<table>
<thead>
<tr>
<th>CHARACTERISTIC</th>
<th>JDM</th>
<th>JPM</th>
<th>JCTM</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median age at diagnosis (yr)</td>
<td>Youngest (7.4 yr)</td>
<td>Oldest (12.1 yr)</td>
<td>Intermediate (10.2 yr)</td>
</tr>
<tr>
<td>Race</td>
<td>Predominantly white (71.2%)</td>
<td>Black (39.4%)</td>
<td>Black or other (49.0%)</td>
</tr>
<tr>
<td>Severity at onset</td>
<td>Mild or moderate severity</td>
<td>Severe or very severe onset</td>
<td>Mild or moderate severity</td>
</tr>
<tr>
<td>Median delay to diagnosis (mo)</td>
<td>4 mo</td>
<td>3.5 mo</td>
<td>Longer delay (7 mo)</td>
</tr>
<tr>
<td><strong>Clinical features</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gottron papules</td>
<td>Heliotrope rash</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Periulnar capillary abnormalities</td>
<td>Malar rash</td>
<td>Photosensitivity</td>
<td>Linear extensor erythema†</td>
</tr>
<tr>
<td>Mucous membrane involvement</td>
<td>Cuticular overgrowth</td>
<td>Mucous membrane involvement</td>
<td>Linear extensor erythema†</td>
</tr>
<tr>
<td>Skin ulcerations</td>
<td>Dyspnea on exertion</td>
<td>Photosensitivity</td>
<td>Cuticular overgrowth</td>
</tr>
<tr>
<td>Weight loss</td>
<td>Failing episodes</td>
<td>Raynaud phenomenon</td>
<td>Malar rash</td>
</tr>
<tr>
<td>Raynaud phenomenon</td>
<td>Abnormal PFT</td>
<td>Cardiac abnormalities on EKG or ECHO</td>
<td>Raynaud phenomenon</td>
</tr>
<tr>
<td>Dyspnea on exertion</td>
<td>Cardiac abnormalities on EKG or ECHO</td>
<td>Interstitial lung disease</td>
<td>Scleroderma</td>
</tr>
<tr>
<td><strong>Autoantibodies</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intermediate ANA titer (median, 1:320)</td>
<td>Intermediate ANA titer (median, 1:320)</td>
<td>Highest ANA titer (median, 1:1280)</td>
<td>Anti-U1-RNP</td>
</tr>
<tr>
<td>Anti-p155/140</td>
<td>Anti-SRP</td>
<td>Anti-PM-Scl</td>
<td>Anti-U1-RNP</td>
</tr>
<tr>
<td>Anti-MJ</td>
<td>Anti-aminoacyl-tRNA synthetase (anti–Jo-1)</td>
<td>Anti-PM-Scl</td>
<td>Anti-PM-Scl</td>
</tr>
<tr>
<td>Anti-Mi-2</td>
<td>Anti-La</td>
<td>Anti-PM-Scl</td>
<td>Anti-PM-Scl</td>
</tr>
<tr>
<td><strong>Laboratory features</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lowest CK level (median, 829 U/L)</td>
<td>Highest CK level (median, 5027 U/L)</td>
<td>Intermediate CK level (median, 1208 U/L)</td>
<td>All other U-RNP autoantibodies</td>
</tr>
<tr>
<td><strong>Outcome</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low mortality (2.4%)</td>
<td>Medium mortality (6.3%)</td>
<td>Highest mortality (14.6%)</td>
<td></td>
</tr>
<tr>
<td>Calcinosi (34.0%)</td>
<td>Frequently hospitalized (71.9%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wheelchair use</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ALT, alanine aminotransferase; ANA, antinuclear antibody; CK, creatine kinase; ECHO, echocardiogram; EKG, electrocardiogram; GI, gastrointestinal; JCTM, juvenile myositis overlapping with another autoimmune or connective tissue disease; JDM, juvenile dermatomyositis; JPM, juvenile polymyositis; PFT, pulmonary function test; tRNA, transfer RNA.

*Bold indicates significant in logistic regression; italics indicates top variables entered in pruned-down random forest models. Other variables included in this table were significant in univariable analysis to p ≤ 0.01.

† Removed from logistic regression analyses because variable was either 100% or 0% in 1 of the compared subgroups. Gottron papules and heliotrope rash, which were part of the definition of cases of dermatomyositis, were not entered into multivariable analyses.


**TREATMENT**

The aid of an experienced pediatric rheumatologist is invaluable in outlining an appropriate course of treatment for a child with JDM. Prior to the advent of corticosteroids, one-third of patients spontaneously improved, one-third had a chronic, lingering course, and one-third died from the disease. Corticosteroids have altered the course of disease, lowering morbidity and mortality. Methotrexate decreases the length of treatment with corticosteroids, thereby reducing morbidity from steroid toxicity. Intravenous gammaglobulin is frequently used as an adjunct for treatment of severe disease.

Corticosteroids are still the mainstay of treatment. In a clinically stable child without debilitating weakness, oral prednisone at 2 mg/kg/day (maximum 60 mg daily) is usually started. Children with GI involvement have decreased absorption of oral steroids and require intravenous administration. In more-severe cases with respiratory or oropharyngeal weakness, high-dose pulse methylprednisolone is used (30 mg/kg/day for 3 days, maximum dose 1 g/day) with ongoing weekly or monthly IV dosing along with daily oral corticosteroids as needed. Corticosteroid dosage is slowly tapered over a period of 12 mo, after indicators of inflammation (muscle enzymes) normalize and strength improves.

Weekly oral, intravenous, or subcutaneous methotrexate (the lesser of 1 mg/kg or 15 mg/m², maximum 40 mg) is commonly used as a steroid-sparing agent in JDM. The concomitant use of methotrexate halves the cumulative dosage of steroids needed for disease control. Risks of methotrexate include immunosuppression, blood count dyscrasias, chemical hepatitis, pulmonary toxicity, nausea/vomiting, and teratogenicity. Folic acid is typically given with methotrexate starting at a dose of 1 mg daily to reduce toxicity and side effects of folate inhibition (oral ulcers, nausea, and anemia). Children who are taking immunosuppressive medications such as methotrexate should avoid live-virus vaccination, although inactivated influenza vaccination is recommended yearly.

Hydroxychloroquine has little toxicity risk and is used as a secondary disease-modifying agent to reduce rash and maintain remission. Typically, it is administered at doses between 4 and 6 mg/kg/day orally.
Most complications from JDM are related to prolonged and severe weakness, including muscle atrophy, to cutaneous calcifications and scarring or atrophy, and to lipodystrophy. Secondary complications from medical treatments are also common. Children with acute and severe weakness are at risk for aspiration pneumonia and respiratory failure and occasionally require nasogastric feeding and mechanical ventilation until weakness improves. Crampy abdominal pain and diarrhea may indicate bowel wall vasculitis and lead to ischemia, GI bleeding, and perforation if not treated with complete bowel rest and aggressive treatment for the underlying inflammation. Surgery should be avoided if possible, because the GI vasculitis is diffuse and not easily amenable to surgical intervention. Contrast-enhanced CT may show dilation or thickening of the bowel wall, intraluminal air, or evidence of bowel necrosis. Cardiac involvement by JDM is rare but includes arrhythmias.

Pathologic calcifications may be related to severity of disease and prolonged delay to treatment and potentially to genetic polymorphisms of tumor necrosis factor-α-308. Calcium deposits tend to form in subcutaneous tissue and along muscle. Some ulcerate through the skin and drain a soft calcific liquid, and others manifest as hard nodules along extensor surfaces or embedded along muscle. Draining lesions serve as a nidus for cellulitis or osteomyelitis. Nodules cause skin inflammation that may mimic cellulitis. Spontaneous regression of calcium deposits may occur, but there is no evidence-based recommendation for treatment of calcinosis.

Lipodystrophy manifests in 10%-40% of patients with JDM and can be difficult to recognize. Fat atrophy may be generalized, partial, or local. Lipodystrophy has been associated with insulin resistance, acanthosis nigricans, dyslipidemia, hypertension, and menstrual irregularity, similar to features seen in polycystic ovarian disease or metabolic syndrome.

Children receiving prolonged corticosteroid therapy are prone to complications such as cessation of linear growth, weight gain, hirsutism, adrenal suppression, immunosuppression, striae, cushingoid fat deposition, mood changes, osteoporosis, cataracts, avascular necrosis, and steroid myopathy. Families should be counseled on the effects of corticosteroids and advised to use medical alert identification and to consult a nutritionist regarding a low-salt, low-fat diet with adequate vitamin D and calcium supplementation.

**PROGNOSIS**

The mortality rate in JDM has decreased since the advent of corticosteroids, from 33% to currently approximately 1%; little is known about the long-term consequences of persistent vascular inflammation. The period of active symptoms has decreased from about 3.5 yr to <1.5 yr with more aggressive immunosuppressive therapy; the vascular, skin, and muscle symptoms of children with JDM generally respond well to therapy. At 7 yr of follow-up, 75% of patients have little to no residual disability, but 25% continue to have chronic weakness and 40% have chronic rash. Up to one-third may need long-term medications to control their disease. Children with JDM appear able to repair inflammatory damage to vasculature and muscle.

*Bibliography is available at Expert Consult.*
Bibliography


Juvenile scleroderma encompasses a range of conditions unified by the presence of fibrosis of the skin. Juvenile scleroderma is divided into 2 major categories, juvenile localized scleroderma (JLS, also known as morphea), which is largely limited to the skin, and juvenile systemic sclerosis (JSSc), with multisystem organ involvement. Localized disease is the predominant type seen in pediatric populations (>95%), but systemic sclerosis is associated with mortality and severe morbidity.
ETIOLOGY AND PATHOGENESIS
The etiology of scleroderma is unknown, but the mechanism of disease appears to be a combination of a vasculopathy, autoimmunity, immune activation, and fibrosis. Triggers, including trauma, infection, and, possibly, subclinical graft-versus-host reaction from persistent maternal cells (microchimerism), injure vascular endothelial cells, resulting in increased expression of adhesion molecules. These molecules entrap platelets and inflammatory cells, resulting in vascular changes with manifestations such as Raynaud phenomenon and pulmonary hypertension. Inflammatory cells infiltrate the area of initial vascular damage, causing further vascular damage and resulting in thickened arteries, walls and reduction in capillary numbers. Macrophages and other inflammatory cells then migrate into affected tissues and secrete cytokines that induce fibroblasts to reproduce and synthesize excessive amounts of collagen, resulting in fibrosis and subsequent lipoatrophy, dermal fibrosis, with loss of sweat glands and hair follicles. In late stages, the entire dermis may be replaced by compact collagen fibers.

Autoimmunity is believed to be a key process in the pathogenesis of both localized and systemic scleroderma, given the high percentage of affected children with autoantibodies. Children with localized disease often have a positive antinuclear antibody (ANA) test result (42%), and 47% of this subgroup have antithistone antibodies. Children with JSSc have higher rates of ANA positivity (80.7%) and may have anti-Scl 70 antibody (34%, antitopoisoenserase 1). The relationship between specific autoantibodies and the various forms of scleroderma is not well understood, and all antibody test results may be negative, especially in JLS.

CLASSIFICATION
Localized scleroderma is distinct from systemic scleroderma and rarely progresses to systemic disease. Within the category of JLS, there are several subtypes that are differentiated by both the distribution of the lesions and the depth of involvement (Table 160-1). Up to 15% of children have a combination of 2 or more subtypes.

EPIDEMIOLOGY
Juvenile scleroderma is rare, with an estimated prevalence of 1/100,000. Localized scleroderma is far more common than SSc in children, by a 10:1 ratio, with linear scleroderma being the most common subtype. LS is predominantly a pediatric condition, with 65% of patients diagnosed before age 18 yr. After age 8 yr the female: male ratio is lower, with a 3:1 ratio. There are several other subtypes of localized disease, with each subtype having its own clinical presentation and natural history.

CLINICAL MANIFESTATIONS
Localized Scleroderma
The onset of scleroderma is generally insidious, and manifestations vary according to disease subtype. The initial skin manifestations of localized disease usually include erythema or a bluish hue seen around an area of waxy induration; subtle erythema may be the only presenting sign (Fig. 160-1). Edema and erythema are followed by induration, hypopigmented or hyperpigmented, atrophic lesions (Fig. 160-2). LS varies in size from a few centimeters to the entire length of the extremity, with varying depth. Patients sometimes present with arthralgias, synovitis, or flexion contractures (Fig. 160-3). Children also experience limb length discrepancies as a result of growth impairment caused by involvement of muscle and bone. Children with en coup de sabre (Fig. 160-4) may have symptoms unique to central nervous system involvement, such as seizures, hemifacial atrophy, ipsilateral uveitis, and learning/behavioral changes.

Up to 25% of children with LS have extracutaneous manifestations, most commonly arthritis (47%) and neurologic symptoms (17%) associated with en coup de sabre.

Systemic Scleroderma
SSc also has an insidious onset with a prolonged course characterized by periods of remission and exacerbation, ending in either remission or, more commonly, chronic disability and death. The skin manifestations of SSc include an early phase of edema that spreads proximally from the dorsum of the hands and fingers and includes the face. An eventual decrease in edema is followed by induration and fibrosis of skin, ultimately resulting in loss of subcutaneous fat, sweat glands, and hair follicles. Later, atrophic skin becomes shiny and waxy in appearance. As lesions spread proximally, flexion contractures develop at the elbows, hips, and knees associated with secondary muscle weakness and atrophy. In the face, this process results in a small oral stoma with decreased mouth aperture. Skin ulceration over pressure points, such as the elbows, may be associated with subcutaneous calcifications. Severe Raynaud phenomenon causes ulceration of the fingertips with subsequent loss of tissue pulp and tapered fingers (sclerodactyly) (Fig. 160-5). Resorption of the distal tufts of the distal phalanges may occur (acroosteolysis). Hyperpigmented postinflammatory changes surrounded by atrophic depigmentation gives a

### Table 160-1: Classification of Pediatric Scleroderma (Morphea)

<table>
<thead>
<tr>
<th>Localization</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Generalized</td>
<td>Involves the scalp and/or face; lesions can extend into the central nervous system, resulting in neurologic sequelae, most commonly seizures and headaches.</td>
</tr>
<tr>
<td>Linear</td>
<td>Involves the scalp and/or face; lesions can extend into the central nervous system.</td>
</tr>
<tr>
<td>Deep</td>
<td>Involved deeper layers, including panniculus, fascia, and muscle; more likely to be bilateral.</td>
</tr>
<tr>
<td>Subcutaneous</td>
<td>Primarily involves the panniculus or subcutaneous tissue.</td>
</tr>
<tr>
<td>Plaques</td>
<td>Hyperpigmented and symmetric.</td>
</tr>
<tr>
<td>Eosinophilic fasciitis</td>
<td>Fasciitis with marked blood eosinophilia.</td>
</tr>
<tr>
<td>Parry Romberg syndrome</td>
<td>Hemifacial atrophy without a clearly definable en coup de sabre lesion; can also have neurologic involvement.</td>
</tr>
<tr>
<td>Deep Morphea</td>
<td>Deep lesion extending to fascia and sometimes muscle, but may be limited to a single plaque, often on trunk.</td>
</tr>
<tr>
<td>Disabling pansclerotic morphea of childhood</td>
<td>Generalized full-thickness involvement of skin on the trunk, face and extremities, sparing finger tips and toes.</td>
</tr>
</tbody>
</table>

SCLERODERMA PHENOMENA

**Localized Scleroderma**

- **Plaque Morphea**: Well-circumscribed, linear lesions can extend through the dermis, subcutaneous tissue, and muscle to underlying bone; more likely unilateral.
- **Linear Scleroderma**: Linear lesions can extend through the dermis, subcutaneous tissue, and muscle to underlying bone; more likely unilateral.
- **Deep Scleroderma**: Deep lesions extending to fascia and sometimes muscle, but may be limited to a single plaque, often on trunk.
- **Subcutaneous Morphea**: Primarily involves the panniculus or subcutaneous tissue.
- **Plaques**: Hyperpigmented and symmetric.
- **Eosinophilic Fasciitis**: Fasciitis with marked blood eosinophilia.
- **Parry Romberg Syndrome**: Hemifacial atrophy without a clearly definable en coup de sabre lesion; can also have neurologic involvement.
- **Deep Morphea**: Deep lesion extending to fascia and sometimes muscle, but may be limited to a single plaque, often on trunk.
- **Disabling Pansclerotic Morphea of Childhood**: Generalized full-thickness involvement of skin on the trunk, face and extremities, sparing finger tips and toes.

**Systemic Sclerosis**

- **Diffuse**: Most common type in childhood.
- **Limited**: Rare in childhood.
- **Previous Known as CREST (Calcinosis cutis, Raynaud phenomenon, esophageal dysfunction, sclerodactyly, and telangiectasia) Syndrome**
Pulmonary disease is the most common visceral manifestation of SSc and includes both arterial and interstitial involvement (alveolitis). Symptoms range from asymptomatic disease to exercise intolerance, dyspnea at rest, and right-sided heart failure. Pulmonary arterial hypertension is a poor prognostic sign, developing either as a consequence of lung disease or independently as part of the vasculopathy. Clinical manifestations of pulmonary arterial hypertension in children appear late in the course, are subtle, and include cough and dyspnea on exertion. Pulmonary evaluation should include pulmonary function testing, bronchoalveolar lavage, and high-resolution chest CT. Pulmonary function tests reveal decreased vital capacity and decreased diffusion of carbon monoxide capacity, while neutrophilia and/or eosinophilia on bronchoalveolar lavage suggest active alveolitis. Chest CT is much more sensitive than chest radiographs, which are often normal, showing typical basilar ground-glass abnormalities, reticular linear opacities, nodules, honeycombing, and mediastinal adenopathy.

Other organ systems include gastrointestinal tract disease, which is seen in 25% of children with the disease. Common manifestations include esophageal and intestinal dysmotility resulting in dysphagia, reflux, dyspepsia, gastroparesis, bacterial overgrowth, dilated bowel loops and pseudoobstruction, and dental caries, as well as malabsorption and failure to thrive. Renal arterial disease can cause chronic or severe episodic hypertension; unlike adult disease, renal crisis is rare. Cardiac fibrosis is associated with arrhythmias, ventricular hypertrophy, and decreased cardiac function. Mortality from JSSc is most commonly a result of cardiopulmonary disease.

Raynaud Phenomenon
Raynaud phenomenon (RP) is the most frequent initial symptom in pediatric systemic sclerosis, present in 70% of affected children months to years before other manifestations. RP refers to the classic triphasic sequence of blanching, cyanosis, and erythema of the digits induced
by cold exposure and/or emotional stress. RP is most commonly independent of an underlying rheumatic disease (Raynaud disease), but it can be a consequence of rheumatic diseases such as scleroderma, systemic lupus erythematosus, and mixed connective tissue disease (Table 160-2). The color changes are brought about by (1) initial arterial vasoconstriction, resulting in hypoperfusion and pallor (blanching), (2) venous stasis (cyanosis), and (3) reflex vasodilation caused by the factors released from the ischemic phase (erythema). The color change is classically reproduced by immersing the hands in iced water and reversing by warming. During the blanching phase, there is inadequate tissue perfusion in the affected area, associated with pain and paresthesias and resulting in ischemic damage only when associated with a rheumatic disease. The blanching usually affects the distal fingers, but may also involve thumbs, toes, ears, and tip of the nose. The affected area is usually well demarcated and uniformly white. Digital ulcers associated with RP are indicative of underlying rheumatic disease.

Raynaud disease often begins in adolescence and is characterized by symmetric occurrence, the absence of tissue necrosis and gangrene, and the lack of manifestations of an underlying rheumatic disease. Children have normal nail-fold capillaries (absence of periungual telangiectasias). RP should be distinguished from acrocyanosis and chilblains. Acrocyanosis is a vasospastic disorder resulting in cool, painless, bluish discoloration in the hands and sometimes feet despite normal tissue perfusion. It may be exacerbated by stimulant medications used to treat attention deficit disorder. Chilblains is a condition with episodic color changes and the development of nodules related to severe cold exposure and spasm-induced vessel and tissue damage; this condition has been associated with systemic lupus erythematosus.

Table 160-2 Classification of Raynaud Phenomenon

<table>
<thead>
<tr>
<th>Isolated Raynaud phenomenon</th>
</tr>
</thead>
<tbody>
<tr>
<td>Occupational Raynaud phenomenon:</td>
</tr>
<tr>
<td>Cold injury</td>
</tr>
<tr>
<td>Vibrating tools</td>
</tr>
<tr>
<td>Polyvinyl chloride exposure</td>
</tr>
<tr>
<td>Secondary Raynaud phenomenon:</td>
</tr>
<tr>
<td>Systemic sclerosis</td>
</tr>
<tr>
<td>Mixed connective tissue disease</td>
</tr>
<tr>
<td>Sjögren syndrome</td>
</tr>
<tr>
<td>Systemic lupus erythematosus</td>
</tr>
<tr>
<td>Polymyositis/dermatomyositis</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
</tr>
<tr>
<td>Arteritis</td>
</tr>
<tr>
<td>Antiphospholipid antibody syndrome</td>
</tr>
<tr>
<td>Primary biliary cirrhosis</td>
</tr>
<tr>
<td>Carpal tunnel syndrome</td>
</tr>
<tr>
<td>Cryoglobulinemia</td>
</tr>
<tr>
<td>Leukemia</td>
</tr>
<tr>
<td>Vasospastic disorders (migraine, Prinzmetal angina)</td>
</tr>
<tr>
<td>Infection:</td>
</tr>
<tr>
<td>Hepatitis B and C (cryoglobulinemia)</td>
</tr>
<tr>
<td>Cyto megalovirus (?)</td>
</tr>
<tr>
<td>Obstructive vascular disease:</td>
</tr>
<tr>
<td>Thromboangiitis obliterans</td>
</tr>
<tr>
<td>Thoracic outlet syndrome (cervical rib)</td>
</tr>
<tr>
<td>Metabolic syndrome:</td>
</tr>
<tr>
<td>Hypothyroid</td>
</tr>
<tr>
<td>Carcinoid syndrome</td>
</tr>
<tr>
<td>Drug-induced:</td>
</tr>
<tr>
<td>Antimigraine medications</td>
</tr>
<tr>
<td>β-Blocker</td>
</tr>
<tr>
<td>Bleomycin</td>
</tr>
<tr>
<td>Interferons</td>
</tr>
<tr>
<td>Ergotamine derivatives</td>
</tr>
</tbody>
</table>


Table 160-3 Provisional Criteria for the Classification of Juvenile Systemic Sclerosis (SSc)

| MAJOR CRITERION (REQUIRED)* |
| Proximal skin sclerosis/induration of the skin proximal to metacarpophalangeal or metatarsophalangeal joints |

| MINOR CRITERIA (AT LEAST 2 REQUIRED) |
| Cutaneous: sclerodactyly |
| Peripheral vascular: Raynaud phenomenon, nailfold capillary abnormalities (telangiectasias), digital tip ulcers |
| Gastrointestinal: dysphagia, gastroesophageal reflux |
| Cardiac: Arrhythmias, heart failure |
| Renal: Renal crisis, new-onset arterial hypertension |
| Respiratory: pulmonary fibrosis (high-resolution computed tomography/radiography), decreased diffusing capacity for carbon monoxide, pulmonary arterial hypertension |
| Neurologic: neuropathy, carpal tunnel syndrome |
| Musculoskeletal: tendon friction rubs, arthritis, myositis |
| Serologic: antinuclear antibodies—SSc-selective autoantibodies (anticentromere, antitopoisomerase I [Scl-70], antifibrillarin, anti-PM/Scl, antifibrillin or anti-RNA polymerase I or III |


**DIAGNOSIS**

The diagnosis of localized scleroderma is based on the distribution and depth of characteristic lesions. Biopsy is helpful to confirm the diagnosis. The diagnosis of JSSc requires proximal sclerosis/induration of the skin as well as the presence of 2 of 20 minor criteria (Table 160-3).

**DIFFERENTIAL DIAGNOSIS**

The most important condition to differentiate from JLS is JSSc. Contractures and synovitis from juvenile arthritis can be differentiated from those due to linear scleroderma by the absence of skin changes. Other conditions to consider include chemically induced scleroderma-like disease, diabetic chiroarthropathy, pseudoscleroderma, and scleredema. Pseudoscleroderma is composed of a group of unrelated diseases characterized by patchy or diffuse cutaneous fibrosis without the other manifestations of scleroderma. These include phenylketonuria, syndromes of premature aging, and localized idiopathic fibrosis. Scleredema is a transient, self-limited disease of both children and adults that has sudden onset after a febrile illness (especially streptococcal infections) and is characterized by patchy sclerodermatous lesions on the neck and shoulders and extending to the face, trunk, and arms.

**LABORATORY FINDINGS**

There are no laboratory studies diagnostic of either localized or systemic scleroderma. Although the results of complete blood counts, serum chemistry analyses, and urinalysis are normal, children may have elevated erythrocyte sedimentation rate, eosinophilia, or hypergammaglobulinemia, all of which normalize with treatment. Elevations of muscle enzymes, particularly aldolase, can be seen with muscle involvement. Patients with JSSc may have anemia, leukocytosis, and eosinophilia and autoantibodies (ANA, anti-Scl 70). Imaging studies delineate the affected area and can be used to follow disease progression. MRI is useful in en coup de sabre and Parry Romberg syndrome for determination of central nervous system or orbital involvement. Infrared thermography utilizes the temperature variation between areas of active and inactive cutaneous disease to help differentiate active disease from damage. The role of ultrasound to look at lesion activity is evolving. High-resolution CT, pulmonary function tests, echocardiography, and manometry are useful tools for diagnosing and monitoring visceral involvement in JSSc.
TREATMENT

Treatment for scleroderma varies according to the subtype and severity. Superficial morphea may benefit from topical corticosteroids or ultraviolet therapy. For lesions involving deeper structures, systemic therapy is recommended. A combination of methotrexate and corticosteroids is effective in treating JLS by preventing lesion extension and resulting in significant skin softening and improved range of motion of affected joints. The treatment plan for JLS includes: (1) weekly subcutaneous methotrexate given at 1 mg/kg weekly (maximum dose: 25 mg); (2) weekly methotrexate as in (1) plus either 3 mo of high-dose intravenous corticosteroids (30 mg/kg, maximum dose: 1,000 mg) for 3 consecutive days a month or weekly corticosteroids at the same dose for 3 mo; (3) high daily oral corticosteroids (2 mg/kg/day, maximum: 60 mg) with a slow taper over 48 wk. Mycophenolate mofetil is a second-line agent for recalcitrant disease. Physical and occupational therapy are important adjuncts to pharmacologic treatment. Eosinophilic fasciitis often responds well to corticosteroids and methotrexate.

Treatments for JSSc target specific disease manifestations. RP is treated with cold avoidance with pharmacologic interventions are reserved for severe disease. Calcium channel blockers (nifedipine 30-60 mg of sustained-release form daily, amlodipine 2.5-10 mg daily) are the most common pharmacologic interventions. Additional potential therapies for RP include losartan, prazosin, bosentan, and sildenafil. Angiotensin-converting enzyme inhibitors (captopril, enalapril) are recommended for hypertension associated with renal disease. Methotrexate or mycophenolate mofetil may be beneficial for skin manifestations. Cyclophosphamide and mycophenolate mofetil are used to treat pulmonary alveolitis and prevent fibrosis. Corticosteroids should be used cautiously in systemic sclerosis because of an association with renal crisis. Adults with systemic sclerosis have been successfully treated with high-dose cyclophosphamide, antithymocyte globulin and autologous stem cell transplantation.

The treatment of RP begins with avoiding cold stimuli, use of hand and foot warmers, and avoiding carrying bags by their handles (impairs circulation). Nifedipine (10-20 mg tid adult dose) reduces but does not eliminate the number and severity of episodes. Side effects include headache, flushing, and hypotension. Topical nitrates may result in digital vasodilation and may reduce the severity of an episode.

PROGNOSIS

Localized scleroderma is generally self-limited, with initial inflammatory stage followed by a period of stabilization and then softening for an average disease duration of 3-5 yr; however there are reports of active disease lasting up to 20 yr. Prolonged disease activity is associated primarily with linear and deep disease subtypes. Localized scleroderma, especially linear and deep subtypes, can result in significant morbidity, disfigurement, and disability as a result of joint contractures, muscle atrophy, limb shortening, facial asymmetry, and hypopigmentation. Death from a en coup de sabre lesion with progressive neurologic decline has been reported.

JSSc has a more variable prognosis. Although many children have a slow, insidious course, others demonstrate a rapidly progressive form with early organ failure and death. Skin manifestations reportedly soften years after disease onset. Overall, the prognosis of JSSc is better than that of the adult form, with 5-, 10-, and 15-year survival rates, respectively, in children of 89%, 80-87%, and 74-87%. The most common cause of death is heart failure caused by myocardial and pulmonary fibrosis.

Bibliography is available at Expert Consult.
Chapter 160  Scleroderma and Raynaud Phenomenon

**Bibliography**


Behçet disease (BD) is classified as a primary variable vessel vasculitis, emphasizing the involvement of any size and type (arterial, venous) of vessel. BD is also recognized as an autoinflammatory disease. Originally described with recurrent oral ulcerations, uveitis and skin abnormalities, the spectrum is much broader.

**Epidemiology**
BD has a high prevalence in countries along the Silk Road, extending from Japan to the eastern Mediterranean. It is increasingly recognized among people of European ancestry. BD has a prevalence of 5-7 per 100,000 adults, which makes it more frequent than the other vasculitides such as granulomatosis polyangiitis (Wegener disease). The increased disease recognition might have had a role in the rising prevalences as well as the immigrations of the 20th century. Prevalence in children is probably not more than 10% of the adult counterparts in eastern Mediterranean countries. In children, boys and girls are equally affected. Family history of BD is present in approximately 20% of the cases. Onset in children is 8-12 yr of age; newborns of affected mothers have demonstrated symptoms of BD.

**Etiology and Pathogenesis**
BD is a polygenic autoinflammatory disorder. Genetic contribution to BD is evident through the well-known association with HLA-B5101, the familial cases, the sibling and twin recurrence rate, the specific frequency of the disease among people along the Silk Road, evidence for genetic anticipation and the genome wide analysis studies that support the genetic contribution in the pathogenesis. Genome wide analysis studies among Turkish and Japanese BD patients confirm the marked association with HLA-B5101. Other significant associations include interleukin (IL)-10 and IL-23R/IL-12RB2 genes. Other possible susceptibility loci in a Turkish cohort demonstrate associations in STAT4 (a transcription factor in a signaling pathway related to cytokines such as IL-12, type I interferons, and IL-23), and ERP1 (an endoplasmic reticulum–expressed aminopeptidase that functions in processing of peptides onto major histocompatibility complex class I).

The autoinflammatory nature of the disease is suggested by the episodic nature of the disease, the prominent innate immune system activation, the absence of identifiable autoantibodies and the co-association with the MEFV (Mediterranean fever) gene. An infectious agent may be responsible for inducing the aberrant innate immune system attacks in the genetically predisposed host. A number of infectious agents have been implicated and include streptococci, herpes simplex virus type 1, and parvovirus B19.

**Clinical Manifestations and Diagnosis**
The course of BD is characterized by exacerbations and remissions. There is also marked heterogeneity in disease manifestation (Table 161-1).

The mean age of the first symptom is between 8 and 12 yr. The most frequent initial symptom is a painful oral ulcer (Fig. 161-1). The oral ulcers are often recurrent, may be single or multiple, range from 2-10 mm, and may be in any location in the oral cavity. They are often very painful. The oral ulcers last 3-10 days and heal without scarring. In contrast, the genital ulcers heal with scars. Genital scars are noted in 60% of the patients, usually occur after puberty, and are seen on the labia, scrotum, penis, or the anal area.

Another key feature of BD that has significant morbidity is bilateral eye involvement seen in 30-60% of pediatric patients. The main symptoms of anterior uveitis are blurred vision, redness, periorbital or
global pain, and photophobia. Although it is often in the form of panuveitis, anterior uveitis may be seen in females. Uveitis in general is more common in males. Vitreitis and retinal vasculitis are the most prominent features of posterior involvement. Complications of uveitis include blindness (unusual with treatment), glaucoma, and cataracts. Retinal vasculitis, retinal detachment, and retrobulbar neuritis (optic neuritis) are less-common eye manifestations of BD.

The skin lesions of BD range from erythema nodosum, papulopustular acneiform lesions, folliculitis, purpura, and ulcers. Pathergy is also a skin feature that is a pustular reaction occurring 24-48 hr after a sterile needle puncture or saline injection; it is not pathognomonic of BD.

The vasculitis of BD involves both arterial or venous thrombosis and aneurysm formation or occlusions or stenosis in arteries of any size. In children deep venous thrombosis of the lower limbs is the most frequent vasculitic feature. If the hepatic vein is thrombosed Budd-Chiari syndrome may occur. Pulmonary aneurysms are the most severe feature of pediatric BD, associated with the highest mortality. Coronary artery aneurysms may confuse BD with Kawasaki disease. Microvascular involvement may be noted in the nail bed capillaries. Central nervous system (CNS) manifestations in children include meningoencephalitis (headache, meningismus, cerebrospinal fluid pleocytosis), encephalomyelitis, pseudotumor cerebri, dural sinus thrombosis, and organic psychiatric disorders (psychosis, depression, dementia). Dural sinus thrombosis is the most common CNS manifestation in children.

Gastrointestinal involvement manifests with abdominal pain, diarrhea, and intestinal ulcers, most often in the ileocecal region. Gastrointestinal BD may be difficult to distinguish from inflammatory bowel disease. Oligoarticular arthritis/arthralgia is present in more than 50% of the patients and can be recurrent, but is nondeforming. Other rare manifestations include orchitis, renal vasculitis, glomerulonephritis, or amyloidosis and cardiac involvement.

**DIAGNOSIS**

The International Study Group criteria are most widely used and require the presence of oral ulcers (at least 3 times per year) along with 2 other major features, including genital ulcers, a positive pathergy test, uveitis, and the characteristic skin lesions (see Table 161-1). If only 1 of the criteria is present along with oral ulcerations, the term incomplete or partial Behçet disease is applied. There are no specific laboratory tests. Acute-phase reactants are often mildly elevated. The diagnosis relies on the constellation of symptoms and excluding other causes.

**TREATMENT AND PROGNOSIS**

Azathioprine is highly recommended to treat inflammatory eye disease. For oral and genital ulcers topical treatment is recommended (sucralfate, steroids). Colchicine is recommended for erythema nodosum arthralgia in males and females and for genital ulcers in females. There is no evidence-based treatment for gastrointestinal disease, but thalidomide, sulfasalazine, steroids, azathioprine and anti–tumor necrosis factor (TNF) agents have been recommended. For CNS disease and vasculitis, steroids, azathioprine, cyclophosphamide, interferon alpha, and in unresponsive CNS disease anti–TNF agents are suggested. There is no consensus about the benefit of anticoagulation in the management of vein thrombosis in BD.

In patients without major organ involvement, colchicine significantly improves oral and genital ulcers, skin features, and disease activity. In pediatric patients with vascular involvement with venous thrombosis, steroids and azathioprine have been used, whereas those with pulmonary arterial or cardiac involvement are initially treated with cyclophosphamide; follow-up of at least 18 mo demonstrated that those treated are free of vascular relapses. Patients treated with anti-TNF drugs have had persistent responses in 90%, 89%, 100%, and 91% of patients with resistant mucocutaneous, ocular, gastrointestinal, and central nervous system involvement, respectively.

Mortality in children with BD is low except for the pulmonary aneurysms. However, BD is a chronic disease associated with significant morbidity. Early diagnosis and effective treatment improves the outcome of BD.
Bibliography
**Sjögren Syndrome** is a chronic, inflammatory, autoimmune disease characterized by progressive lymphocytic and plasma cell infiltration of the exocrine glands, especially salivary and lacrimal, with potential for systemic manifestations. It is rare in children and predominantly affects middle-age women with classic symptoms of dry eyes (keratoconjunctivitis sicca) and dry mouth (xerostomia).

**EPIDEMIOLOGY**

Sjögren syndrome typically manifests at 35-45 yr of age, with 90% of cases among women, but it is underrecognized in children as symptoms often start in childhood. The mean age at diagnosis in children is 9-10 yr; 75% are girls. The disease can occur as an isolated disorder, referred to as primary Sjögren syndrome (sicca complex), or as a secondary Sjögren syndrome in association with other rheumatic disorders such as systemic lupus erythematosus, scleroderma, or mixed connective tissue disease, and usually precedes the associated autoimmune disease by years.

**ETIOLOGY AND PATHOGENESIS**

The etiology of Sjögren syndrome is complex and includes genetic predisposition and possibly an infectious trigger. Lymphocytes and plasma cells infiltrate salivary glands, forming distinct periductal and pericinar foci that become confluent and may replace epithelial structure. Several genes regulating apoptosis influence the chronicity of lymphocytic infiltration.

**CLINICAL MANIFESTATIONS**

International classification criteria have been developed for the diagnosis of Sjögren syndrome in adult patients, but these criteria apply poorly to children. Although diagnostic criteria in children have been proposed, they have not been validated (Table 162-1). Recurrent parotid gland enlargement and parotitis are the most common manifestations in children (>70%), whereas sicca syndrome (dry mouth, painful mucosa, sensitivity to spicy foods, hallitosis, widespread dental caries) predominate in adults. In a cross sectional study of children with Sjögren syndrome, manifestations included recurrent parotitis (72%), sicca symptoms (38%), polyarthritis (18%), vulvovaginitis (12%), hepatitis (10%), Raynaud phenomenon (10%), fever (8%), renal tubular acidosis (9%), lymphadenopathy (8%), and central nervous system involvement (5%).

Subjective symptoms of xerostomia complaints are relatively rare in juvenile cases, perhaps indicating that Sjögren syndrome is a slowly progressive disease; however increased dental caries is seen clinically in children. Serologic markers (antinuclear antibodies, and antibodies to Ro [SSA] and SSB [La]) and articular manifestations are significantly more frequent in adults. Frequencies of the finding of antinuclear antibodies and SSA and SSB antibodies in children are reported to be 78%, 75%, and 65%, respectively, with rheumatoid factor present in 67%. Additional clinical manifestations from a variety of organ involvement patterns include a decreased sense of smell, hoarseness, chronic otitis media, leukocytoclastic vasculitis (purpura), and internal organ exocrine disease involving the lungs (diffuse interstitial lymphocytosis), pancreas, hepatobiliary system, gastrointestinal tract, kidneys (renal tubular acidosis), musculoskeletal (arthritis and arthralgia), hematologic (cytopenias), peripheral nervous system (sensory and autonomic neuropathy), and central nervous system (optic neuritis, transverse myelitis, meningencephalitis).

**Table 162-1 Proposed Criteria for Pediatric Sjögren Syndrome**

<table>
<thead>
<tr>
<th>I. CLINICAL SYMPTOMS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Oral: recurrent parotitis or enlargement of parotid gland, dry mouth (xerostomia)</td>
</tr>
<tr>
<td>2. Ocular: dry eyes (xerophthalmia) recurrent conjunctivitis without obvious allergic or infectious etiology, keratoconjunctivitis sicca</td>
</tr>
<tr>
<td>3. Other mucosal: recurrent vaginitis</td>
</tr>
<tr>
<td>4. Systemic: fever, non-inflammatory arthralgias, hypokalemic paralysis, abdominal pain</td>
</tr>
</tbody>
</table>

| II. IMMUNOLOGIC ABNORMALITIES: presence of at least 1 of the following antibodies: anti-SSA, anti-SSB, high titer antinuclear antibody, rheumatoid factor |

<table>
<thead>
<tr>
<th>III. OTHER ABNORMALITIES OR INVESTIGATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Biochemical: elevated serum amylase</td>
</tr>
<tr>
<td>2. Hematologic: leukopenia, high sedimentation rate</td>
</tr>
<tr>
<td>3. Immunologic: polyclonal hyperimmunoglobulinemia</td>
</tr>
<tr>
<td>4. Renal: renal tubular acidosis</td>
</tr>
<tr>
<td>5. Histologic proof of lymphocytic infiltration or salivary glands or other organs (i.e., liver)</td>
</tr>
<tr>
<td>6. Objective documentation of ocular dryness (Bengal red staining or Schirmer test)</td>
</tr>
<tr>
<td>7. Positive findings of parotid gland scintigraphy</td>
</tr>
</tbody>
</table>

IV. Exclusion of all other autoimmune diseases

Non–exocrine disease manifestations of Sjögren syndrome may be related to inflammatory vascular disease (in skin, muscle and joints, serosal surfaces, and peripheral and central nervous systems), noninflammatory vascular disease (Raynaud phenomenon), mediator-induced disease (hematologic cytopenias, fatigue, and fever), and autoimmune endocrinopathy (thyroiditis).

**DIAGNOSIS**

Clinical presentation of recurrent parotitis and or recurrent parotid gland swelling in a child or adolescent is characteristic and should raise the suspicion for this disorder. The diagnosis is based on clinical features supported by biopsy of salivary or parotid glands demonstrating foci of lymphocytic infiltration, the current gold standard for diagnosis. Children are more likely to have normal minor salivary gland but abnormal parotid gland biopsies. Supporting laboratory abnormalities include cryoglobulinemia, elevated erythrocyte sedimentation rate, hypergammaglobulinemia, positive rheumatoid factor, and detection of SSA and SSB antibodies. Anti-β-fodrin autoantibodies, directed against an apoptotic cleavage product of α-fodrin, are a useful diagnostic marker for juvenile Sjögren syndrome. The Schirmer test detects abnormal tear production (≤5 mm of wetting of filter paper strip in 5 min) and Rose-Bengal staining detects damaged ocular epithelial conjunctival and corneal cells. Imaging studies, including MRI, technetium 99mTc scintigraphy, and sialography, are useful in the diagnostic evaluation for Sjögren syndrome (Fig. 162-1).

**DIFFERENTIAL DIAGNOSIS**

The differential diagnosis of Sjögren syndrome in children includes juvenile recurrent parotitis, characterized by intermittent unilateral parotid swelling typically lasting only a few days. It is frequently associated with fever and may undergo remission with puberty. Unlike in Sjögren syndrome, there is a male predominance, it is seen in the younger children (3-6 yr of age), and there is a lack of focal lymphocytic infiltrates on biopsy. Other conditions in the differential diagnosis include eating disorders, infectious parotitis (mumps, streptococcal and staphylococcal infections, Epstein-Barr virus, cytomegalovirus, HIV, parainfluenza, influenza enterovirus) and local trauma to the buccal mucosa. Rarely, polycystic parotid disease, tumors, and sarcoidosis may present with recurrent parotid swelling. In these conditions,
TREATMENT
Symptomatic treatment of Sjögren syndrome includes the use of artificial tears, massage of the parotids, oral lozenges, and fluids to limit the damaging effects of decreased secretions. Corticosteroids, nonsteroidal antiinflammatory drugs, and hydroxychloroquine are among the more commonly used agents for treatment, with reports of methotrexate and etanercept used for treatment of arthritis. Stronger immunosuppressive agents, such as cyclosporine and cyclophosphamide, are reserved for severe functional disorders and life-threatening complications.

COMPLICATIONS AND PROGNOSIS
The symptoms of Sjögren syndrome develop and progress slowly. Diminished salivary flow typically remains constant for years. Because monoclonal B-lymphocyte disease originates chiefly from lymphocytic foci within salivary glands or from parenchymal internal organs, there is increased risk for mucosa-associated lymphoid tissue lymphoma. Maternal Sjögren syndrome can be an antecedent to the neonatal lupus syndrome (see Chapter 158.1).

Bibliography is available at Expert Consult.
Bibliography


Chapter 163
Hereditary Periodic Fever Syndromes and Other Systemic Autoinflammatory Diseases

Amanda K. Ombrello and Daniel L. Kastner

The hereditary periodic fever syndromes are a group of monogenic diseases that present with recurrent bouts of fever and associated pleural and/or peritoneal inflammation, arthritis, and various types of skin rash. They are subsumed among a larger group of disorders, the systemic autoinflammatory diseases, that were first recognized for their seemingly unprovoked episodes of inflammation, without the high-titer autoantibodies or antigen-specific T cells commonly seen in autoimmune diseases such as systemic lupus erythematosus or rheumatoid arthritis. Whereas the autoimmune diseases are disorders of the adaptive immune system, with its lymphocyte effector cells and receptors that somatically rearrange and mutate, the autoinflammatory diseases largely represent disorders of the phylogenetically more primitive innate immune system, mediated by myeloid effector cells and germline-encoded receptors. The autoinflammatory diseases can cause an intense acute phase response with elevation of the erythrocyte sedimentation rate, C-reactive protein, and serum amyloid A, in some cases leading to amyloid A (AA) amyloidosis (see Chapter 164).

The hereditary periodic fever syndromes include 2 illnesses with an autosomal recessive mode of inheritance, familial Mediterranean fever (FMF; MIM249100) and the hyperimmunoglobulinemia D with periodic fever syndrome (HIDS; MIM260920). Hereditary periodic fever syndromes with an autosomal dominant mode of inheritance include the tumor necrosis factor (TNF) receptor-associated periodic syndrome (TRAPS; MIM191190) and a spectrum of disorders known as the cryopyrin-associated periodic syndromes (CAPSs), or cryopyrinopathies. From mildest to most severe, CAPS includes the familial cold autoinflammatory syndrome (FCAS1; MIM120100), Muckle-Wells syndrome (MWS; MIM191100), and neonatal-onset multisystem inflammatory disease (NOMID; MIM607115) (also known as chronic infantile neurologic cutaneous and articular syndrome, or CINCA) (Table 163-1).

There are a number of other mendelian autoinflammatory diseases that present in childhood and are not considered hereditary periodic fever syndromes. These include the syndrome of pyogenic arthritis with pyoderma gangrenosum and acne (PAPA; MIM604416), deficiency of the interleukin 1 (IL-1) receptor antagonist (DIRA; MIM612852), Blau syndrome (also known as early-onset sarcoidosis; MIM186580), chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE; MIM256040), autoinflammation with phospholipase Cγ₂-associated antibody deficiency and immune dysregulation (APLAID; MIM614878), and deficiency of adenosine deaminase-2 (DADA2) (Table 163-2). Other disorders include congenital sideroblastic anemia with B-cell immunodeficiency, periodic fevers and developmental delay (SIFD) due to biallelic mutations of the TRNT1 gene as well as disease produced by mutations in the phospholipase Cγ₂ gene (cold-induced urticaria, granulomatous rash, bronchiolitis, enterocolitis, eye inflammation) or by mutations in the cat-eye syndrome chromosome region, candidate 1 (CECR1) causing fever, stroke, rash, and vasculitis. An interferonopathy due to upregulation of TMEM173 that encodes STING (stimulation of
<table>
<thead>
<tr>
<th>Differential Diagnosis of Familial Autoinflammatory Syndromes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FAMILIAL MEDITERRANEAN FEVER (FMF)</strong></td>
</tr>
<tr>
<td>Mode of Inheritance</td>
</tr>
<tr>
<td>Age at Onset (yr)</td>
</tr>
<tr>
<td>Duration of attack (days)*</td>
</tr>
<tr>
<td>Cutaneous Involvement</td>
</tr>
<tr>
<td>Musculoskeletal Involvement</td>
</tr>
<tr>
<td>Abdominal Involvement</td>
</tr>
<tr>
<td>Eye Involvement</td>
</tr>
<tr>
<td>Distinguishing Clinical Symptoms</td>
</tr>
<tr>
<td>Gene Involved</td>
</tr>
<tr>
<td>Protein Involved</td>
</tr>
</tbody>
</table>

Note: For details on Blau syndrome, DIRA, and pyogenic sterile arthritis, pyoderma gangrenosum, and acne (PAPA) syndrome, see text.

*Duration may vary, this is a typical duration.

interferon genes) produces infantile onset of neutrophilic rash, increased acute-phase reactants, fever, interstitial lung disease, paratrabecular adenopathy, and facial nodules.

There are also a number of autoinflammatory disorders with a complex mode of inheritance. These include the syndrome of periodic fever with aphthous stomatitis, pharyngitis, and adenitis (PFAPA) and several other disorders from the other autoinflammatory syndromes. The N-terminal ~90 amino acids of pyrin are the prototype for a motif (the PYRIN domain) that mediates protein-protein interactions, pyrin can activate caspase-1, the enzyme that converts the 31 kDa pro–IL-1β into the biologically active 17 kDa IL-1β, which is a major mediator of fever and inflammation.

Many of the FMF-associated mutations in pyrin are found at the C-terminal B30.2 domain of pyrin, encoded by exon 10 of MEFV. More than 50 such FMF mutations are listed in an online database (http://fmf.igh.cnrs.fr/ISSAID/infevers/), nearly all of which are missense substitutions. Homozygosity for the M694V mutation may be associated with an earlier age of onset, arthritis, and an increased risk of amyloidosis. The substitution of glutamine for glutamic acid at residue 148 (E148Q), is considered to be either a mild mutation or a functional polymorphism in the pyrin protein. The combined frequencies of FMF mutations among several Mediterranean populations are extraordinary high (up to 1:3), suggesting the possibility of a heterozygote advantage. It is also noteworthy that there is a small percentage of patients of typical ethnicity and the clinical findings of FMF who have no demonstrable MEFV mutations, suggesting the possibility of a second FMF locus.

**Epidemiology**

FMF occurs primarily among ethnic groups of Mediterranean ancestry, most commonly Jews, Turks, Armenians, Arabs, and Italians. Owing to a higher frequency of the M694V mutation, FMF is more severe and more readily recognized in the Sephardic (North African) than the Ashkenazi (East European) Jewish population. Nevertheless, due to demographics, most Jewish FMF patients in the US are of Ashkenazi ancestry. With the advent of genetic testing, mutation-positive FMF has been documented worldwide, although at lower frequency than in the Mediterranean basin and Middle East. Most patients present with symptoms in childhood, with 90% of patients presenting prior to the age of 20 yr.

**Pathogenesis**

It appears that FMF mutations lead to a gain-of-function and IL-1β-dependent inflammation, with a gene-dosage effect. These results may explain why many heterozygous carriers of FMF mutations have biochemical evidence of inflammation, why as many as 30% of symptomatic FMF patients have only 1 demonstrable MEFV mutation, and why IL-1 inhibitors have a therapeutic effect in FMF.
Clinical Manifestations

Clinical features of FMF may include fever, serositis presenting as pleuritic chest pain or severe abdominal pain, arthritis, and rash. The pleural pain is typically unilateral, whereas the abdominal pain can be generalized or localized to 1 quadrant, similar to other forms of periarticular pain. FMF-associated arthritis occurs primarily in the large joints, may be accompanied by large, neutrophil-rich effusions, and is usually nonerosive and nondestructive. The hallmark cutaneous finding is an erysipeloid erythematous rash that overlies the ankle or dorsum of the foot (Fig. 163-3). Other clinical findings include scrotal pain caused by inflammation of the tunica vaginalis testis, febrile myalgia, exercise-induced myalgia (particularly common in children), and an association with various forms of vasculitis, including Henoch-Schönlein purpura in as many as 5% of pediatric patients. FMF episodes may be triggered by stress, menses, or infections. Between flares, patients are generally symptom-free but may have persistent elevation of their inflammatory markers. The attack frequency can vary from weekly to 1-2 flares/year.

Diagnosis

The diagnosis of FMF can often be made clinically, paying special attention to the duration and recurrence of episodes, documentation of fever, the characteristic serositis, synovitis, or erysipeloid rash, responsiveness to daily colchicine prophylaxis, and the absence of other causative factors. The differential diagnosis includes other hereditary periodic fever syndromes, and, depending on the specific circumstances, may include PFAPA, systemic-onset juvenile idiopathic arthritis (Still disease), cyclic hematopoiesis, gynecologic disorders (when abdominal pain predominates), porphyria, hereditary angioedema, septic arthritis, and the crystalline arthritides.

Genetic testing can be used as adjunctive evidence in ambiguous cases, and in circumstances in which the clinician has little experience with FMF or related conditions. Although FMF is often regarded as a recessively inherited disorder, with the attendant expectation that patients will have 2 mutations in MEFV, genetic testing may be further complicated by the presence of complex associations and incomplete penetrance. Genetic testing can be used as adjunctive evidence in ambiguous cases. The interpretation of genetic testing may be further complicated by the presence of complex alleles in which 2 mutations may be found in cis.

Treatment

Prophylactic daily oral colchicine decreases the frequency, duration, and intensity of FMF flares. This regimen also prevents the development of systemic AA amyloidosis. Colchicine is generally well-tolerated and safe in children, with the most common side effects being diarrhea and other gastrointestinal complaints. Some patients develop lactose intolerance while taking colchicine. Gastrointestinal side effects can be minimized by initiating therapy at a low dose (for young children, 0.3 mg/day) and slowly titrating upward. A dose-related transaminitis may also be observed; bone marrow suppression is rarely seen at the dosages prescribed for FMF. Pediatric patients may require doses of colchicine similar to those needed in adults (1-2 mg/day), reflecting the fact that children metabolize the drug more rapidly than adults. It is not always possible to find a tolerated dose of colchicine at which all

<table>
<thead>
<tr>
<th>Table 163-3</th>
<th>Autoinflammatory Bone Disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethnicity</td>
<td>CRMO</td>
</tr>
<tr>
<td>Fever</td>
<td>Worldwide, but mostly European</td>
</tr>
<tr>
<td>Sites of osseous involvement</td>
<td>Metaphyses of long bones &gt; vertebralae, clavicle, sternum, pelvis, others</td>
</tr>
<tr>
<td>Extraosseous manifestations</td>
<td>PPP, psoriasis, IBD, others</td>
</tr>
<tr>
<td>Family history of inflammatory disorders</td>
<td>Psoriasis, PPP, arthritis, IBD, others</td>
</tr>
<tr>
<td>Inheritance</td>
<td>Not clear</td>
</tr>
<tr>
<td>Gene defect</td>
<td>Unknown</td>
</tr>
<tr>
<td>Protein name</td>
<td>Lipin2</td>
</tr>
<tr>
<td>Protein function</td>
<td>Fat metabolism: (PAP enzyme activity), ↑ message to oxidative stress, ↑ role in mitosis</td>
</tr>
<tr>
<td>Cytokine abnormalities</td>
<td>↑ serum TNF-α</td>
</tr>
<tr>
<td>CRMO, chronic recurrent multifocal osteomyelitis; CSF, colony-stimulating factor; DIRA, deficiency of interleukin-1 receptor antagonist; HSM, hepatosplenomegaly; IBD, inflammatory bowel disease; IL, interleukin; IL-1Ra, interleukin-1 receptor antagonist; IP-10, interferon-inducible protein-10; M-CSF, macrophage-colony-stimulating factor; MIP-1α, macrophage inflammatory protein-1α; PAP, phosphatidate phosphatase; PPP, palmar-plantar pustulosis; PSTPIP2, proline-serine-threonine phosphatase interacting protein; RANKL, receptor activator of nuclear factor-κB ligand; RANTES, regulated upon activation, normal T-cell expressed and secreted; SH3BP2, SH3 binding protein 2; TGF, transforming growth factor; TNF-α, tumor necrosis factor α. From Ferguson PJ, Laxer RM: Autoinflammatory bone disorders. In Cassidy JT, Petty RE, Laxer RM, et al, editors: Textbook of pediatric rheumatology, ed 6, Philadelphia, 2010, Saunders, Table 44-2.</td>
<td></td>
</tr>
</tbody>
</table>
Differential Diagnosis of Periodic Fever

Table 163-3

<table>
<thead>
<tr>
<th>Table 163-4 Clues That May Assist in the Diagnosis of Autoinflammatory Syndromes</th>
</tr>
</thead>
<tbody>
<tr>
<td>AGE OF ONSET</td>
</tr>
<tr>
<td>At birth</td>
</tr>
<tr>
<td>Infancy and 1st yr of life</td>
</tr>
<tr>
<td>Toddler</td>
</tr>
<tr>
<td>Late childhood</td>
</tr>
<tr>
<td>Most common of autoinflammatory syndromes to have onset in adulthood</td>
</tr>
<tr>
<td>Variable (mostly in childhood)</td>
</tr>
<tr>
<td>ETHNICITY AND GEOGRAPHY</td>
</tr>
<tr>
<td>Armenians, Turks, Italian, Sephardic Jews</td>
</tr>
<tr>
<td>Arabs</td>
</tr>
<tr>
<td>Dutch, French, German, Western Europe</td>
</tr>
<tr>
<td>United States</td>
</tr>
<tr>
<td>Can occur in blacks (West Africa origin)</td>
</tr>
<tr>
<td>Eastern Canada, Puerto Rico</td>
</tr>
<tr>
<td>Worldwide</td>
</tr>
<tr>
<td>TRIGGERS</td>
</tr>
<tr>
<td>Vaccines</td>
</tr>
<tr>
<td>Cold exposure</td>
</tr>
<tr>
<td>Stress, menses</td>
</tr>
<tr>
<td>Minor trauma</td>
</tr>
<tr>
<td>Exercise</td>
</tr>
<tr>
<td>Pregnancy</td>
</tr>
<tr>
<td>Infections</td>
</tr>
<tr>
<td>ATTACK DURATION</td>
</tr>
<tr>
<td>&lt;24 h</td>
</tr>
<tr>
<td>1–3 d</td>
</tr>
<tr>
<td>3–7 d</td>
</tr>
<tr>
<td>&gt;7 d</td>
</tr>
<tr>
<td>Almost always “in attack”</td>
</tr>
<tr>
<td>INTERVAL BETWEEN ATTACKS</td>
</tr>
<tr>
<td>3–6 wk</td>
</tr>
<tr>
<td>&gt;6 wk</td>
</tr>
<tr>
<td>Mostly unpredictable</td>
</tr>
<tr>
<td>Truly periodic</td>
</tr>
<tr>
<td>USEFUL LABORATORY TESTS</td>
</tr>
<tr>
<td>Acute-phase reactants must be normal between attacks</td>
</tr>
<tr>
<td>Urine mevalonic acid in attack</td>
</tr>
<tr>
<td>IgG &gt; 100 mg/dl</td>
</tr>
<tr>
<td>Proteinuria (amyloidosis)</td>
</tr>
<tr>
<td>RESPONSE TO THERAPY</td>
</tr>
<tr>
<td>Corticosteroid dramatic</td>
</tr>
<tr>
<td>Corticosteroid partial</td>
</tr>
<tr>
<td>Colchicine</td>
</tr>
<tr>
<td>Cimetidine</td>
</tr>
<tr>
<td>Etanercept</td>
</tr>
<tr>
<td>Anti–IL-1 dramatic</td>
</tr>
<tr>
<td>Anti–IL-1 mostly</td>
</tr>
<tr>
<td>Anti–IL-1 partial</td>
</tr>
<tr>
<td>Anti–IL-1 partially</td>
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</tbody>
</table>


Table 163-5

<table>
<thead>
<tr>
<th>Table 163-5 Differential Diagnosis of Periodic Fever</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Hereditary (see Table 163-1)</td>
</tr>
<tr>
<td>2 Nonhereditary</td>
</tr>
<tr>
<td>a Infectious</td>
</tr>
<tr>
<td>i Hidden infectious focus (e.g., aortoenteric fistula, Caroli disease)</td>
</tr>
<tr>
<td>ii Recurrent reinflection (e.g., chronic meningococcemia, host defense defect)</td>
</tr>
<tr>
<td>iii Specific infection (e.g., Whipple disease, malaria)</td>
</tr>
<tr>
<td>b Noninfectious inflammatory disorder, e.g.:</td>
</tr>
<tr>
<td>i Adult-onset Still disease</td>
</tr>
<tr>
<td>ii Juvenile chronic rheumatoid arthritis</td>
</tr>
<tr>
<td>iii Periodic fever, aphthous stomatitis, pharyngitis, and adenitis</td>
</tr>
<tr>
<td>iv Schnitzler syndrome</td>
</tr>
<tr>
<td>v Behçet syndrome</td>
</tr>
<tr>
<td>vi Crohn disease</td>
</tr>
<tr>
<td>vii Sarcoidosis</td>
</tr>
<tr>
<td>viii Extrinsic alveolitis</td>
</tr>
<tr>
<td>ix Humidifier lung, polymer fume fever</td>
</tr>
<tr>
<td>c Neoplastic</td>
</tr>
<tr>
<td>i Lymphoma (e.g., Hodgkin disease, angioimmunoblastic lymphoma)</td>
</tr>
<tr>
<td>ii Solid tumor (e.g., pheochromocytoma, myoxma, colon carcinoma)</td>
</tr>
<tr>
<td>d Vascular (e.g., recurrent pulmonary embolism)</td>
</tr>
<tr>
<td>e Hypothalamic</td>
</tr>
<tr>
<td>f Psychogenic periodic fever</td>
</tr>
<tr>
<td>g Factitious or fraudulent</td>
</tr>
</tbody>
</table>


Symptoms are suppressed, but approximately 90% of patients have a marked improvement in disease-related symptoms. Colchicine is generally continued during pregnancy and lactation.

A small percentage of FMF patients are either unresponsive to or intolerant of therapeutic doses of colchicine. Based on the role of pyrin in IL-1β activation, a randomized placebo-controlled trial demonstrated the safety and effectiveness of rilonacept, an IL-1 inhibitor, in FMF, and there are case reports of the effectiveness of anakinra, a recombinant IL-1 receptor antagonist.

Complications and Prognosis

Amyloidosis is the most serious complication of FMF, and in its absence FMF patients may live a normal life span. Amyloidosis may develop when serum AA, an acute-phase reactant found at extremely high levels in the blood during FMF attacks, is clevated to produce a 76 amino acid fragment that misfolds and deposits ectopically, most commonly in the kidneys, gastrointestinal tract, spleen, lungs, testes, thyroid, and adrenals. Rarely, cardiac amyloidosis may develop; macroglossia and amyloid neuropathy are generally not seen with the amyloidosis of FMF. The most common presenting sign of AA amyloidosis is proteinuria. The diagnosis is then usually confirmed by rectal or renal biopsy. There are a small number of case reports, mostly from the Middle East, in which amyloidosis may actually precede overt FMF attacks, presumably because of subclinical inflammation.

Risk factors for the development of amyloidosis in FMF include homozygosity for the M694V MEFV mutation, polymorphisms of the serum AA gene (encoding AA), noncompliance with colchicine treatment, male gender, and a positive family history of AA amyloid. For reasons that are unclear, country of origin is also a major risk factor for amyloidosis in FMF, with patients raised in the Middle East having a much higher risk than genotypically identical patients raised in the West. Aggressive lifelong suppression of the acute phase reactants should be the goal in patients with FMF amyloidosis, and there are documented cases in which this may result in resorption of amyloid deposits. The natural history of untreated amyloidosis in FMF is the inexorable progression to renal failure, often within 3–5 yr.
HYPERIMMUNOGLOBULINEMIA D WITH PERIODIC FEVER SYNDROME

HIDS, also known as mevalonate kinase deficiency, was initially described in a cohort of Dutch patients and occurs primarily in patients of Northern European descent. HIDS is recessively inherited and caused by mutations of MVK, a gene located on the long arm of chromosome 12 that encodes mevalonate kinase (MK). HIDS-associated mutations are distributed throughout the MK protein, but the 2 most common mutations are the substitution of isoleucine for valine at residue 377 (V377I), a variant that is quite common in the Dutch population, and the substitution of threonine for isoleucine at residue 268 (I268T).

MK is expressed in multiple tissues, and catalyzes the conversion of mevalonic acid to 5-phosphomevalonic acid in the biosynthesis of cholesterol and nonsterol isoprenoids. Patients with HIDS-associated mutations have markedly reduced, but not absent, MK enzymatic activity. HIDS patients usually have low-normal serum cholesterol levels, but the deficiency of isoprenoids may cause increased IL-1β production by aberrant activation of the small guanosine triphosphatase Rac1. Temperature elevation may further exacerbate this process by more complete inhibition of MK activity, leading to a possible positive feedback loop. Complete genetic deficiency of MK results in a more severe phenotype known as mevalonic aciduria (see Chapter 85).

The clinical features of HIDS generally appear within the 1st 6 mo of life. Febrile attacks last between 3 and 7 days with abdominal pain that is often accompanied by diarrhea, nausea, and vomiting. Other clinical manifestations include cervical lymphadenopathy, diffuse macular rash, aphthous ulcers, headaches, and occasional splenomegaly (Figs. 163-4 to 163-6). Arthritis/arthralgia can be present in an oligoarticular or polyarticular pattern. Inflammatory disease–like illness and Kawasaki disease–like presentation have also been reported. Attacks are often precipitated by intercurrent illness, immunizations, and surgery. Families frequently recount flares around the time of birthdays, holidays, and family vacations. Patients with mevalonic
increased serum levels of acute-phase reactants and proinflammatory cytokines are commonly present.

The symptoms of HIDS may persist for years but tend to become less prominent in adulthood. Patients with HIDS usually have a normal life span. Unlike FMF and TRAPS, the incidence of AA amyloidosis is quite low. Standards for the treatment of HIDS are evolving. Very few aciduria present with severe mental retardation, ataxia, myopathy, cataracts, and failure to thrive (see Chapter 85).

The diagnosis of HIDS may be confirmed either by the presence of 2 mutations in MVK (approximately 10% of patients with seemingly typical disease have only a single identifiable mutation) and/or elevated levels of mevalonate in the urine during acute attacks. The eponymous elevation in serum IgD levels is not universally present, especially in young children, and is thought to be an epiphenomenon. Conversely, serum IgD levels may be increased in other autoimmune inflammatory diseases as well as some chronic infections. During attacks, leukocytosis and

Figure 163-2 Characteristic patterns of body temperature during inflammatory attacks in the familial autoinflammatory syndromes. Interindividual variability for each syndrome is considerable, and even for the individual patient, the fever pattern may vary greatly from episode to episode. Note the different time scales on the x-axes. CINCA/NOMID, chronic infantile neurologic cutaneous and articular syndrome/neonatal-onset multisystemic inflammatory disease; FCAS, familial cold autoinflammatory syndrome; HIDS, hyper-IgD syndrome; MWS, Muckle-Wells syndrome; TRAPS, tumor necrosis factor receptor–associated periodic syndrome. (From Simon A, van der Meer JWM, Drenth JPH: Familial autoinflammatory syndromes. In Firestein GS, Budd RC, Gabriel SE, et al, editors: Kelley’s textbook of rheumatology, ed 9, Philadelphia, 2012, Saunders, Fig. 97-1.)

Figure 163-3 Characteristic erysipeloid erythema associated with familial Mediterranean fever. This rash appears during a flare and overlies the ankle or dorsum of the foot.

Figure 163-4 Polymorphic rash on the hands, arms, and legs of a patient with hyperimmunoglobulinemia D syndrome (HIDS). (From Takada K, Aksentijevich I, Mahadevan V, et al. Favorable preliminary experience with etanercept in two patients with the hyperimmunoglobulinemia D and periodic fever syndrome. Arthritis Rheum 48:2646, 2003.)
ASSOCIATED PERIODIC SYNDROME

THE TUMOR NECROSIS FACTOR RECEPTOR-ASSOCIATED PERIODIC SYNDROME

Like FMF and HIDS, TRAPS is characterized by recurrent fevers and localized inflammation, but it is inherited in an autosomal dominant fashion and has a number of distinguishing clinical and immunologic features. TRAPS was first recognized in patients of Irish descent and denoted familial Hibernian fever to draw a contrast with FMF, but the current nomenclature was proposed when mutations in TNFRSF1A were discovered not only in the original Irish family, but in families from a number of other ethnic backgrounds. TNFRSF1A is located on the short arm of chromosome 12, and encodes the 55 kDa receptor (denoted p55, TNFR1, or CD120a) for TNF that is widely expressed on a number of cell types. A second 75 kDa receptor largely restricted to leukocytes is encoded on chromosome 1.

TRAPS was originally defined as an autoinflammatory disorder resulting from TNFRSF1A mutations, and thus genetic testing is required to make the diagnosis. To date, more than 90 disease-associated TNFRSF1A mutations are listed on the online Infevers database, as well as a smaller number of variants of unknown significance. Nearly all of the TRAPS-associated mutations in are in the extracellular domain of the TNFR1 protein, with about one-third involving the substitution of another amino acid for a highly conserved cysteine residue, thus disrupting disulfide bonds and leading to protein misfolding. A number of other missense mutations not involving cysteine residues have been shown to have a similar effect on TNFR1 protein folding. Misfolded TNFR1 aggregates intracellularly and leads to constitutive signaling through mitogen-activated protein kinases, resulting in the release of proinflammatory cytokines such as IL-1β and TNF-α. The substitution of glutamine for arginine at residue 92 (R92Q) and the substitution of leucine for proline at residue 46 (P46L) are seen in greater than 1% of the white and African-American populations, respectively. These variants do not lead to the same biochemical or signaling abnormalities seen with more-severe TRAPS mutations, and, like E148Q in FMF, there is debate as to whether they are mild mutations or functional polymorphisms.

Patients with TRAPS typically present within the 1st decade of life. Flares can occur with variable frequency but the duration is often substantially longer when compared to FMF or HIDS flares. The febrile episodes of TRAPS last at least 3 days and can persist for weeks at a time. As in FMF, there may be pleural and/or peritoneal involvement. At times patients present with signs of an acute abdomen; on exploration such patients have sterile peritonitis, sometimes with adhesions from previous episodes. Patients may also have nausea and frequently report constipation at the onset of flares that progresses to diarrhea by the conclusion. Ocular signs include periorbital edema and conjunctivitis. TRAPS patients may also experience severe myalgia and on imaging the muscle groups may have focal areas of edema. There are a number of rashes that can be seen in TRAPS patients, but the most common is an erythematous macular rash that on biopsy contains superficial and deep perivascular infiltrates of mononuclear cells. Patients often report that the rash migrates distally on a limb during its course with an underlying myalgia and can resemble cellulitis. Other rashes include erythematous annular patches as well as a serpiginous rash (Fig. 163-7). Approximately 10-15% of patients with TRAPS may develop AA amyloidosis; the presence of cysteine mutations and a positive family history are risk factors for this complication. If amyloidosis does not develop, TRAPS patients have a normal life expectancy.

Colchicine is generally not effective in TRAPS. For relatively mild disease, nonsteroidal anti-inflammatory agents may suffice. For more severe disease with infrequent attacks, corticosteroids at the time of an attack may be effective, but it is not unusual for steroid requirements to increase over time. Because some patients with TRAPS exhibit a defect in activation-induced TNF receptor shedding, and have diminished levels of immune modulatory soluble TNFR in the blood, etanercept, the soluble p75 TNFR:Fc fusion protein has been studied in this disorder. Etanercept is often effective in reducing the severity and frequency of flares, but longitudinal follow-up of TRAPS patients treated with etanercept indicates waning efficacy with time. Of note, treatment of TRAPS with anti-TNF monoclonal antibodies has sometimes led to a paradoxical worsening of disease. Experience with both anakinra, a recombinant IL-1 receptor antagonist, and canakinumab, a monoclonal anti–IL-1β antibody, has been favorable in TRAPS patients.

Figure 163-5 Petechiae on the leg of a hyper-IgD syndrome patient during a febrile attack. (From Simon A, van der Meer JWM, Drenth JPH: Familial autoinflammatory syndromes. In Firestein GS, Budd RC, Gabriel SE, et al, editors: Kelley’s textbook of rheumatology, ed 9, Philadelphia, 2012, Saunders, Fig. 97-7.)

Figure 163-6 Aphthous ulceration detected on the tongue of a patient with hyper-IgD syndrome. (Courtesy Dr. K. Antila, North Carelian Central Hospital, Joensuu, Finland; from Simon A, van der Meer JWM, Drenth JPH: Familial autoinflammatory syndromes. In Firestein GS, Budd RC, Gabriel SE, et al, editors: Kelley’s textbook of rheumatology, ed 9, Philadelphia, 2012, Saunders, Fig. 97-8.)

patients respond to colchicine; milder disease may respond to nonsteroidal antiinflammatory drugs. Corticosteroids are of limited utility. Small trials of both etanercept and either intermittent or daily anakinra in HIDS are promising.
Chapter 163 ◆ Hereditary Periodic Fever Syndromes and Other Systemic Autoinflammatory Diseases

CRYOPYRIN-ASSOCIATED PERIODIC FEVER SYNDROMES

CAPS represents a spectrum of clinical disorders, including FCAS, MWS, and NOMID/CINCA. Although 3 separate clinical diagnoses have been defined, it should be emphasized that the cryopyrinopathies are really a continuum, and that patients may present with overlap syndromes that do not fit neatly into a single diagnosis. This spectrum of illness is caused by mutations in NLRP3 (formerly known as CIAS1), located on the long arm of chromosome 1, which encodes a protein variously denoted cryopyrin or NLRP3. More than 100 disease-associated NLRP3 mutations have been enumerated on the Infevers online database. Advances in next-generation sequencing have also permitted the identification of symptomatic individuals with somatic NLRP3 mosaicism.

NLRP3 is a PYRIN domain-containing protein that is strongly expressed in myeloid cells, and to a lesser degree in other tissues. It is a part of a macromolecular complex termed the NLRP3 inflammasome that activates pro–IL-1β to its mature form in response to a variety of endogenous danger-associated molecular patterns and pathogen-associated molecular patterns. Patients with cryopyrinopathies have gain-of-function mutations in NLRP3 that result in constitutive or easily-triggered activation of the NLRP3 inflammasome.

The cryopyrinopathies are characterized by recurrent fevers and an urticaria-like rash that develops early in infancy (Fig. 163-8). Histopathologic examination reveals a perivascular neutrophilic infiltrate without the mast cells or mast cell degranulation seen with true urticaria. In patients with FCAS, febrile attacks generally begin 1-3 hr after generalized cold exposure. FCAS patients also experience polyarthritis of the hands, knees, and ankles, and conjunctivitis may also develop during attacks. FCAS episodes are self-limited and generally resolve within 24 hr. AA amyloidosis rarely occurs in FCAS.

In contrast to FCAS, the febrile episodes of MWS are not cold-induced, but are characterized by the same urticarial rash seen in FCAS (Fig. 163-9). Many MWS patients also develop progressive sensorineural hearing loss, and, untreated, approximately 30% of MWS patients develop AA amyloidosis. NOMID patients present in the neonatal
Targeted therapy with anakinra, a recombinant IL-1 receptor antagonist, has been life-changing for NOMID patients, not only controlling fever and rash, but also preventing end-organ damage. Anakinra was FDA-approved for NOMID. Rilonacept, a soluble IL-1 receptor decoy, and canakinumab, a long-acting, fully humanized IgG1 anti–IL-1\( \beta \) monoclonal antibody, are effective in both FCAS and MWS, and are FDA-approved for both conditions. Aggressive IL-1 blockade has resulted in attenuation of amyloidosis in the cryopyrinopathies.

OTHER MENDELIAN AUTOINFLAMMATORY DISEASES

The Syndrome of Pyogenic Arthritis with Pyoderma Gangrenosum and Acne

PAPA syndrome is a rare autosomal dominant disorder caused by mutations in PSTPIP1, a gene located on chromosome 15 that encodes the cytoskeletal proline serine threonine phosphatase-interacting (PSTPIP) protein. The PSTPIP1 protein interacts with a number of immunologically important molecules, including CD2, the Wiskott-Aldrich syndrome protein (WASP), and pyrin. PAPA-associated PSTPIP1 mutations markedly increase its affinity to pyrin and cause increased IL-1\( \beta \) production.

Clinical manifestations of PAPA syndrome include recurrent episodes of sterile, pyogenic arthritis that leads to erosions and joint destruction, and appears to develop spontaneously or after minor trauma. The onset of arthritis is often in early childhood. Cutaneous manifestations tend to develop in adolescence, at which time patients are prone to developing severe cystic acne. Additionally, PAPA patients commonly develop ulcerating pyoderma gangrenosum lesions (Fig. 163-13), and some develop pathergy reactions.

The treatment of PAPA syndrome may involve the use of corticosteroids, IL-1 antagonists, and TNF inhibitors, sometimes in combination. The joint manifestations of PAPA appear to respond to IL-1

period with a diffuse, urticarial rash, daily fevers, and dysmorphic features. Significant joint deformities, particularly of the knees, may develop because of bony overgrowth of the epiphyses of the long bones (Figs. 163-10 and 163-11). NOMID patients also develop chronic aseptic meningitis, leading to increased intracranial pressure, optic disc edema, visual impairment, progressive sensorineural hearing loss, and intellectual disability (Fig. 163-12). Because of the severe disabilites associated with untreated NOMID, this disorder appeared to be sporadic before NLRP3 mutations were identified in these patients.
Blau Syndrome

Blau syndrome is a rare autosomal dominant disorder that manifests as early-onset granulomatous arthritis, uveitis, and rash. The arthritis may affect the ankles and wrists, and may lead to flexion contractures of the fingers and toes (camptodactyly). Early-onset sarcoidosis presents with a similar clinical picture, sometimes with visceral involvement, and both conditions are caused by mutations in CARD15/
NOD2 on chromosome 16. The protein encoded by this gene, variously denoted caspase recruitment domain protein 15 or nucleotide-binding oligomerization domain 2 protein, is an intracellular sensor of bacterial products in dendritic cells, myelomonocytic cells, and Paneth cells. Mutations in the NALP1 oligomerization domain of this protein cause Blau syndrome/early-onset sarcoidosis, while variants primarily in the leucine-rich repeat domain of this protein are associated with susceptibility to Crohn disease. Corticosteroids have been the mainstay of therapy for Blau syndrome. There are a number of case reports of the beneficial effects of TNF inhibitors, in Blau syndrome.

**Chronic Atypical Neutrophilic Dermatosis with Lipodystrophy and Elevated Temperature**

CANDLE is an autosomal recessive disease resulting from mutations in PSMB8. This gene encodes the β5i subunit of the immunoproteasome, a macromolecular complex that degrades proteins in immune cells for presentation on major histocompatibility complex class I molecules. Disease-associated mutations result in a loss of function. Patients present in the 1sr yr of life with recurrent fevers, violaceous swollen eyelids, purpuric skin lesions with a mixed mononuclear and neutrophilic infiltrate, arthralgia, delayed physical development, and anemia. Acute-phase reactants are also elevated in these patients and, over time, they develop progressive lipodystrophy. On gene expression profiling, CANDLE patients have a robust interferon signature. There is no established therapy for CANDLE, although the interferon pathway may represent a therapeutic target. Two other disorders, Nakajo-Nishimura syndrome and the syndrome of joint contractures, muscular atrophy, microcytic anemia, and panniculitis-induced lipodystrophy, are clinically similar to CANDLE and are also caused by mutations in PSMB8.

**Autoinflammation with Phospholipase Cγ2-Associated Antibody Deficiency and Immune Dysregulation**

APLAI is a dominantly-inherited disorder characterized by recurrent blistering skin lesions, bronchiolitis, arthralgia, ocular inflammation, enterocolitis, absence of autoantibodies, and mild immunodeficiency. It is caused by gain-of-function mutations in PLCG2, leading to increased signaling through the phospholipase Cγ2 pathway in immune cells. To date there is no established therapy for APLAID.

**Deficiency of Adenosine Deaminase 2**

DADA2 is an autoinflammatory disorder caused by loss-of-function mutations in CECR1, encoding adenosine deaminase 2, characterized by recurrent fevers and a spectrum of vascular manifestations that includes livedo racemosa, early-onset ischemic lacunar strokes, and polyarteritis nodosa. Patients may also present with hepatosplenomegaly and a mild immunodeficiency. ADA2 is a protein produced primarily by monocytes and macrophages, which appear to act as a growth factor both for endothelial cells and for the antiinflammatory M2 subset of macrophages. Patients experience a vicious circle of vasculopathy and inflammation. Although there is no established therapy, there is anecdotal evidence supporting the use of etanercept.

**GENETICALLY COMPLEX AUTOINFLAMMATORY DISEASES**

**Periodic Fever, Aphthous Stomatitis, Pharyngitis, and Adenitis**

PFAPA is the most common recurrent fever syndrome in children. It usually presents between the ages of 2 and 5 yr with recurring episodes of fever, malaise, exudative-appearing tonsillitis with negative throat cultures, cervical lymphadenopathy, oral aphthae, and, less commonly, headache, abdominal pain, and arthralgia. The episodes last 4-6 days, regardless of antipyretic or antibiotic treatment, and often occur with clock-like regularity on 3-6 wk cycles. Findings during the episodes may include mild hepatosplenomegaly, mild leukocytosis, and elevated acute-phase reactants. Both the frequency and the intensity of the episodes diminish with increasing age.

The etiology and pathogenesis of PFAPA remain unknown. The majority of patients show dramatic response to a single oral dose of prednisone (0.6–2.0 mg/kg), although this approach does not prevent recurrence and may actually shorten the interval between flares. Cimetidine given at doses of 20–40 mg/kg/day is effective at preventing recurrences in approximately one-third of cases. Complete resolution has also been reported after tonsillectomy in some but not all patients. A pilot study of anakinra (1 mg/kg subcutaneously) given for 1-2 days at the onset of symptoms showed promising results.

**Chronic Recurrent Multifocal Osteomyelitis**

CRMO is a form of inflammatory bone disease most commonly seen in children (see Table 163-3). Histologically and radiologically, CRMO is virtually indistinguishable from infectious osteomyelitis. Patients typically present with bone pain and may also have fever, soft-tissue swelling, and elevated acute-phase reactants. Cultures are sterile. The etiology of sporadic CRMO is unknown. Rarely CRMO can occur with congenital dyserythropoietic anemia (Majede syndrome), caused by mutations in LPIN2. CRMO has also been seen in association with inflammatory bowel disease and inflammatory skin disease such as palmoplantar pustulosis. There is evidence for reduced production of the antiinflammatory cytokine IL-10 in CRMO. Initial therapy includes nonsteroidal antiinflammatory medications. Second-line treatments include corticosteroids, TNF inhibitors, and bisphosphonates.

**Bibliography is available at Expert Consult.**

*Figure 163-15 A*, Widening of multiple ribs (*) and clavicles (arrows) in DIRA osteomyelitis; *B*, chest deformity. Inflammatory clinical manifestations and organ damage in the IL-1-mediated diseases, in neonatal-onset multisystem inflammatory disease (NOMID), which is the severe form of cryopyrin-associated periodic syndromes (CAPS); and deficiency of interleukin-1 receptor antagonist (DIRA). (From Jesus AA, Goldbach-Mansky R: IL-1 blockade in autoinflammatory syndromes. Annu Rev Med 65:223–244, 2014, Fig. 2.)
Bibliography


Amyloidosis comprises a group of diseases characterized by extracellular deposition of insoluble, fibrous amyloid proteins in various body tissues.

**ETIOLOGY**

Amyloidosis is a disease caused by protein misfolding. These misfolded proteins infiltrate, aggregate, and form insoluble fibrils that can affect the normal function of a number of vital organs.

In the amyloidosis nomenclature, there is a distinction made between amyloidosis that develops from mutations in the *amyloid fibril protein itself* versus amyloidosis associated with genetic mutation in nonamyloid proteins. The former are referred to as hereditary amyloidoses; examples include mutations in the genes for transthyretin and apolipoprotein A, both of which are uncommon in children. This is in contrast to amyloid A (AA) amyloidosis, which develops in patients with chronic inflammatory states. It is estimated that, worldwide, approximately 45% of all amyloid cases are AA amyloidosis. In the past, chronic infectious diseases such as tuberculosis, malaria, leprosy, and chronic osteomyelitis accounted for most cases of AA amyloidosis. With effective treatment for these infections, other causes of AA have become more common. A number of chronic inflammatory rheumatic diseases such as rheumatoid arthritis (RA), juvenile idiopathic arthritis (JIA), ankylosing spondylitis, as well as hereditary autoinflammatory diseases, have an increased risk for the development of AA amyloidosis. AA amyloidosis has also been associated with granulomatous diseases such as sarcoidosis, cystic fibrosis, Crohn disease, malignancies such as mesothelioma and Hodgkin diseases, intravenous drug abuse, and other infections, such as bronchiectasis and HIV. Approximately 6% of AA amyloidosis cases have no identified disease association. AL amyloidosis (formally known as idiopathic amyloidosis or myeloma-associated amyloidosis) is extremely rare in children, occurring in middle-aged or older individuals.

**EPIDEMIOLOGY**

Only AA amyloidosis affects children in appreciable numbers. The factors that determine the risk for amyloidosis as a complication of inflammation are not clear, because many individuals with longstanding inflammatory disease do not demonstrate tissue amyloid deposition, while some children with relatively recent onset of disease may develop amyloidosis. In developed countries, prior to the initiation of therapy with disease-modifying anti-rheumatic drugs (DMARDs) and biologic agents, RA was the most common inflammatory disease associated with AA amyloidosis. Patients who had a long history of poorly controlled severe disease with extraarticular manifestations were the most at risk for developing amyloidosis and the median time from first symptoms of their rheumatic condition to the diagnosis of amyloidosis was 212 mo. The full effect of DMARD and biologic therapy in RA-associated amyloidosis has yet to be fully appreciated, but studies are showing a sustained decline in the number of new cases.

JIA is another rheumatic disease that is associated with the development of AA amyloidosis with the highest prevalence in patients with systemic JIA followed by those with polyarticular disease (see Chapter 155). In the pre-DMARD and biologic era, the prevalence of AA amyloidosis in JIA patients ranged from 1-10%. Higher prevalence was seen in Northern European patients, especially Polish patients who had a prevalence of 10.6%; lower prevalence was observed in North America. The reasons for this discrepancy are not completely understood although it is speculated that selection bias, genetic background, and tendency toward more early aggressive therapy in North Americans may have played a role.

The hereditary autoinflammatory diseases define a group of illnesses that are characterized by attacks of seemingly unprovoked recurrent inflammation without significant levels of either autoantibodies or antigen-specific T cells, which are typically found in patients with autoimmune diseases (see Chapter 163). Whereas autoimmune diseases such as systemic lupus erythematosus and RA result from a derangement in the adaptive immune system, the autoinflammatory syndromes are a result of malfunctions in the innate immune system. The inflammatory attacks are mediated by cells of the innate immune system (neutrophils and macrophages). Although seemingly unprovoked, these attacks are often initiated by stress, immunization, or trauma, suggesting that gene–environment interactions play an important role in pathogenesis. Although there is some variability among the autoinflammatory diseases, common findings include fevers, cutaneous rashes, arthritis, serositis, and ocular involvement. The inflammatory attacks are accompanied by intense acute phase responses (erythrocyte sedimentation rate and C-reactive protein) and high levels of serum amyloid A (SAA). Amyloidosis AA is associated with some but not all the hereditary autoinflammatory diseases.

Familial Mediterranean fever (FMF) is the most common of the mendelian autoinflammatory diseases and is seen most frequently in the Armenian, Arab, Turkish, and Sephardi Jewish populations. FMF is an autosomal recessive disease that results from mutations in the *MEFV* gene, which encodes the pyrin/marenostrin protein. *MEFV* mutations affecting the M680 and M694 amino acid residues are associated with early onset of FMF, severe disease, and an increased risk of AA amyloidosis. Patients residing in Armenia, Turkey, and Arabian countries have an increased risk of developing AA amyloidosis compared to patients with the same mutations of *MEFV* living in North America.

Tumor necrosis factor receptor associated periodic syndrome (TRAPS) is associated with mutations in the *TNFRSF1A* gene, which encode the 55 kDa tumor necrosis factor (TNF) receptor protein (TNFR1). It is estimated that 14-25% of patients with TRAPS develop AA amyloidosis. Patients with mutations in *TNFRSF1A* that affect cysteine residues have the highest risk of developing AA amyloidosis. It is thought that these cysteine residues participate in assembly of disulfide bonds important for TNFR1 folding and disruption of these bonds affects protein folding.

Mutations in the NLRP3 gene (also known as CIAS1, cold-induced autoinflammatory syndrome 1) cause 3 clinically distinct diseases: familial cold autoinflammatory syndrome, Muckle-Wells syndrome (MWS), and neonatal onset multisystem inflammatory disease (NOMID) (see Chapter 164). Whereas autoimmune diseases (see Chapter 163) involve recurrent inflammation without significant levels of either autoantibodies or antigen-specific T cells, which are typically found in patients with autoimmune diseases (see Chapter 163). Whereas autoimmune diseases such as systemic lupus erythematosus and RA result from a derangement in the adaptive immune system, the autoinflammatory syndromes are a result of malfunctions in the innate immune system. The inflammatory attacks are mediated by cells of the innate immune system (neutrophils and macrophages). Although seemingly unprovoked, these attacks are often initiated by stress, immunization, or trauma, suggesting that gene–environment interactions play an important role in pathogenesis. Although there is some variability among the autoinflammatory diseases, common findings include fevers, cutaneous rashes, arthritis, serositis, and ocular involvement. The inflammatory attacks are accompanied by intense acute phase responses (erythrocyte sedimentation rate and C-reactive protein) and high levels of serum amyloid A (SAA). Amyloidosis AA is associated with some but not all the hereditary autoinflammatory diseases.
in patients with ulcerative colitis is extremely rare, with estimated prevalence of 0.07%. The patients have a long-standing history of aggressive, poorly controlled disease; however there are reports of amyloidosis in patients with well-controlled inflammatory markers.

PATHOGENESIS

The deposition of AA amyloid fibrils is a result of a prolonged inflammatory state that leads to misfolding of the AA amyloid protein and deposition into tissues. The precursor protein of the fibrils in AA amyloidosis is an apolipoprotein called SAA. SAA is produced in the liver in response to proinflammatory cytokines such as interleukin (IL)-1, IL-6, and TNF-α and can increase more than 1,000-fold during inflammation. It has been speculated that SAA has a role as a chemoattractant and an inflammatory mediator. Supporting this theory is the finding that amyloid deposition occurs initially in organs that are major sites of lipid and cholesterol metabolism such as the kidney, liver, and spleen.

Under normal circumstances SAA is secreted by the liver and completely degraded by macrophages. The secreted SAA protein is 104 amino acids in length and is primarily secreted in an α-helix structure. For reasons not completely understood, patients with AA amyloidosis have a flaw resulting in incomplete degradation and accumulation of intermediate SAA products. In these patients, SAA is transferred to the lysosome where the C-terminal portion of the SAA protein is cleaved, allowing the remaining protein to fold into a β-pleated sheet configuration. Deposited amyloid contains only 66–76 amino acids compared to the 104 in secreted SAA. These cleaved fragments polymerize and form fibrils that are deposited in the extracellular space and bind proteoglycans and other proteins such as serum amyloid P. These fibrils then become resistant to proteolysis and deposit in organ tissues.

CLINICAL MANIFESTATIONS

Although organ involvement may vary, AA amyloidosis most commonly affects the kidneys; 90% of patients have some degree of renal involvement. Unexplained proteinuria may be the presenting feature in some patients. Nephrotic syndrome and renal failure may develop if the underlying inflammatory condition is not controlled or if diagnosis is delayed. Median survival after diagnosis has been reported to be 133 mo; patients with higher SAA levels had significantly higher risk of death than those with lower SAA levels. Gastrointestinal involvement is seen in approximately 20% of patients and usually manifests as chronic diarrhea, gastrointestinal bleeding, abdominal pain, and malabsorption, whereas testes are frequently involved (87%). Relatively uncommon findings associated with AA amyloidosis include anemia, amyloid goiter, hepatomegaly, splenomegaly, adrenal involvement, and pulmonary involvement. Tissues, such as the heart, tongue, and skin, are rarely involved.

DIAGNOSIS

The diagnosis of amyloidosis is established by biopsy demonstrating amyloid fibril proteins in affected tissues. The tissues most commonly tested include kidney, rectum, abdominal fat pad, and gingiva. Amyloid deposits are composed of seemingly homogeneous eosinophilic material that stains with Congo red dye and demonstrates the pathognomonic “apple-green birefringence” in polarized light. Amyloid can also be recognized with routine hematoxylin and eosin staining and electron microscopy.

LABORATORY FINDINGS

Patients with AA amyloidosis usually show elevated acute-phase reactants and high levels of immunoglobulins. Specific laboratory testing is possible only for AL amyloidosis, and most patients with this form of amyloidosis show increased plasma cells in the bone marrow and serum or urine monoclonal immunoglobulin (Ig) or free light chain. A biopsy showing amyloid deposition along with a monoclonal serum protein distinguishes AL amyloidosis from monoclonal gammopathy of uncertain significance, which is common in older adults.

TREATMENT

There is no established therapy to AA amyloidosis and, thus, the primary means of treatment of AA amyloidosis is aggressive management of the underlying inflammatory or infectious disease, which decreases levels of SAA protein. As newer therapies have been developed to treat the underlying condition, there is emerging evidence that the incidence of AA amyloidosis is decreasing. Colchicine is effective not only in controlling the attacks of FMF but also in preventing the development of amyloidosis associated with FMF. Children with FMF who are homozygous for the M694V mutation in the MEFV gene are at greater risk for development of amyloidosis and should be monitored closely.

Unlike AA amyloidosis associated with FMF, AA amyloidosis associated with other autoinflammatory diseases (including TRAPS, cryopyrin-associated periodic syndrome, and HIDS) and chronic rheumatic diseases (JIA, RA, and anklyosing spondylitis) do not respond to colchicine. Although AA amyloidosis associated with JIA may respond to chlorambucil, this drug is associated with chromosome breakage and a risk of subsequent malignancy.

Increasing use of biologic medicines against proinflammatory cytokines to treat RA, JIA, spondyloarthropathies, and the hereditary autoinflammatory diseases seems to impact risk factors for the development of AA amyloidosis. The class of medications referred to as the anti–TNF-α drugs have been paramount in the management of RA and other autoimmune disease. In both autoimmune and autoinflammatory conditions with accompanying AA amyloidosis, there are reports documenting the effectiveness of anti-TNF agents in blunting the progression of amyloidosis. Adverse effects of anti-TNF medications include reactivation of tuberculosis and hepatitis B, thus careful screening should be performed before instituting therapy. Additionally, the development of various antibodies, autoantibodies, and autoimmune disease has been noted in patients taking anti-TNF agents. Extreme caution should be used in prescribing anti-TNF agents to patients with a history of heart failure or demyelinating disease, as use can cause exacerbations in their underlying cardiac and neurologic diseases.

The IL-1 pathway is the target of multiple biologic medications used in autoimmune and autoinflammatory diseases. The 3 available IL-1 antagonists are anakinra (IL-1 receptor antagonist), rilonacept (soluble IL-1 receptor decoy), and canakinumab (long-acting fully humanized IgG1 anti–IL-1β monoclonal antibody). The various IL-1 inhibitors have been successful at slowing the progression of AA amyloidosis, and in some cases treatment results in regression of amyloid associated proteinuria.

Tocilizumab, an anti–IL-6 receptor antibody, has been shown to attenuate experimental AA amyloid and to reverse AA amyloidosis complicating JIA and RA. Eprudisate disodium is currently in international trial in patients with AA amyloidosis–associated nephropathy. By binding the amyloidogenic precursor proteins, eprudisate disodium attempts to prevent the deposition of amyloid in organ, hence preserving renal function.

COMPLICATIONS AND PROGNOSIS

End-stage renal failure is the underlying cause of death in 40–60% of patients with amyloidosis, with a median survival time from diagnosis of 2-10 yr. According to a large-scale study of 374 patients with AA amyloidosis, the factors associated with a poor prognosis include older age, a lower albumin serum level, end-stage renal disease at baseline, and prolonged serum elevation of SAA. An elevated SAA value was the most powerful risk factor for end-stage renal disease and death from AA amyloidosis.

PREVENTION

The primary means of preventing AA amyloidosis is treatment of the underlying inflammatory or infectious disease, resulting in decreases in the level of SAA protein and the risk of amyloid deposition. Although the period of latency between the onset of inflammation (of the underlying disease) and the initial clinical signs of AA amyloidosis may vary and is often prolonged, progression of the amyloid depositions can be rapid.

Bibliography is available at Expert Consult.
Bibliography


Sarcoidosis is a rare multisystem granulomatous disease of unknown etiology. The name is derived from a Greek word meaning “flesh-like condition,” in reference to the characteristic skin lesions. There appear to be 2 age-dependent distinct patterns of disease among children with sarcoidosis. The clinical features in older children are similar to those in adults (pediatric onset adult sarcoidosis), with frequent systemic features (fever, weight loss, malaise), pulmonary involvement and lymphadenopathy. In contrast, early-onset sarcoidosis manifesting in children <4 yr of age is characterized by the triad of rash, uveitis, and polyarthritis.

**ETIOLOGY**

The etiology of sarcoidosis remains obscure but likely results from exposure of a genetically susceptible individual to 1 or more unidentified antigens. This exposure initiates an exaggerated immunologic response that ultimately leads to the formation of granulomas. The human major histocompatibility complex is located on chromosome 6, and specific human leukocyte antigen class I and class II alleles are associated with disease phenotype. Genetic polymorphisms involving various cytokines and chemokines may also have a role in development of sarcoidosis. Familial clustering supports the contribution of genetic factors to sarcoidosis susceptibility. Environmental and occupational exposures are also associated with disease risk. There are positive associations between sarcoidosis and agricultural employment, occupational exposure to insecticides, and moldy environments typically associated with microbial bioaerosols.

Blau syndrome is an autosomal dominant, familial form of sarcoidosis and is typified by the early onset of granulomatous inflammation involving the skin, eyes, and joints. Missense mutations in the CARD15/NOD2 gene on chromosome 16 have been found in affected family members and appear to be associated with development of sarcoidosis. The 2 most common amino acid substitutions are R334W (arginine to glutamine) and R334Q (arginine to tryptophan). Similar genetic mutations also have been found in individuals with a sporadic early-onset sarcoidosis (EOS) (rash, uveitis, arthritis), suggesting that this nonfamilial form and Blau syndrome are genetically and phenotypically identical (see Chapter 163).

**EPIDEMIOLOGY**

A nationwide patient registry of childhood sarcoidosis in Denmark estimated the annual incidence to be 0.22-0.27 per 100,000 children. The incidence increases with age, and peak onset occurs at 20-39 yr. The most common age of reported childhood cases is 13-15 yr. Annual incidence is about 11 per 100,000 in adult white Americans and is 3 times higher in African-Americans. There is no clear sex predominance in childhood sarcoidosis. Within the United States, the majority of childhood sarcoidosis cases are reported in the Southeastern and South Central states.

An international registry and Spanish cohort of Blau syndrome and EOS reported the mean age of disease onset as 30 mo and 36 mo, respectively. All but 3 of these young patients presented before 5 yr of age. There does not appear to be a sex preference in either condition.

**PATHOLOGY AND PATHOGENESIS**

Noncaseating, epithelioid granulomatous lesions are a cardinal feature of sarcoidosis. Activated macrophages, epithelioid cells, and multinucleated giant cells as well as CD4+ T lymphocytes accumulate and become tightly packed in the center of the granuloma. The causative agent that initiates this inflammatory process is not known. The periphery of the granuloma contains a loose collection of monocytes, CD4+ and CD8+ T lymphocytes, and fibroblasts. The interaction between the macrophages and CD4+ T lymphocytes is important in the formation and maintenance of the granuloma. The activated macrophages secrete high levels of tumor necrosis factor-α (TNF-α) and other proinflammatory mediators. The CD4+ T lymphocytes differentiate into type 1 helper T cells and release interleukin (IL)-2 and interferon-γ; promoting proliferation of lymphocytes. Granulomas may heal or resolve with complete preservation of the parenchyma. In approximately 20% of the lesions, the fibroblasts in the periphery proliferate and produce fibrotic scar tissue, leading to significant and irreversible organ dysfunction.

The sarcoid macrophage is able to produce and secrete 1,25-(OH)2-vitamin D or calcitriol, an active form of vitamin D typically produced in the kidneys. The hormone’s natural functions are to increase intestinal absorption of calcium and bone resorption and to decrease renal excretion of calcium and phosphate. An excess of calcitriol may result in hypercalcemia and hypercalciuria in patients with sarcoidosis.

**CLINICAL MANIFESTATIONS**

Sarcoidosis is a multisystem disease, and granulomatous lesions may occur in any organ of the body. The clinical manifestations depend on the extent and degree of granulomatous inflammation and are extremely variable. Children may present with nonspecific symptoms, such as fever, weight loss, and general malaise. In adults and older children, pulmonary involvement is most frequent, with infiltration of the thoracic lymph nodes and lung parenchyma. Isolated bilateral hilar adenopathy (Fig. 165-1) on chest radiograph is the most common finding, but parenchymal infiltrates and miliary nodules may also be seen (Fig. 165-2). Patients with lung involvement are commonly found to have restrictive changes on pulmonary function testing. Symptoms of pulmonary disease are seldom severe and generally consist of a dry, persistent cough.

Extrathoracic lymphadenopathy and infiltration of the liver, spleen, and bone marrow also occur often. Infiltration of the liver and spleen typically leads to isolated hepatomegaly and splenomegaly, respectively, but actual organ dysfunction is rare. Cutaneous disease, such as plaques, nodules, erythema nodosum in acute disease, or lupus pernio in chronic sarcoidosis, appears in one quarter of cases and is usually present at onset. Red-brown to purple maculopapular lesions < 1 cm

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*Figure 165-1 Chest radiograph demonstrating a stage I disease with enlarged mediastinal and hilar lymph nodes. (From Iannuzzi M: Sarcoidosis. In Goldman L, Schafer Al, editors: Goldman’s Cecil medicine, ed 24, Philadelphia, 2012, Saunders, Fig. 95-1, p. 582.)*
In contrast to the variable clinical presentation of sarcoidosis in older children, Blau syndrome and EOS (NOD2-associated sarcoidosis) classically manifest as the triad of uveitis, arthritis, and rash. Pulmonary disease and lymphadenopathy are less common. The arthritis is polyarticular and symmetric, with large boggy effusions. Large and small joints are involved; tenosynovitis is an associated finding. Joints are stiff and moderately tender. The rash may wax and wane and is diffuse (mostly truncal), erythematous or tan, macular–papular, and often desquamates at times being confused with eczema or ichthyosis vulgaris. Tender subcutaneous nodules resembling erythema nodosum may be seen on the legs. Noncaseating granulomas are demonstrated with biopsy of the skin or joint synovium.

Granulomatous iridocyclitis and posterior uveitis may progress to panuveitis, which has a high risk for vision loss. Iris nodules, photophobia, erythema, cataracts, or glaucoma may be present or develop over time.

Patients with NOD2 mutations in particular display this more restricted phenotype but may also have visceral disease, whereas those without a NOD2 mutation often show extended manifestations, including fever, hepatosplenomegaly, lymphadenopathy, and lung, kidney, and CNS involvement.

Infantile onset panniculitis with uveitis and systemic granulomatosis is an uncommon manifestation of sarcoidosis. Sarcoidosis has also been reported in adults treated with type 1 interferons for hepatitis or multiple sclerosis.

LABORATORY FINDINGS

There is no single standard laboratory test diagnostic of sarcoidosis. Anemia, leukopenia, and eosinophilia may be seen. Other nonspecific findings include hypergammaglobulinemia and elevations in acute-phase reactants, including erythrocyte sedimentation rate and C-reactive protein value. Hypercalcemia and/or hypercalciuria occur in only a small proportion of children with sarcoidosis. Angiotensin-converting enzyme (ACE) is produced by the epithelioid cells of the granuloma, and its serum value may be elevated, but this finding lacks diagnostic sensitivity and specificity. ACE levels are estimated to be elevated in more than 50% of children with sarcoidosis. In addition, ACE values may be difficult to interpret because reference values for serum ACE are age dependent. Fluorodeoxyglucose F18 positron emission tomography can help identify nonpulmonary sites for a diagnostic biopsy.

DIAGNOSIS

Definitive diagnosis ultimately requires demonstration of the characteristic noncaseating granulomatous lesions in a biopsy specimen (usually taken from the most readily available affected organ) and exclusion of other known causes of granulomatous inflammation. Skin and transbronchial lung biopsies have higher yield, greater specificity, and fewer associated adverse events than biopsy of mediastinal lymph nodes or liver. Additional diagnostic testing should include chest radiography, pulmonary function testing with measurement of diffusion capacity, hepatic enzyme measurements, and renal function assessment. Ophthalmologic slit-lamp examination is essential, as ocular findings are frequent in sarcoidosis and vision loss is a sequela of untreated disease.

Bronchoalveolar lavage may be used to assess for disease activity, and the fluid typically reveals an excess of lymphocytes with an increased CD4+/CD8+ ratio of 2-13:1. In addition to flexible bronchoscopy with transbronchial biopsy, endosonographic guided intrathoracic node aspiration has been valuable in obtaining tissue to assess for noncaseating granulomas.

DIFFERENTIAL DIAGNOSIS

Because of its protean manifestations, the differential diagnosis of sarcoidosis is extremely broad and depends largely on the initial clinical manifestations. Granulomatous infections, including tuberculosis, cryptococcosis, pulmonary mycoses (histoplasmosis, blastomycosis, coccidioidomycosis), brucellosis, tularemia, and toxoplasmosis, must be excluded. Other causes of granulomatous inflammation are
granulomatosis with polyangiitis (formerly Wegener granulomatosis), hypersensitivity pneumonia, chronic berylliosis, and other occupational exposures to metals. Immunodeficiencies that may manifest with granulomatous lesions include common variable immunodeficiency, selective immunoglobulin A deficiency, chronic granulomatous disease, ataxia telangiectasia, and severe combined immunodeficiency. Granulomas of the lung, skin or lymph nodes have been reported in patients treated with anti-TNF agents. Lymphoma should be ruled out in cases of hilar or other lymphadenopathy. Sarcoid arthritis may mimic juvenile idiopathic arthritis. Evaluation for endocrine disorders is needed in the setting of hypercalcemia or hypercalciuria.

TREATMENT

Treatment should be based on disease severity as well as the number and type of organs involved. Corticosteroids are the mainstay of treatment for most acute and chronic disease manifestations. The optimal dose and duration of corticosteroid therapy in children have not been established. Induction treatment typically begins with oral prednisone or prednisolone (1-2 mg/kg/day up to 40 mg daily) for 8-12 wk until manifestations improve. Corticosteroid dosage is then gradually decreased over 6-12 mo to the minimal effective maintenance dose (e.g., 5-10 mg/day) that controls symptoms, or discontinued if symptoms resolve. Methotrexate or leflunomide may be effective as a corticosteroid-sparing agent. On the basis of the role of TNF-α in the formation of granulomas, there is rationale for use of TNF-α antagonists. Results of small clinical trials showed modest effects with infliximab and adalimumab treatment of selected disease manifestations (CNS, lupus pernio, pulmonary, ocular), whereas etanercept does not appear to be particularly effective. Other therapeutics used for sarcoidosis manifestations include topical corticosteroids (eye), inhaled corticosteroids (lung), azathioprine (CNS), cyclophosphamide (cardiac, CNS), hydroxychloroquine (skin), mycophenolate mofetil (CNS, skin), thalidomide or its analogs (skin), and nonsteroidal antiinflammatory drugs (joints).

With regard to treatment of EOS, there are also few case reports on the successful use of thalidomide and infliximab. Findings of elevated IL-1 levels and response to human IL-1 receptor antagonist (anakinra) in EOS, however, have been inconsistent.

PROGNOSIS

The prognosis of childhood sarcoidosis is not well defined. The disease may be self-limited with complete recovery or may persist with a progressive or relapsing course. Outcome is worse in the setting of multi-organ or CNS involvement. Most children requiring treatment experience considerable improvement with corticosteroids, though a significant number have morbid sequelae, mainly involving the lungs and eyes. Children with EOS have a poorer prognosis and generally experience a more chronic, progressive disease course. The greatest morbidity is associated with ocular involvement, including cataract formation, development of synechiae, and loss of visual acuity or blindness; long-term systemic treatment may be required for the eye disease. Progressive polyarthritis may result in joint destruction. The overall mortality rate in childhood sarcoidosis is low.

Serial pulmonary function tests and chest radiographs are useful in following the course of lung involvement. Monitoring for other organ involvement should also include electrocardiogram with consideration of an echocardiogram, urinalysis, renal function tests, and measurements of hepatic enzymes and serum calcium. Other potential indicators of disease activity include inflammatory markers and serum ACE, although changes in ACE level do not always correlate with other indicators of disease status. Given the frequency of asymptomatic eye disease and the ocular morbidity associated with pediatric sarcoidosis, all patients should have an ophthalmologic examination at presentation with monitoring at regular intervals, perhaps every 3-6 mo as recommended in children with juvenile idiopathic arthritis.

Bibliography is available at Expert Consult.
Bibliography
Kawasaki disease (KD), formerly known as mucocutaneous lymph node syndrome and infantile polyarteritis nodosa, is an acute febrile illness of childhood seen worldwide with the highest incidence occurring in Asian children. KD is a vasculitis with a predilection for the coronary arteries. Approximately 20-25% of untreated children develop coronary artery abnormalities (CAA) including aneurysms, whereas <5% of children treated with intravenous gammaglobulin (IVIG) develop CAA. Nonetheless, KD is the leading cause of acquired heart disease in children in most developed countries, including the United States and Japan.

ETIOLOGY
The cause of KD remains unknown, but certain epidemiologic and clinical features support an infectious origin. These features include the young age group affected, epidemics with wave-like geographic spread of illness, the self-limited nature of the acute febrile illness, and the clinical features of fever, rash, enanthem, conjunctival injection, and cervical lymphadenopathy. Further evidence of an infectious trigger includes the infrequent occurrence of the illness in infants younger than 3 mo, likely the result of maternal antibodies, and the rarity of cases in adults, likely the result of prior exposures with subsequent immunity. However, there are features that are not consistent with an infectious origin. For example, it is unusual to have multiple cases present at the same time within a family or daycare center. Furthermore, no single infectious etiologic agent has been successfully identified, despite a comprehensive search.

A genetic role in the pathogenesis of KD seems likely, as evidenced by the higher risk of KD in Asian children regardless of country of residence, and in siblings and children of individuals with a history of KD. Furthermore, linkage studies and genome-wide association studies have identified significant associations between polymorphisms in the ITPKC gene, a T-cell regulator, with increased susceptibility to KD and to more-severe disease. Polymorphisms in a high-affinity receptor for immunoglobulin G (FCGR2A) have also been identified as significant variants in KD patients.

EPIDEMIOLOGY
For the majority of patients, KD is a disease of early childhood and nearly all epidemiologic studies show a higher susceptibility to KD in boys. Utilizing the Kids Inpatient Database to study trends in KD hospitalizations in 2006, Holman et al reported that more than 75% of all KD-associated hospitalizations in patients <18 yr were recorded in children <5 yr, with a mean age of 3 yr. Children of Asian and Pacific Islander descent had the highest hospitalization rate of 30.3/100,000 children, compared with 17.5/100,000 black, non-Hispanic children, 15.7/100,000 Hispanic children, and 12/100,000 white, non-Hispanic children. The hospitalization rate for KD in 2006 was 20.8/100,000 in children <5 yr of age, which was consistent with the prior 10 yr of hospitalization rates in the United States. In other countries, such as the United Kingdom, Korea, and Japan, the rate of KD seems to be increasing.

In Japan, nationwide surveys have been administered every 2 yr to monitor trends in KD incidence. In 2010, the highest recorded rate thus far of 239.6 per 100,000 children ages 0-4 yr was described, with the highest rate in very young children ages 6-11 mo. Infants <6 mo and children >5 yr were at the highest risk for CAA in the latest Japanese survey.

Several risk stratification models have been constructed to determine which patients with KD are at highest risk for CAA. Predictors of poor outcome across several studies include young age, male gender,
persistent fever, poor response to IVIG, and laboratory abnormalities including neutrophilia, thrombocytopenia, transaminis, hyponatremia, hypoalbuminemia, elevated levels of N-terminal-pro-brain natriuretic protein and elevated C-reactive protein levels. Asian and Pacific Islander race and Hispanic ethnicity are also risk factors for CAA. Three specific risk scores have been constructed by Japanese researchers; of these, the Kobayashi score is the most widely used and has high sensitivity and specificity. Unfortunately, application of these risk scores in non-Japanese populations does not appear to accurately identify all children at risk for IVIG resistance and CAA.

**PATHOLOGY**

KD is a vasculitis that predominantly affects the medium-size arteries. The coronary arteries are the most commonly involved, although other arteries, such as the popliteal and brachial arteries, can also develop dilation. A 3-phase process to the arteriopathy of KD has been described. The 1st phase is a neutrophilic necrotizing arteritis occurring in the 1st 2 wk of illness that begins in the endothelium and moves through the coronary wall. Saccular aneurysms may form from this arteritis. The second phase is a subacute/chronic vasculitis driven by lymphocytes, plasma cells, and eosinophils, which may last weeks to years and results in fusiform aneurysms. The vessels affected by the subacute/chronic vasculitis then develop smooth muscle cell myofibroblasts, which cause progressive stenosis. Thrombi may form in the lumen and obstruct blood flow.

**CLINICAL MANIFESTATIONS**

Fever is characteristically high (>38.3°C [101°F]), unremitting, and unresponsive to antibiotics. The duration of fever without treatment is generally 1-2 wk, but may persist for 3-4 wk. In addition to fever, the 5 principal clinical criteria of KD are: bilateral nonexudative conjunctival injection with limbal sparing; erythema of the oral and pharyngeal mucosa with strawberry tongue and red, cracked lips; edema and erythema of the hands and feet; rash of various forms (maculopapular, erythema multiforme, or scarlatiniform); and nonsuppurative cervical lymphadenopathy, usually unilateral, with node size >1.5 cm (Table 166-1; Figs. 166-1 to 166-4). Perineal desquamation is common in the acute phase. Periungual desquamation of the fingers and toes begins 2-3 wk after the onset of illness and may progress to involve the entire hand and foot (Fig. 166-5).

Symptoms other than the clinical criteria are common in the 10 days prior to diagnosis of KD, which may be explained in part by the finding that up to a third of patients with KD have confirmed, concurrent infections. Gastrointestinal symptoms (vomiting, diarrhea, or abdominal pain) occur in more than 60% of patients, and at least 1 respiratory symptom (rhinorrhea or cough) occurs in 35%. Other clinical findings include significant irritability that is especially prominent in infants and likely a consequence of aseptic meningitis, mild hepatis, hydrops of the gallbladder, urethritis and meatitis with sterile pyuria, and arthritis. Arthritis may occur early in the illness or may develop in the 2nd or 3rd wk. Small or large joints may be affected, and the arthralgias

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**Table 166-1 Clinical and Laboratory Features of Kawasaki Disease**

<table>
<thead>
<tr>
<th>Clinical and Laboratory Features of Kawasaki Disease</th>
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<tbody>
<tr>
<td>Fever persisting at least 5 days&lt;sup&gt;1&lt;/sup&gt;</td>
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<tr>
<td>Presence of at least 4 principal features:</td>
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<tr>
<td>Changes in extremities:</td>
</tr>
<tr>
<td>Acute: Erythema of palms, soles; edema of hands, feet</td>
</tr>
<tr>
<td>Subacute: Periungual peeling of fingers, toes in weeks 2 and 3</td>
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<tr>
<td>Polyomorphous exanthem</td>
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<tr>
<td>Bilateral bulbar conjunctival injection without exudate</td>
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<tr>
<td>Changes in lips and oral cavity: erythema, lip cracking, strawberry tongue, diffuse injection of oral and pharyngeal mucosa</td>
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<tr>
<td>Central nervous system:</td>
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<tr>
<td>Arthritis, arthralgias</td>
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<tr>
<td>Gastrointestinal tract:</td>
</tr>
<tr>
<td>Diarrhea, vomiting, abdominal pain</td>
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<tr>
<td>Hepatic dysfunction</td>
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<tr>
<td>Hydrops of gallbladder</td>
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<tr>
<td>Central nervous system:</td>
</tr>
<tr>
<td>Extreme irritability</td>
</tr>
<tr>
<td>Aseptic meningitis</td>
</tr>
<tr>
<td>Sensorineural hearing loss</td>
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<tr>
<td>Genitourinary system:</td>
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<tr>
<td>Urethritis/meatitis</td>
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<tr>
<td>Other findings:</td>
</tr>
<tr>
<td>Erythema, induration at bacille Calmette-Guérin inoculation site</td>
</tr>
<tr>
<td>Anterior uveitis (mild)</td>
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<tr>
<td>Desquamating rash in groin</td>
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</table>

**EPIDEMIOLOGIC CASE DEFINITION (CLASSIC CLINICAL CRITERIA)**

1. Fever persisting at least 5 days
2. Presence of at least 4 principal features:
   1. Changes in extremities:
      - Acute: Erythema of palms, soles; edema of hands, feet
      - Subacute: Periungual peeling of fingers, toes in weeks 2 and 3
   2. Polyomorphous exanthem
   3. Bilateral bulbar conjunctival injection without exudate
   4. Changes in lips and oral cavity: erythema, lip cracking, strawberry tongue, diffuse injection of oral and pharyngeal mucosa

**OTHER CLINICAL AND LABORATORY FINDINGS**

- Cardiovascular findings:
  - Congestive heart failure, myocarditis, pericarditis, valvular regurgitation
  - Coronary artery abnormalities
  - Aneurysms of medium-size noncoronary arteries
  - Raynaud phenomenon
  - Peripheral gangrene
  - Musculoskeletal system:
    - Arthritis, arthralgias
  - Gastrointestinal tract:
    - Diarrhea, vomiting, abdominal pain
  - Hepatic dysfunction
  - Hydrops of gallbladder
  - Central nervous system:
    - Extreme irritability
  - Aseptic meningitis
  - Sensorineural hearing loss
  - Genitourinary system:
    - Urethritis/meatitis
  - Other findings:
    - Erythema, induration at bacille Calmette-Guérin inoculation site
    - Anterior uveitis (mild)
    - Desquamating rash in groin

**LABORATORY FINDINGS IN ACUTE KAWASAKI DISEASE**

- Leukocytosis with neutrophilia and immature forms
- Elevated erythrocyte sedimentation rate
- Elevated C-reactive protein
- Anemia
- Abnormal plasma lipids
- Hypoalbuminemia
- Hyponatremia
- Thrombocytosis after week 1<sup>5</sup>
- Sterile pyuria
- Elevated serum transaminases
- Elevated serum gamma glutamyl transpeptidase
- Pleocytosis of cerebrospinal fluid
- Leukocytosis in synovial fluid

1. Patients with fever at least 5 days and <4 principal criteria can be diagnosed with Kawasaki disease when coronary artery abnormalities are detected by 2-dimensional echocardiography or angiography.
2. In the presence of 24 principal criteria, Kawasaki disease diagnosis can be made on day 4 of illness. Experienced clinicians who have treated many patients with Kawasaki disease may establish diagnosis before day 4.
3. Some infants present with thrombocytopenia and disseminated intravascular coagulation.


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**Figure 166-1 Clinical symptoms and signs of Kawasaki disease.** A summary of the clinical features from 110 cases of Kawasaki disease seen in Kaohsiung, Taiwan. LAP, lymphadenopathy in head and neck area; BCG, reactivation of bacille Calmette-Guérin inoculation site; CAD, coronary artery dilation, defined by an internal diameter >3 mm. (From Wang CL, Wu YT, Liu CA, et al: Kawasaki disease: infection, immunity and genetics, Pediatr Infect Dis J 24:998–1004, 2005.)
Clinical features that are less consistent with KD include exudative conjunctivitis, exudative pharyngitis, generalized lymphadenopathy, discrete oral lesions, and bullous, pustular, or vesicular rashes.

Cardiac involvement is the most important manifestation of KD. Myocarditis occurs in most patients with acute KD and manifests as tachycardia disproportionate to fever, along with diminished left ventricular systolic function. Occasionally, patients with KD present in cardiogenic shock (KD shock syndrome), with markedly diminished left ventricular function. Pericarditis with a small pericardial effusion can also occur during the acute illness. Mitral regurgitation of at least mild severity is evident on echocardiography in 10-25% of patients at presentation but diminishes over time, except among rare patients with coronary aneurysms and ischemic heart disease. CAA develop in up to 25% of untreated patients in the 2nd to 3rd wk of illness. Giant coronary artery aneurysms (classic definition of >8 mm internal diameter) pose the greatest risk for rupture, thrombosis or stenosis, and myocardial infarction (Fig. 166-6). Axillary, popliteal, iliac, or other arteries may also become dilated, which manifest as a localized pulsating mass.

Occasionally KD initially presents with only fever and lymphadenopathy (node-first KD). This presentation may be confused with...
bacterial or viral cervical lymphadenopathy/lymphadenitis and may delay the diagnosis of KD. Persistence of high fever, unresponsive to antibiotics and the eventual development of other signs of KD result in the diagnosis. Children with node-first KD tend to be older (4 vs. 2 yr) and have more days of fever and higher C-reactive protein levels. In addition to cervical adenopathy, many had retropharyngeal and peritonsillar inflammation on CT scans (Fig. 166-7).

KD can be divided into 3 clinical phases. The acute febrile phase is characterized by fever and the other acute signs of illness and usually lasts 1-2 wk. The subacute phase is associated with desquamation, thrombocytosis, the development of CAA, the highest risk of sudden death in patients in whom aneurysms have developed, and generally lasts about 3 wk. The convalescent phase begins when all clinical signs of illness have disappeared and continues until the erythrocyte sedimentation rate (ESR) returns to normal, typically about 6-8 wk after the onset of illness.

LABORATORY AND RADIOLOGY FINDINGS

There is no diagnostic test for KD, but patients usually have characteristic laboratory findings. The leukocyte count is often elevated, with a predominance of neutrophils and immature forms. Normocytic, normochromic anemia is common. The platelet count is generally normal in the 1st wk of illness and rapidly increases by the 2nd to 3rd wk of illness, sometimes exceeding 1,000,000/mm³. An elevated ESR and/or C-reactive protein value is universally present in the acute phase of illness. The ESR may remain elevated for weeks, in part from the effect of IVIG. Sterile pyuria, mild elevations of the hepatic transaminases, hyperbilirubinemia, and cerebrospinal fluid pleocytosis may also be present.

Two-dimensional echocardiography is the most useful test to monitor for development of CAA and should be performed by a pediatric cardiologist. Although frank aneurysms are rarely detected early allowing differentiation from KD. A common clinical problem is the differentiation of scarlet fever from KD in a child who is a group A streptococcal carrier. Patients with scarlet fever typically have a rapid clinical response to appropriate antibiotic therapy. Such treatment for 24-48 hr with clinical reassessment generally clarifies the diagnosis. Furthermore, ocular findings are quite rare in group A streptococcal pharyngitis and may assist in the diagnosis of KD.

Features of measles that distinguish it from KD include exudative pharyngitis and exudative conjunctivitis, Koplik spots, rash that begins on the face and hairline and behind the ears, as well as leukopenia. Cervical lymphadenitis can

<table>
<thead>
<tr>
<th>Table 166-2</th>
<th>Differential Diagnosis of Kawasaki Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>VIRAL INFECTIONS</strong></td>
<td>• Adenovirus • Enterovirus • Measles • Epstein-Barr virus • Cytomegalovirus</td>
</tr>
<tr>
<td><strong>BACTERIAL INFECTIONS</strong></td>
<td>• Scarlet fever • Rocky Mountain spotted fever • Leptospirosis • Bacterial cervical lymphadenitis • Meningococccemia</td>
</tr>
<tr>
<td><strong>RHEUMATOLOGIC DISEASE</strong></td>
<td>• Systemic-onset juvenile idiopathic arthritis • Behçet disease</td>
</tr>
<tr>
<td><strong>OTHER</strong></td>
<td>• Toxic shock syndromes • Staphylococcal scalded skin syndrome • Drug hypersensitivity reactions • Stevens-Johnson syndrome</td>
</tr>
</tbody>
</table>

**DIAGNOSIS**

The diagnosis of KD is based on the presence of characteristic clinical signs. For classic KD, the diagnostic criteria require the presence of fever for at least 4 days and at least 4 of 5 of the principal characteristics of the illness (see Table 166-1). In atypical or incomplete KD, patients have persistent fever but fewer than 4 of the 5 characteristics. In these patients, laboratory and echocardiographic data can assist in the diagnosis (Fig. 166-8). Incomplete cases are most frequent in infants, who, unfortunately, also have the highest likelihood of development of CAA. Ambiguous cases should be referred to a center with experience in the diagnosis of KD. Establishing the diagnosis with prompt institution of treatment is essential to prevent potentially devastating coronary artery disease.

**DIFFERENTIAL DIAGNOSIS**

Adenovirus, measles, and scarlet fever lead the list of common childhood infections that mimic KD (Table 166-2). Children with adenovirus typically have exudative pharyngitis and exudative conjunctivitis, allowing differentiation from KD. A common clinical problem is the differentiation of scarlet fever from KD in a child who is a group A streptococcal carrier. Patients with scarlet fever typically have a rapid clinical response to appropriate antibiotic therapy. Such treatment for 24-48 hr with clinical reassessment generally clarifies the diagnosis. Furthermore, ocular findings are quite rare in group A streptococcal pharyngitis and may assist in the diagnosis of KD.

Features of measles that distinguish it from KD include exudative conjunctivitis, Koplik spots, rash that begins on the face and hairline and behind the ears, as well as leukopenia. Cervical lymphadenitis can
be the initial diagnosis in children who are ultimately recognized to have KD. Less common infections such as Rocky Mountain spotted fever and leptospirosis are occasionally confused with KD. Rocky Mountain spotted fever is a potentially lethal bacterial infection and appropriate antibiotics should not be withheld if the diagnosis is under consideration. Its distinguishing features include pronounced myalgias and headache at onset, centripedal rash, and petechiae on the palms and soles. Leptospirosis can also be an illness of considerable severity. Risk factors include exposure to water contaminated with urine from infected animals. The classic description of leptospirosis is of a biphasic illness with a few asymptomatic days between an initial period of fever and headache and a late phase with renal and hepatic failure. In contrast, patients with KD have consecutive days of fever at diagnosis and rarely have renal or hepatic failure.

Children with KD and pronounced myocarditis may demonstrate hypotension with a clinical picture similar to that of toxic shock syndrome. Features of toxic shock syndrome that are not commonly seen in KD include renal insufficiency, coagulopathy, pancytopenia, and myositis. Drug hypersensitivity reactions, including Stevens-Johnson syndrome, share some characteristics with KD. Drug reaction features such as the presence of periorbital edema, oral ulcerations, and a normal or minimally elevated ESR are not seen in KD. Systemic-onset juvenile idiopathic arthritis is also characterized by fever and rash, but physical findings include diffuse lymphadenopathy and hepatosplenomegaly. Arthritis is required to develop at some point in the disease course to make the diagnosis, but may not be present in the 1st few wk of illness. Laboratory findings may include coagulopathy, elevated fibrin degradation product values, and hyperferritinemia. Interestingly, there are reports of children with systemic-onset juvenile idiopathic arthritis who have echocardiographic evidence of abnormal coronary arteries. Coronary aneurysms have also been reported in Behçet disease, primary cytomegalovirus infection, and meningococcemia.

**TREATMENT**

Patients with acute KD should be treated with 2 g/kg of IVIG and high-dose aspirin (80-100 mg/kg/day divided q6h) within 10 days of disease onset and ideally as soon as possible after diagnosis (Table 166-3). The
The mechanism of action of IVIG in KD is unknown, but treatment results in defervescence and resolution of clinical signs of illness in approximately 85% of patients. The prevalence of coronary disease, 20–25% in children treated with aspirin alone, is <5% in those treated with IVIG and aspirin within the 1st 10 days of illness. Strong consideration should be given to treating patients with persistent fever and/or signs of systemic inflammation who are diagnosed after the 10th day of fever. The dose of aspirin is usually decreased from antiinflammatory to antithrombotic doses (3-5 mg/kg/day as a single dose) after the patient has been afebrile for 48 hr, although some experts prescribe high-dose aspirin until the 14th day of illness. Aspirin is continued for its antithrombotic effect until 6-8 wk after illness onset and is then discontinued in patients who have had normal echocardiography findings throughout the course of their illness. Patients with CAA continue with aspirin therapy and may require anticoagulation, depending on the degree of coronary dilation (see later).

Corticosteroids have been trialed as primary therapy with the first dose of IVIG in hopes of improving coronary outcomes. A North American trial using a single pulse dose of intravenous methylprednisolone (30 mg/kg) with IVIG as primary therapy did not improve coronary outcomes. However, a trial in Japan utilizing the Kobayashi score to identify high-risk children demonstrated improved coronary outcomes with a regimen of prednisolone (2 mg/kg) plus IVIG as primary therapy. Despite these promising results, administration of corticosteroids, as primary therapy to all children with KD awaits the development of a risk score that identifies high-risk children in a multicrural population.

IVIG-resistant KD occurs in approximately 15% of patients and is defined by persistent or recrudescent fever 36 hr after completion of the initial IVIG infusion. Patients with IVIG resistance are at increased risk for CAA. Typically, another dose of IVIG at 2 g/kg is administered to patients with IVIG resistance. Corticosteroids in varying doses and via different routes have also been used as secondary or “rescue” therapy when fever persists after the first IVIG. However, the lack of clear data regarding the most effective way to administer corticosteroids as rescue therapy has led to significant practice variation across centers. Tumor necrosis factor inhibitors, including infliximab and etanercept, have also been given for the treatment of IVIG-resistant disease. To date, there is no evidence of improved coronary outcomes with the use of these medications.

### COMPLICATIONS

The patient with KD who has had a small solitary aneurysm should continue aspirin indefinitely. Patients with larger or numerous aneurysms may require the addition of other antiplatelet agents or anticoagulation; such decisions should be made in consultation with a pediatric cardiologist. Acute thrombosis may occasionally occur in an aneurysmal or stenotic coronary artery; thrombolytic therapy may be lifesaving in this circumstance.

Long-term follow-up of patients with coronary artery aneurysms should include periodic echocardiography with stress testing and possibly angiography if large aneurysms are present. Catheter intervention with percutaneous transluminal coronary rotational ablation, directional coronary athectomy, and stent implantation have been used for the management of coronary stenosis due to KD, with some patients requiring coronary artery bypass grafting.

Patients undergoing long-term aspirin therapy should receive annual influenza vaccination to reduce the risk of Reye syndrome. A different antiplatelet agent can be substituted for aspirin during the 6 wk after varicella vaccination. As IVIG may interfere with the immune response to live virus vaccines as a result of specific antiviral antibody, the measles-mumps-rubella and varicella vaccinations should generally be deferred until 11 mo after IVIG administration. Non-live vaccinations do not need to be delayed.

### PROGNOSIS

The vast majority of patients with KD return to normal health, as timely treatment reduces the risk of coronary aneurysms to less than 5%. Acute KD recurs in 1–3% of cases. The prognosis for patients with coronary abnormalities depends on the severity of coronary disease; therefore, recommendations for follow-up and management are stratified according to coronary artery status. Published fatality rates are very low, generally <1.0%. Overall, 50% of coronary artery aneurysms regress to normal lumen diameter by 1-2 yr after the illness, with smaller aneurysms being more likely to regress. Intravascular ultrasonography has demonstrated that regressed aneurysms are associated with marked myointimal thickening and abnormal functional behavior of the vessel wall. Giant aneurysms are less likely to regress to normal lumen diameter and are most likely to lead to thrombosis or stenosis. Coronary artery bypass grafting may be required if myocardial perfusion is significantly impaired; it is best accomplished with the use of arterial grafts, which grow with the child and are more likely than venous grafts to remain patent over the long-term. Heart transplantation has been required in rare cases in which revascularization is not feasible because of distal coronary stenoses, distal aneurysms, or severe ischemic cardiomyopathy. A study from Japan reported outcomes in adult patients with a history of KD and giant aneurysms. These patients required multiple cardiac and surgical procedures, but the 50-year survival rate approached 90%.

Whether children who have had KD and normal echocardiography findings throughout their course are at higher risk for the development of atherosclerotic heart disease in adulthood remains unclear, as studies of endothelial dysfunction in children with a history of KD and normal coronary dimensions have produced conflicting results. Reassuring data suggest that the standardized mortality ratio among adults in Japan who had KD in childhood without aneurysms is indistinguishable from that of the general population. All children with a history of KD should be counseled regarding a heart-healthy diet, adequate amounts of exercise, tobacco avoidance, and intermittent lipid monitoring. Among children with coronary aneurysms, the American Heart Association recommends treatment thresholds for risk factors for atherosclerotic heart disease that are lower than those for the normal population.

*Bibliography is available at Expert Consult.*
Bibliography


Childhood vasculitis encompasses a broad spectrum of diseases that share in common inflammation of the blood vessels as the central pathophysiologic. The pathogenesis of the vasculitides is generally idiopathic; some forms of vasculitis are associated with infectious agents and medications; others may occur in the setting of preexisting autoimmune disease. The pattern of vascular injury provides insight into the form of vasculitis and serves as a framework to delineate the different vasculitic syndromes. The distribution of vascular injury includes small vessels (capillaries, arterioles, and postcapillary venules), medium vessels (renal arteries, mesenteric vasculature, and coronary arteries), and large vessels (the aorta and its proximal branches). Additionally, some forms of small vessel vasculitis are characterized by the presence of antineutrophil cytoplasmic antibodies (ANCAs) (Table 167-1), whereas others are associated with immune complex deposition in affected tissues. A combination of clinical features, histologic appearance of involved vessels, and laboratory data is utilized to classify vasculitis (Tables 167-2 to 167-4).

Childhood vasculitis varies from a relatively benign and self-limited disease such as Henoch-Schönlein purpura to catastrophic disease with end-organ damage as can be seen in granulomatosis with polyangiitis (formerly Wegener granulomatosis). Vasculitis generally manifests as a heterogeneous multisystem disease. Although some features, such as purpura, are easily identifiable, others, such as hypertension secondary to renal artery occlusion or glomerulonephritis, can be more subtle. Ultimately, the key to recognizing vasculitis relies heavily on pattern recognition. Demonstration of vessel injury and inflammation on biopsy or vascular imaging is required to confirm a diagnosis of vasculitis.

**Bibliography is available at Expert Consult.**

### Table 167-2 Classification of Childhood Vasculitis

<table>
<thead>
<tr>
<th>Classification</th>
<th>I. Predominantly Large Vessel Vasculitis</th>
<th>II. Predominantly Medium Vessel Vasculitis</th>
<th>III. Predominantly Small Vessel Vasculitis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Takayasu arteritis</td>
<td>Kawasaki disease</td>
<td>Childhood polyarteritis nodosa</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Cutaneous polyarteritis nodosa</td>
</tr>
</tbody>
</table>

### Table 167-3 Features That Suggest a Vasculitic Syndrome

**CLINICAL FEATURES**
- Fever, weight loss, fatigue of unknown origin
- Skin lesions (palpable purpura, vasculitic urticaria, livedo reticularis, nodules, ulcers)
- Neurologic lesions (headache, mononeuritis multiplex, focal central nervous system lesions)
- Arthralgia or arthritis, myalgia, or myositis
- Serositis
- Hypertension
- Pulmonary infiltrates or hemorrhage

**LABORATORY FEATURES**
- Increased erythrocytes sedimentation rate or C-reactive protein level
- Leukocytosis, anemia
- Eosinophilia
- Antineutrophil cytoplasmic antibodies
- Elevated factor VIII–related antigen (von Willebrand factor)
- Cryoglobulins
- Circulating immune complexes
- Hematuria, proteinuria, elevated serum creatinine

---

**Table 167-1 Common Disease Associations with Antibodies to Neutrophil Cytoplasmic Antigens**

<table>
<thead>
<tr>
<th>ANTIGEN</th>
<th>ANCA PATTERN</th>
<th>DISEASE ASSOCIATION</th>
<th>FREQUENCY (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PR3</td>
<td>cANCA</td>
<td>Wegener granulomatosis Churg-Strauss</td>
<td>30 to 90, 25 to 50</td>
</tr>
<tr>
<td>MPO</td>
<td>pANCA</td>
<td>Microscopic polyarteritis Ulcerative colitis Sclerosing cholangitis Cohn disease</td>
<td>25 to 75, 40 to 80, 65 to 85, 10 to 40</td>
</tr>
<tr>
<td>BPI</td>
<td>ANCA</td>
<td>Cystic fibrosis</td>
<td>80 to 90</td>
</tr>
<tr>
<td>Actin</td>
<td>pANCA</td>
<td>Autoimmune hepatitis type 1</td>
<td>70 to 75</td>
</tr>
</tbody>
</table>

ANCA, Antibodies directed at neutrophil cytoplasmic antigen; BPI, Bactericidal permeability increasing protein. cANCA, cytoplasmic ANCA; pANCA, perinuclear ANCA.

Bibliography
HSP occasionally clusters in families, suggesting a genetic component. That HSP is a disease mediated by IgA and IgA immune complexes. Infectious triggers such as group A β-hemolytic streptococcus, *Staphylococcus aureus*, mycoplasma, and adenovirus have been suspected. Mycoplasma, and adenovirus have been suspected. The exact pathogenesis of HSP remains unknown. Given the seasonal-patterned to a lesser extent by deposition of C3, fibrin, and IgM. Identifies IgA deposition in walls of small vessels (Fig. 167-1), accompanied to a lesser extent by deposition of C3, fibrin, and IgM. The common finding of deposition of IgA, specifically IgA1, suggests that HSP is a disease mediated by IgA and IgA immune complexes. HSP occasionally clusters in families, suggesting a genetic component. HLA-B34 and HLA-DRB1*01 alleles have been linked to HSP nephritis. Patients with familial Mediterranean fever, hereditary periodic fever syndromes, and complement deficiencies are at increased risk for developing HSP, suggesting that genetically determined immune dysregulation may contribute.

**Table 167-4**

<table>
<thead>
<tr>
<th>SYNDROME</th>
<th>FREQUENCY</th>
<th>VESSELS AFFECTED</th>
<th>CHARACTERISTIC PATHOLOGY</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>POLYARTERITIS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Polyarteritis nodosa</td>
<td>Rare</td>
<td>Medium-size and small muscular arteries and sometimes arterioles</td>
<td>Focal segmental (often near bifurcations); fibrinoid necrosis; gastrointestinal, renal microaneurysms; lesions at various stages of evolution</td>
</tr>
<tr>
<td>Kawasaki disease</td>
<td>Common</td>
<td>Coronary and other muscular arteries</td>
<td>Thrombosis, fibrosis, aneurysms, especially of coronary vessels</td>
</tr>
<tr>
<td><strong>LEUKOCYTOLASTIC VASCULITIS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Henoch-Schönlein purpura</td>
<td>Common</td>
<td>Arterioles and venules, often small arteries and veins</td>
<td>Leukocytoclasis; mixed cells, eosinophils, immunoglobulin A deposits in affected vessels</td>
</tr>
<tr>
<td>Hypersensitivity angitis</td>
<td>Rare</td>
<td>Arterioles and venules</td>
<td>Leukocytoclasic or lymphocytic, varying eosinophils, occasionally granulomatous; widespread lesions at same stage of evolution</td>
</tr>
<tr>
<td><strong>GRANULOMATOUS VASCULITIS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Granulomatosis with polyangiitis</td>
<td>Rare</td>
<td>Small arteries and veins, occasionally larger vessels</td>
<td>Upper and lower respiratory tract, necrotizing granulomata glomerulonephritis</td>
</tr>
<tr>
<td>Eosinophil granulomatosis</td>
<td>Rare</td>
<td>Small arteries and veins, often arterioles and venules</td>
<td>Necrotizing extravascular granulomata; lung involvement; eosinophilia</td>
</tr>
<tr>
<td>with polyangiitis (Churg-</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Strauss syndrome)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>GIANT CELL ARTERITIS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Takayasu arteries</td>
<td>Uncommon</td>
<td>Large arteries</td>
<td>Granulomatous inflammation, giant cells; aneurysms, dissection</td>
</tr>
<tr>
<td>Temporal arteritis</td>
<td>Rare</td>
<td>Medium-size and large arteries</td>
<td>Granulomatous inflammation, giant cell arteries</td>
</tr>
</tbody>
</table>


### 167.1 Henoch-Schönlein Purpura

*Stacy P. Ardoin and Edward Fels*

Henoch-Schönlein purpura (HSP) is the most common vasculitis of childhood and is characterized by leukocytoclastic vasculitis and immunoglobulin (Ig) A deposition in the small vessels in the skin, joints, gastrointestinal tract, and kidney.

**EPIDEMIOLOGY**

HSP occurs worldwide and affects all ethnic groups but is more common in white and Asian populations. The incidence of HSP is estimated at 14-20/100,000 children per year and affects males more than females, with a 1.2-1.8:1 male:female ratio. Approximately 90% of HSP cases occur in children, usually between the ages of 3 and 10 yr. HSP is distinctly less common in adults, in whom severe and chronic complications are often encountered. HSP is more common in the winter and spring, and is unusual in summer months. Many cases of HSP follow a documented upper respiratory infection.

**PATHOLOGY**

Skin biopsies demonstrate vasculitis of the dermal capillaries and postcapillary venules. The inflammatory infiltrate includes neutrophils and monocytes. Renal histopathology typically shows endocapillary proliferative glomerulonephritis, ranging from a focal segmental process to extensive crescentic involvement. In all tissues, immunofluorescence identifies IgA deposition in walls of small vessels (Fig. 167-1), accompanied to a lesser extent by deposition of C3, fibrin, and IgM.

**PATHOGENESIS**

The exact pathogenesis of HSP remains unknown. Given the seasonality of HSP and the frequency of preceding upper respiratory infections, infectious triggers such as group A β-hemolytic streptococcus, *Staphylococcus aureus*, mycoplasma, and adenovirus have been suspected.

The common finding of deposition of IgA, specifically IgA1, suggests that HSP is a disease mediated by IgA and IgA immune complexes. HSP occasionally clusters in families, suggesting a genetic component.
DIAGNOSIS

The diagnosis of HSP is a clinical one and is often straightforward when the typical rash is present. However, in at least 25% of cases, the rash appears after other manifestations, making early diagnosis challenging. Table 167-5 summarizes the classification criteria for HSP. The differential diagnosis for HSP depends on specific organ involvement but usually includes other small vessel vasculitides, infections, acute post streptococcal glomerulonephritis, hemolytic-uremic syndrome, coagulopathies, and other acute intraabdominal processes.

Acute hemorrhagic edema (AHE), an isolated cutaneous leukocytoclastic vasculitis that affects infants <2 yr of age, resembles HSP clinically. AHE manifests as fever; tender edema of the face, scrotum, hands, and feet; and ecchymosis (usually larger than the purpura of HSP) on the face and extremities (Fig. 167-3). The trunk is spared, but petechiae may be seen in mucous membranes. The patient usually appears well except for the rash. The platelet count is normal or elevated, and the urinalysis results are normal. The younger age, the nature of the lesions, absence of other organ involvement, and a biopsy may help distinguish AHE from HSP.

Papular-purpuric gloves-and-socks syndrome is most commonly caused by parvovirus B19 and initially manifests with symmetric edema and erythema over the hands and feet. These well-demarcated lesions end at the ankle and wrist and evolve into purpuric papules. Fever, oral lesions, and leukopenia are inconsistent findings. Complications include mononeuritis multiplex. Adolescents are more often affected than young children. In contrast to erythema infectiosum, patients with papular-purpuric gloves-and-socks syndrome are usually infectious at the time of appearance of the rash.

LABORATORY FINDINGS

No laboratory finding is diagnostic of HSP. Common but nonspecific findings include leukocytosis, thrombocytosis, mild anemia, and elevations of erythrocyte sedimentation rate (ESR) and C-reactive protein.
involvement with blood pressure, urinalysis, and serum creatinine is necessary.

Ultrasound is often used in the setting of gastrointestinal complaints to look for bowel wall edema or the rare occurrence of an associated intussusception. Barium enema can also be used to both diagnose and treat intussusception. Although often unnecessary in typical HSP, biopsies of skin and kidney can provide important diagnostic information, particularly in atypical or severe cases, and characteristically show IgA deposition in affected tissues.

**TREATMENT**

Treatment for mild and self-limited HSP is supportive, with an emphasis on assuring adequate hydration, nutrition, and analgesia. Steroids are most often used to treat significant gastrointestinal involvement or other life-threatening manifestations. Prednisone (1 mg/kg/day for 1-2 wk, followed by taper) reduces abdominal and joint pain but does not alter overall prognosis nor prevent renal disease. Rapid tapering of corticosteroids may lead to a flare of HSP symptoms. Although few data are available to demonstrate efficacy, intravenous immune globulin and plasma exchange are sometimes used in the setting of severe disease. In some cases, chronic HSP renal disease is managed with a variety of immunosuppressants, including azathioprine, cyclophosphamide, cyclosporine, and mycophenolate mofetil. End-stage renal disease develops in up to 8% of children with HSP nephritis.

**COMPLICATIONS**

Acutely, serious gastrointestinal involvement such as intestinal perforation imparts significant morbidity and mortality. Renal disease is the major long-term complication, occurring in 1-2% of children with HSP. Renal disease can develop up to 6 mo after diagnosis but rarely does so if the initial urinalyses findings are normal. It is recommended that children with HSP undergo serial monitoring of blood pressure and urinalyses for several months after diagnosis to monitor for the development of nephritis.

**PROGNOSIS**

Overall, the prognosis for childhood HSP is excellent, and most children experience an acute, self-limited course lasting on average 4 wk. From 15-60% of children with HSP experience 1 or more recurrences, typically within 4-6 mo of diagnosis. With each relapse, symptoms are usually milder than at presentation. Children with a more-severe initial course are at higher risk for relapse. The long-term prognosis usually depends upon the severity and duration of gastrointestinal or renal involvement. Chronic renal disease develops in 1-2% of children with HSP, and approximately 8% of those with HSP nephritis go on to have end-stage renal disease. The risk of HSP recurrence and graft loss following renal transplantation is estimated at 7.5% after 10 yr.

**BIBLIOGRAPHY**

Available at Expert Consult.

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### 167.2 Takayasu Arteritis

**Stacy P. Ardoin and Edward Fels**

Takayasu arteritis (TA), also known as “pulseless disease,” is a chronic large vessel vasculitis of unknown etiology that predominantly involves the aorta and its major branches.

**EPIDEMIOLOGY**

Although TA occurs worldwide and can affect all ethnic groups, the disease is most common in Asians. Age of onset is typically between 10 and 40 yr. Most children are diagnosed as adolescents, on average at 13 yr of age. Up to 20% of individuals with TA are diagnosed prior to age 19 yr. Younger children may be affected but diagnosis in infancy is rare. TA preferentially affects females with a reported 2:4:1 male:female ratio in children and adolescents and a 9:1 ratio among

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**Figure 167-3** Typical lesions of acute hemorrhagic edema on the arm of an infant. (From Eichenfield LF, Frieden IJ, Esterly NB: Textbook of neonatal dermatology, Philadelphia, 2001, WB Saunders.)

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**Table 167-5**

| Classification Criteria for Henoch-Schönlein Purpura*
| --- |
| **AMERICAN COLLEGE OF RHEUMATOLOGY CLASSIFICATION CRITERIA**
| Two of the following criteria must be present: |
| • Palpable purpura |
| • Age at onset ≤2 yr |
| • Bowel angina (postprandial abdominal pain, bloody diarrhea) |
| • Biopsy demonstrating intramural granulocytes in small arterioles and/or venules |
| **EUROPEAN LEAGUE AGAINST RHEUMATISM/PEDIATRIC RHEUMATOLOGY EUROPEAN SOCIETY CRITERIA†** |
| Palpable purpura (in absence of coagulopathy or thrombocytopenia) and 1 or more of the following criteria must be present: |
| • Abdominal pain (acute, diffuse, colicky pain) |
| • Arthritis or arthralgia |
| • Biopsy of affected tissue demonstrating predominant immunoglobulin A deposition |
| • Renal involvement (proteinuria >3 grams/24 hr), hematuria or red cell casts |

*(Classification criteria are developed for use in research and not validated for clinical diagnosis.

(CRP). The platelet count is normal in HSP. Occult blood is frequently found in stool specimens. Serum albumin levels may be low due to renal or intestinal protein loss. Autoantibody testing is not useful diagnostically except to exclude other diseases. Serum IgA values are often elevated but are not routinely measured. Assessment of renal
Bibliography
adults. Occlusive complications are more common in the United States, Western Europe, and Japan, whereas aneurysms predominate in Southeast Asia and Africa.

**PATHOLOGY**
TA is characterized by inflammation of the vessel wall, starting in the vas vasorum. Involved vessels are infiltrated by T cells, natural killer cells, plasma cells, and macrophages. Giant cells and granulomatous inflammation develop in the media. Persistent inflammation damages the elastic lamina and muscular media, leading to blood vessel dilation and the formation of aneurysms. Progressive scarring and intimal proliferation can result in stenotic or occluded vessels. The subclavian, renal, and carotid arteries are the most commonly involved aortic branches; pulmonary, coronary, and vertebral arteries may also be affected.

**PATHOGENESIS**
The etiology of TA remains unknown. The presence of abundant T cells with a restricted repertoire of T-cell receptors in TA vascular lesions points to the importance of cellular immunity and suggests the existence of a specific but unknown aortic tissue antigen. Expression of interleukin (IL)-1, IL-6, and tumor necrosis factor-α (TNF-α) is reported to be higher in patients with active TA than in patients with inactive TA and in healthy controls. In some patient populations, IL-1 genetic polymorphisms are linked to TA. Some individuals with TA have elevated serum values of antiendothelial antibodies. The increased prevalence of TA in certain ethnic populations and its occasional occurrence in monozygotic twins and families suggest a genetic predisposition to the disease.

**CLINICAL MANIFESTATIONS**
The diagnosis of TA is challenging, because early disease manifestations are often nonspecific. As a result, diagnosis can be delayed for several months, and the time to diagnosis is usually longer in children than in adults. Fever, malaise, weight loss, headache, hypertension, myalgias, arthralgias, dizziness, and abdominal pain are common early complaints in the “pre-pulseless” phase of the disease. Among children, hypertension and headache are particularly common presenting manifestations and should prompt consideration of TA when present without alternative explanation. Some individuals with TA report no systemic symptoms and instead present with vascular complications. It is only after substantial vascular injury that evidence of hyperperfusion becomes clinically evident. Later manifestations of disease include diminished pulses, asymmetric blood pressures, claudication, Raynaud phenomenon, renal failure, and symptoms of pulmonary or cardiac ischemia. Inflammation can extend to the aortic valve, resulting in valvular insufficiency. Other findings may include pericardial effusion, pericarditis, pleuritis, splenomegaly, and arthritis.

Supradiaphragmatic (aortic arch) disease often manifests with CNS (stroke, transient ischemic attack), and cardiac (heart failure, palpitations) symptoms, while infradiaphragmatic (mid-aortic syndrome) disease may produce hypertension, abdominal bruits, and pain. Most patients have involvement in both areas.

**DIAGNOSIS**
Specific pediatric criteria for TA have been proposed (Table 167-6). Radiographic demonstration of large vessel vasculitis is necessary. A thorough physical examination is required to detect an aortic murmur, diminished or asymmetric pulses, and vascular bruits. Four extremity blood pressures should be measured >10 mm Hg; asymmetry in systolic pressure is indicative of disease.

**DIFFERENTIAL DIAGNOSIS**
In the early phase of TA, when nonspecific symptoms predominate, the differential diagnosis includes a wide array of systemic infections, autoimmune conditions, and malignancies. Although giant cell arteritis, also known as “temporal arteritis,” is a common large vessel vasculitis in older adults, this entity is exceedingly rare in childhood. Noninflammatory conditions that can cause large vessel compromise include fibromuscular dysplasia, Marfan syndrome, and Ehlers-Danlos syndrome.

**LABORATORY FINDINGS**
The laboratory findings in TA are nonspecific, and there is no specific diagnostic laboratory test. ESR and CRP value are typically elevated, and other nonspecific markers of chronic inflammation may include leukocytosis, thrombocytosis, anemia of chronic inflammation, and hypergammaglobulinemia. Autoantibodies are not useful in diagnosing TA except to help exclude other autoimmune diseases.

Radiographic assessment is essential to establish large vessel arterial involvement. Conventional arteriography of the aorta and major branches, including carotid, subclavian, pulmonary, renal, and mesenteric branches can identify luminal defects, including dilation, aneurysms, and stenoses, even in smaller vessels such as the mesenteric arteries. Figure 167-4 shows a conventional arteriogram in a child with TA. Although not yet thoroughly validated in TA, magnetic resonance angiography and CT angiography also provide important information about vessel wall thickness and enhancement, although they may not image smaller vessels as well as conventional angiography. Positron emission tomography may detect vessel wall inflammation but has not been studied extensively. Ultrasound with duplex color-flow Doppler imaging also identifies vessel wall thickening and assesses arterial flow. Echocardiography is recommended to assess for aortic valvular involvement. Serial vascular imaging is usually necessary to assess response to treatment and to detect progressive vascular damage.

**TREATMENT**
Glucocorticoids are the mainstay of therapy, typically starting with high doses (1-2 mg/kg/day of prednisone) followed by gradual dosing tapering. When TA progresses or recurs, steroid-sparing therapy is often required, usually involving methotrexate or azathioprine. Cyclophosphamide is reserved for severe or refractory disease. Results of small case series also suggest that mycophenolate mofetil, tocilizumab or anti-TNF-α therapy may be beneficial in select patients. Antiinflammatory medications are often necessary to control blood pressure caused by renovascular disease.

**COMPLICATIONS**
Progressive vascular damage can result in arterial stenoses, aneurysms, and occlusions, which produce ischemic symptoms and can be organ- or life-threatening. Potential ischemic complications include stroke, renal impairment or failure, myocardial infarction, mesenteric ischemia, and limb-threatening arterial disease. When these complications occur or are imminent, intervention with surgical vascular grafting or catheter-based angioplasty and stent placement may be necessary to restore adequate blood flow. A high rate of recurrent stenosis has been reported following angioplasty and stent placement. Aortic valve replacement may be required if significant aortic insufficiency develops.

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### Table 167-6 Proposed Classification Criteria for Pediatric-Onset Takayasu Arteritis

<table>
<thead>
<tr>
<th>Angiographic abnormalities (conventional, CT, or magnetic resonance angiography) of the aorta or its main branches and at least one of the following criteria:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Decreased peripheral artery pulse(s) and/or claudication of extremities</td>
</tr>
<tr>
<td>• Blood pressure difference between arms or legs of &gt;10 mm Hg</td>
</tr>
<tr>
<td>• Bruits over the aorta and/or its major branches</td>
</tr>
<tr>
<td>• Hypertension (defined by childhood normative data)</td>
</tr>
<tr>
<td>• Elevated acute phase reactant (erythrocyte sedimentation rate or C-reactive protein)</td>
</tr>
</tbody>
</table>

parvovirus B19, and hepatitis C virus, have also been associated with PAN. As in Henoch-Schönlein purpura, there is a possible association between PAN and familial Mediterranean fever.

PATHOLOGY
Biopsies show necrotizing vasculitis with granulocytes and monocytes infiltrating the walls of small and medium-size arteries (Fig. 167-5). Involvement is usually segmental and tends to occur at vessel bifurcations. Granulomatous inflammation is not present, and deposition of complement and immune complexes is rarely observed. Different stages of inflammation are found, ranging from mild inflammatory changes to panmural fibrinoid necrosis associated with aneurysm formation, thrombosis, and vascular occlusion.

PATHOGENESIS
Immune complexes are believed to be pathogenic, but the mechanism is poorly understood. There is no clear genetic association with PAN, and it is not known why PAN has a predilection for small- and medium-size blood vessels. The inflamed vessel wall becomes thickened and narrowed, impeding blood flow and contributing to end-organ damage characteristic of this disease. Familial disease in Georgian Jewish patients has been reported to be due to mutations in the \textit{CECR1} gene, which encodes adenosine deaminase 2.

CLINICAL MANIFESTATIONS
The clinical presentation of PAN is variable but generally reflects the distribution of inflamed vessels. Constitutional symptoms are present in most children at disease onset. Weight loss and severe abdominal pain suggest mesenteric arterial inflammation and ischemia. Renovascular arteritis can cause hypertension, hematuria, or proteinuria, although glomerulonephritis is not typical. Cutaneous manifestations include purpura, livedo reticularis, ulcerations, digital ischemia and painful nodules. Arteritis affecting the nervous system can result in cerebrovascular accidents, transient ischemic attacks, psychosis, and ischemic motor or sensory peripheral neuropathy (mononeuritis multiplex). Myocarditis or coronary arteritis can lead to heart failure and myocardial ischemia; pericarditis and arrhythmias have also been reported. Arthralgias, arthritis, or myalgias are frequently present. Less common symptoms include testicular pain that mimics testicular torsion, bone pain, and vision loss as a result of retinal arteritis. The pulmonary vasculature is usually spared in PAN.

DIAGNOSIS
The diagnosis of PAN requires demonstration of vessel involvement on biopsy or angiography (Table 167-7). Biopsy of cutaneous lesions...
Bibliography

Proposed Classification Criteria for Pediatric-Onset Polyarteritis Nodosa*

<table>
<thead>
<tr>
<th>Table 167-7</th>
<th>Proposed Classification Criteria for Pediatric Polyarteritis Nodosa*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Histopathology</strong></td>
<td>Necrotizing vasculitis in medium or small arteries</td>
</tr>
<tr>
<td><strong>Angiographic abnormalities</strong></td>
<td>Angiography showing aneurysm, stenosis, or occlusion of a medium or small size artery not from a noninflammatory cause</td>
</tr>
<tr>
<td><strong>Cutaneous findings</strong></td>
<td>Livedo reticularis, tender subcutaneous nodules, superficial skin ulcers, deep skin ulcers, digital necrosis, nail bed infarctions or splinter hemorrhages</td>
</tr>
<tr>
<td><strong>Muscle involvement</strong></td>
<td>Myalgia or muscle tenderness</td>
</tr>
<tr>
<td><strong>Hypertension</strong></td>
<td>Systolic or diastolic blood pressure &gt;95th percentile for height</td>
</tr>
<tr>
<td><strong>Peripheral neuropathy</strong></td>
<td>Sensory peripheral neuropathy, motor mononeuropathies multiplex</td>
</tr>
<tr>
<td><strong>Renal involvement</strong></td>
<td>Proteinuria (&gt;300 mg/24 hr equivalent), hematuria or red blood cell casts, impaired renal function (glomerular filtration rate &lt;30% normal)</td>
</tr>
</tbody>
</table>

*The presence of all 5 criteria provides 89.6% sensitivity and 99.6% specificity for the diagnosis of childhood onset polyarteritis nodosa.


Most cases of cutaneous PAN can be treated with less-intense therapy such as corticosteroids alone, nonsteroidal antiinflammatory agents, and methotrexate. Azathioprine, mycophenolate mofetil, intravenous immunoglobulin, thalidomide, cyclosporine, and anti-TNF have all been reported as successful in treatment of refractory cutaneous or systemic PAN, although clinical trials are lacking. If an infectious trigger for PAN is identified, antibiotic prophylaxis can be considered.

**COMPLICATIONS**

Cutaneous nodules may ulcerate and become infected. Hypertension and chronic renal disease may develop from renovascular involvement in PAN. Cardiac involvement may lead to decreased cardiac function or coronary artery disease. Mesenteric vasculitis can predispose to bowel infarction, rupture, and malabsorption. Stroke and rupture of hepatic arterial aneurysm are uncommon complications of this disorder.

**PROGNOSIS**

The course of PAN varies from mild disease with few complications to a severe, multiorgan disease with high morbidity and mortality. Poor prognostic factors in PAN include elevated serum creatinine, proteinuria, severe gastrointestinal involvement, cardiomyopathy, and CNS involvement. Early and aggressive immunosuppressive therapy increases the likelihood of clinical remission. Compared with disease in adults, childhood PAN is associated with less mortality. Cutaneous PAN is unlikely to transition to systemic disease. Early recognition and treatment of the disease are important to minimizing potential long-term vascular complications.

*Bibliography is available at Expert Consult.

167.4 Antineutrophilic Cytoplasmic Antibody–Associated Vasculitis

Stacy P. Ardoin and Edward Fels

The ANCA-associated vasculitides are characterized by small vessel involvement, circulating ANCA, and pauci-immune complex deposition in affected tissues. ANCA-associated vasculitis is categorized into 3 distinct forms: granulomatosis with polyangiitis (GPA; formerly...
Bibliography

Wegener granulomatosis), microscopic polyangitis (MPA), and eosinophilic granulomatosis with polyangiitis, formerly called Churg-Strauss syndrome (CSS) (see Table 167-1).

**EPIDEMIOLOGY**

GPA is a necrotizing granulomatous small and medium vessel vasculitis that occurs at all ages and targets the upper and lower respiratory tracts and the kidneys. Although most cases of GPA occur in adults, the disease also occurs in children with a mean age at diagnosis of 14 yr. There is a female predominance of 3:4:1, and pediatric GPA is most prevalent in whites.

MPA is a small vessel necrotizing vasculitis with clinical features similar to those of GPA. CSS is a small vessel necrotizing granulomatous (allergic granulomatosis) vasculitis associated with a history of refractory asthma and peripheral eosinophilia. MPA and CSS are rare in children, and there does not appear to be a gender predilection in either disease.

**PATHOLOGY**

Necrotizing vasculitis is the cardinal histologic feature in both GPA and MPA. Kidney biopsies typically demonstrate crescentic glomerulonephritis with little or no immune complex deposition ("pauci-immune"), in contrast to biopsies from patients with systemic lupus erythematosus. Although granulomatous inflammation is common in GPA and CSS, it is typically not present in MPA. Biopsies showing perivascular eosinophilic infiltrates distinguish CSS syndrome from both MPA and GPA (see Table 167-7).

**PATHOGENESIS**

The etiology of ANCA-associated vasculitis remains unknown, although neutrophils, monocytes, and endothelial cells are involved in disease pathogenesis. Neutrophils and monocytes are activated by ANCs, specifically by the ANCA-associated antigens proteinase-3 (PR3) and myeloperoxidase (MPO), and release proinflammatory cytokines such as TNF-α and IL-8. Localization of these inflammatory cells to the endothelium results in vascular damage characteristic of the ANCA vasculitides. Why the respiratory tract and kidneys are preferential targets in GPA and MPA is unknown.

**CLINICAL MANIFESTATIONS**

Early disease course is characterized by nonspecific constitutional symptoms, including fever, malaise, weight loss, myalgias, and arthralgias. In GPA, upper airway involvement can manifest as sinusitis, nasal ulceration, epistaxis, otitis media, and hearing loss. Lower respiratory tract symptoms in GPA include cough, wheezing, dyspnea, and hemoptysis. Pulmonary hemorrhage can cause rapid respiratory failure. Compared with adults, childhood GPA is more frequently complicated by subglottic stenosis (see Fig. 167-5). Inflammation-induced damage to the nasal cartilage can produce a saddle nose deformity (Fig. 167-7). Ophthalmic involvement includes conjunctivitis, scleritis, uveitis, optic neuritis, and invasive orbital pseudotumor (causing proptosis). Perinerveal vasculitis or direct compression on nerves by granulomatous lesions can cause cranial and peripheral neuropathies. Hematuria, proteinuria, and hypertension in GPA signal renal disease. Cutaneous lesions include palpable purpura and ulcers. Venous thromboembolism is a rare but potentially fatal complication of GPA. The frequencies of organ system involvement throughout the disease course in GPA are: respiratory tract, 84%; kidneys, 88%; joints, 44%; eyes, 60%; skin, 48%; sinuses, 56%; and nervous system, 12%. Table 167-8 outlines the classification criteria for pediatric-onset GPA.

The clinical presentation of MPA closely resembles that of GPA, although sinus disease is less common; systemic features of fever, malaise, weight loss, myalgias, arthralgias may be dominant. MPA predominantly affects the kidney and lungs; other organ systems include skin, CNS, muscle, heart, and eyes. CSS frequently causes inflammation of the upper and lower respiratory tracts, but cartilage destruction is rare. CSS may initially demonstrate chronic or recurrent rhinitis/sinusitis, nasal polyposis, and difficult to treat asthma. Eosinophilia with pulmonary infiltrates may precede a vasculitic phase. Other organ involvement includes skin, cardiac, peripheral nerves, gastrointestinal tract, and muscle. Renal involvement in CSS is uncommon.

**DIAGNOSIS**

GPA should be considered in children who have recalcitrant sinusitis, pulmonary infiltrates, and evidence of nephritis. Chest radiography often fails to detect pulmonary lesions, and chest CT may show nodules, ground-glass opacities, mediastinal lymphadenopathy, and cavity lesions (Fig. 167-8). The diagnosis is confirmed by the presence of anti-PR3–specific ANCs (PR3-ANCs) and the finding of necrotizing granulomatous vasculitis on pulmonary, sinus, or renal biopsy. The ANCA test result is positive in approximately 90% of children with GPA, and the presence of anti-PR3 increases the specificity of the test.

In MPA, ANCs are also frequently present but have reactivity to MPO (MPO-ANCAs). MPA can be distinguished from PAN by the
presence of ANCAs and the tendency for small vessel involvement. The ANCA test result is positive in approximately 70% of cases of CSS, and MPO-ANCAs are more common than PR3-ANCAs. The presence of chronic asthma and peripheral eosinophilia suggests the diagnosis of CSS.

**DIFFERENTIAL DIAGNOSIS**
ANCAs are absent in other granulomatous diseases, such as sarcoidosis and tuberculosis. Goodpasture disease is characterized by antibodies to glomerular basement membrane. Medications such as propylthiouracil, hydralazine, and minocycline are associated with drug-induced ANCA (usually perinuclear ANCA) vasculitis. Systemic lupus erythematosus and HSP can manifest as pulmonary hemorrhage and nephritis.

**LABORATORY FINDINGS**
Elevated ESR and CRP values, leukocytosis, and thrombocytosis are present in most patients with an ANCA-associated vasculitis but are nonspecific. Anemia may be caused by chronic inflammation or pulmonary hemorrhage. ANCA antibodies show 2 distinct immunofluorescence patterns: perinuclear and cytoplasmic. In addition, ANCAs can also be defined by their specificity for PR3 or MPO antigen. GPA is strongly associated with cytoplasmic ANCAs/anti-PR3 antibodies (see Tables 167-1 and 167-9).

**TREATMENT**
When the lower respiratory tract or kidneys are significantly involved, initial induction therapy usually consists of corticosteroids (2 mg/kg/day oral or 30 mg/kg/day × 3 days given intravenously) in conjunction with daily oral cyclophosphamide (2 mg/kg/day). Rituximab is an option for induction therapy in ANCA positive vasculitides although

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**Table 167-8**

<table>
<thead>
<tr>
<th>Feature</th>
<th>Henoch-Schönlein Purpura</th>
<th>Granulomatosis with Polyangiitis</th>
<th>Churg-Strauss Syndrome</th>
<th>Microscopic Polyangiitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>EULAR/PRRS Classification Criteria for Pediatric-Onset Granulomatosis with Polyangiitis&lt;sup&gt;*&lt;/sup&gt;</td>
<td>Histopathology showing granulomatous inflammation</td>
<td>Upper airway involvement</td>
<td>Laryngeal, tracheal or bronchial involvement</td>
<td>ANCA positivity</td>
</tr>
</tbody>
</table>

<sup>*</sup>Diagnosis requires 3 of 6 criteria.


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**Table 167-9**

<table>
<thead>
<tr>
<th>Feature</th>
<th>Henoch-Schönlein Purpura</th>
<th>Granulomatosis with Polyangiitis</th>
<th>Churg-Strauss Syndrome</th>
<th>Microscopic Polyangiitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Signs and symptoms of small vessel vasculitis&lt;sup&gt;+&lt;/sup&gt;</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Immunoglobulin A–dominant immune deposits</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Circulating antineutrophil cytoplasmic antibodies</td>
<td>–</td>
<td>+ (PR3)</td>
<td>+ (MPO &gt; PR3)</td>
<td>+ (MPO)</td>
</tr>
<tr>
<td>Necrotizing vasculitis</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Granulomatous inflammation</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Asthma and eosinophilia</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>–</td>
</tr>
</tbody>
</table>

MPO, myeloperoxidase-reactive antibodies; PR3, proteinase 3-reactive antibodies; +, presence; –, absent.

<sup>+</sup>SSigns and symptoms of small vessel vasculitis include purpura, other rash, arthralgias, arthritis, and constitutional symptoms.


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has been studied primarily in adults. Patients are transitioned to a less toxic maintenance medication (usually methotrexate, azathioprine, or mycophenolate mofetil) within 3-6 mo once remission is achieved. Trimethoprim-sulfamethoxazole (one 180 mg/800 mg tablet 3 days/wk) is often prescribed both for prophylaxis against *Pneumocystis jiroveci* infection and to reduce upper respiratory bacterial colonization with *S. aureus*, which may trigger disease activity. If disease is limited to the upper respiratory tract, corticosteroids (1-2 mg/kg/day) and methotrexate (0.5-1.0 mg/kg/wk) may be first-line treatment.

**COMPLICATIONS**
Upper respiratory tract lesions can invade the orbit and threaten the optic nerve, and lesions in the ear can cause permanent hearing loss. Respiratory complications include potentially life-threatening pulmonary hemorrhage and upper airway obstruction due to subglottic stenosis. Chronic lung disease secondary to granulomatous inflammation, cavitary lesions, and scarring can predispose to infectious complications. Chronic glomerulonephritis may progress to end-stage renal disease in a subset of patients with advanced or undertreated disease.

**PROGNOSIS**
The course is variable but disease relapse occurs in up to 60% of patients. Mortality has been reduced with the introduction of cyclophosphamide and other immunosuppressive agents. Compared with adults, children are more likely to develop multiple organ involvement, renal involvement, and subglottic stenosis.

Bibliography is available at Expert Consult.

167.5 Other Vasculitis Syndromes

Stacy P. Ardoin and Edward Fels

In addition to the more common vasculitides discussed earlier in this chapter, other vasculitic conditions can occur in childhood, the most common of which is Kawasaki disease (see Chapter 166). **Hypersensitivity vasculitis** is a cutaneous vasculitis triggered by medication or toxin exposure. The rash consists of palpable purpura or other nonspecific rash. Skin biopsies reveal characteristic changes of **leukocytoclastic vasculitis** (small vessels with neutrophilic perivascular or extravascular neutrophilic infiltration). **Hypocomplementemic urticarial vasculitis** involves small vessels and manifests as recurrent urticaria that resolves over several days but leaves residual hyperpigmentation. **Cryoglobulinemic vasculitis** represents vasculitis confined to the CNS and requires exclusion of other systemic vasculitides. Large vessel disease (angiography positive) may manifest with focal deficits similar to an occlusive stroke with hemiparesis, focal gross or fine motor deficits, language disorders, or cranial nerve deficits. Diffuse cognitive, memory, and concentration deficits plus behavioral disorders are seen in 30-40%. Small vessel (angiography negative, biopsy positive) involvement more often demonstrates language problems and diffuse deficits such as cognitive, memory, behavior, and concentration problems as well as focal seizures.

**Primary angiitis of the CNS** represents vasculitis confined to the CNS and requires exclusion of other systemic vasculitides. Large vessel disease (angiography positive) may manifest with focal deficits similar to an occlusive stroke with hemiparesis, focal gross or fine motor deficits, language disorders, or cranial nerve deficits. Diffuse cognitive, memory, and concentration deficits plus behavioral disorders are seen in 30-40%. Small vessel (angiography negative, biopsy positive) involvement more often demonstrates language problems and diffuse deficits such as cognitive, memory, behavior, and concentration problems as well as focal seizures.

**Benign angiitis of the CNS**, also known as transient CNS angiopathy, represents a self-limited variant. **Cogan syndrome** is rare in children; its potential clinical manifestations include constitutional symptoms, inflammatory eye disease, vestibulouderital dysfunction, arthritis, and aortitis.

Identification of these vasculitis syndromes requires a comprehensive history and physical exam. Table 167-10 outlines other diagnostic considerations. Although treatment is tailored to disease severity, treatment generally includes prednisone (up to 2 mg/kg/day) plus steroid-sparing immunosuppressive medications if necessary. For hypersensitivity vasculitis, withdrawal of the triggering medication or toxin is indicated if possible.

Bibliography is available at Expert Consult.

| Table 167-10 Diagnostic Considerations for Other Vasculitis Syndromes |
|-----------------------------|--------------------------------------------------|
| **VASCULITIS SYNDROME**     | **APPROACH TO DIAGNOSIS**                        |
| Hypersensitivity vasculitis | Skin biopsy demonstrating leukocytoclastic vasculitis |
| Hypocomplementemic urticarial vasculitis | Biopsy of affected tissue demonstrating small vessel vasculitis |
| Low levels of circulating C1q |
| Cryoglobulinemic vasculitis | Biopsy of affected tissue demonstrating small vessel vasculitis Measurement of serum cryoglobulins Exclusion of hepatitides B and C infections |
| Primary angiitis of the CNS | Conventional, CT, or MR angiographic evidence of CNS vasculitis Consideration of dura or brain biopsy |
| Benign angiitis of the CNS  | Conventional, CT, or MR angiographic evidence of CNS vasculitis |
| Cogan syndrome              | Ophthalmology and audiology evaluations Conventional, CT, or MR angiographic evidence of CNS or aortic vasculitis |

CNS, central nervous system; CT, computed tomography; MR, magnetic resonance.
Bibliography


Bibliography


Musculoskeletal pain is a frequent complaint of children presenting to general pediatricians and is the most common presenting problem of children referred to pediatric rheumatology clinics. Prevalence estimates of persistent musculoskeletal pain in community samples range from roughly 10-30%. Although diseases such as juvenile idiopathic arthritis and systemic lupus erythematosus may manifest as persistent musculoskeletal pain, the majority of musculoskeletal pain complaints in children turn out to be benign in nature and attributable to trauma, overuse, and normal skeletal growth variations. There is a subset of children in whom chronic pain complaints develop in the absence of physical and laboratory abnormalities. Children with idiopathic musculoskeletal pain syndromes, also typically develop marked subjective distress and functional impairment. Therefore, the treatment of children with musculoskeletal pain syndromes optimally includes both pharmacologic and nonpharmacologic interventions.

CLINICAL MANIFESTATIONS
Chronic musculoskeletal pain syndromes involve pain complaints of at least 3 mo in duration in the absence of objective abnormalities on physical examination and laboratory screening. Additionally, children and adolescents with musculoskeletal pain syndromes often complain
of persistent pain despite previous treatment with nonsteroidal anti-inflammatory drugs and analgesic agents. The location varies, with pain complaints either localized to a single extremity or more diffuse and involving multiple extremities. It is not uncommon for the pain to start in a single area of the body before intensifying and radiating to other areas over time. The prevalence of musculoskeletal pain syndromes increases with age and is higher in females, thus rendering adolescent girls at highest risk.

The somatic complaints of children and adolescents with musculoskeletal pain syndromes are commonly accompanied by psychological distress, sleep difficulties, and functional impairment across home, school, and peer domains. Psychological distress may include symptoms of anxiety and depression, such as frequent crying spells, fatigue, sleep disturbance, feelings of worthlessness, poor concentration, and frequent worry. Indeed, a substantial number of children with musculoskeletal pain syndromes display the full range of psychological symptoms warranting an additional diagnosis of a comorbid mood or anxiety disorder (e.g., major depressive episode, generalized anxiety disorder). Sleep disturbance in children with musculoskeletal pain syndromes may include difficulty falling asleep, multiple night awakenings, disrupted sleep-wake cycles with increased daytime sleepiness, nonrestorative sleep, and fatigue.

For children and adolescents with musculoskeletal pain syndromes, the constellation of pain, psychological distress, and sleep disturbance often leads to a high degree of functional impairment. Poor school attendance is common, and children may struggle to complete other daily activities relating to self-care and participation in household chores. Decreased physical fitness can also occur, as well as changes in gait and posture, as children avoid contact with or use of the body area affected by pain. Peer relationships may also be disrupted due to decreased opportunities for social interaction due to pain. As such, children and adolescents with musculoskeletal pain syndromes often report loneliness and social isolation characterized by having few friends and lack of participation in extracurricular activities.

**DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS**

The diagnosis of a musculoskeletal pain syndrome is typically one of exclusion when careful, repeated physical examinations and laboratory testing do not reveal an etiology. At initial presentation, children with pain complaints require a thorough clinical history and a complete physical examination to look for an obvious etiology (e.g., sprains, strains, or fractures), characteristics of the pain (localized or diffuse), and evidence of systemic involvement. A comprehensive history can often lead to a high degree of functional impairment. Poor school attendance is common, and children may struggle to complete other daily activities relating to self-care and participation in household chores. Decreased physical fitness can also occur, as well as changes in gait and posture, as children avoid contact with or use of the body area affected by pain. Peer relationships may also be disrupted due to decreased opportunities for social interaction due to pain. As such, children and adolescents with musculoskeletal pain syndromes often report loneliness and social isolation characterized by having few friends and lack of participation in extracurricular activities.

**TREATMENT**

The primary goal of treatment for pediatric musculoskeletal pain syndromes is to improve function rather than relieve pain, and these two desirable outcomes may not occur simultaneously. Indeed, it is common for children with musculoskeletal pain syndromes to continue complaining of pain even as they resume normal function (e.g., increased school attendance and participation in extracurricular activities). For all children and adolescents with pediatric musculoskeletal pain syndromes, regular school attendance is crucial, as this is a hallmark of normal functioning in this age group. The dual nature of treatment, targeting both function and pain, needs to be clearly

**Table 168-1** Potential Indicators of Benign Versus Serious Causes of Musculoskeletal Pain

<table>
<thead>
<tr>
<th>CLINICAL FINDING</th>
<th>BENIGN CAUSE OF MUSCULOSKELETAL PAIN</th>
<th>SERIOUS CAUSE OF MUSCULOSKELETAL PAIN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effects of rest versus activity on pain</td>
<td>Relieved by rest and worsened by activity</td>
<td>Relieved by activity and present at rest</td>
</tr>
<tr>
<td>Time of day pain occurs</td>
<td>End of the day and nights</td>
<td>Morning*</td>
</tr>
<tr>
<td>Objective joint swelling</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Joint characteristics</td>
<td>Hypermobile/normal</td>
<td>Stiffness, limited range of motion</td>
</tr>
<tr>
<td>Bony tenderness</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Muscle strength</td>
<td>Normal</td>
<td>Muscle weakness</td>
</tr>
<tr>
<td>Growth</td>
<td>Normal growth pattern or weight gain</td>
<td>Poor growth and/or weight loss</td>
</tr>
<tr>
<td>Constitutional symptoms</td>
<td>Fatigue without other constitutional symptoms</td>
<td>Yes</td>
</tr>
<tr>
<td>Lab findings</td>
<td>Normal CBC, ESR, CRP</td>
<td>Abnormal CBC, raised ESR and CRP</td>
</tr>
<tr>
<td>Radiographic findings</td>
<td>Normal</td>
<td>Effusion, osteopenia, radiolucent metaphyseal lines, joint space loss, bony destruction</td>
</tr>
</tbody>
</table>

CBC, complete blood count; CRP, C-reactive protein level; ESR, erythrocyte sedimentation rate.

*Cancer pain is often severe and worst at night.

explained to children and their families to better outline the goals by which treatment success will be measured. Indeed, children and families need to be supported in disengaging from the sole pursuit of pain relief and embracing broader treatment goals of improved functioning.

Recommended treatment modalities typically include physical and/or occupational therapy, pharmacologic interventions, and cognitive-behavioral and/or other psychotherapeutic interventions. The overarching goal of physical therapy is to improve children’s physical function and should emphasize participation in aggressive, but graduated aerobic exercise. Pharmacologic interventions should be used judiciously. Low-dose tricyclic antidepressants (amitriptyline 10–50 mg orally 30 min before bedtime) are indicated for treatment of sleep disturbance; selective serotonin reuptake inhibitors (sertraline 10–20 mg daily) may prove useful in treating symptoms of depression and anxiety if present. Referral for psychological evaluation is warranted if these symptoms do not resolve with initial treatment efforts or if suicidal ideation is present. Cognitive-behavioral and/or other psychotherapeutic interventions are typically designed to teach children and adolescents coping skills for controlling the behavioral, cognitive, and physiologic responses to pain. Specific components often include cognitive restructuring, relaxation, distraction, and problem-solving skills; additional targets of therapy include sleep hygiene and activity scheduling, all with the goal of restoring normal sleep patterns and activities of daily living. Parent education and involvement in the psychological intervention is important to ensure maintenance of progress. More intensive family-based approaches are warranted if barriers to treatment success are identified at the family level. These could include parenting strategies or family dynamics that serve to maintain children’s pain complaints, such as overly solicitous responses to child pain, and maladaptive models for pain coping in the family.

**COMPLICATIONS AND PROGNOSIS**

Musculoskeletal pain syndromes can negatively affect child development and future role functioning. Worsening pain and the associated symptoms of depression and anxiety can lead to substantial school absences, peer isolation, and developmental delays later in adolescence and early adulthood. Specifically, adolescents with musculoskeletal pain syndromes may fail to achieve the level of autonomy and independence necessary for age-appropriate activities such as attending college, living away from home, and maintaining a job. Fortunately, not all children and adolescents with musculoskeletal pain syndromes experience this degree of impairment and the likelihood of positive health outcomes is increased with multidisciplinary treatment.

**168.1 Growing Pains**

*Kelly K. Anthony and Laura E. Schanberg*

More appropriately termed *benign nocturnal pains of childhood* growing pains affect 10–20% of children, with a peak age incidence between 4 and 12 yr. Pain does not occur during periods of rapid growth or at growth sites. The most common cause of recurrent musculoskeletal pain in children, growing pains are intermittent and bilateral, predominantly affecting the anterior thigh, shin, and calf but not joints. Occasionally there may be bilateral upper extremity pain associated with leg pain; isolated upper extremity pain does not occur. Children most commonly describe cramping or aching that occurs in the late afternoon or evening. Pain may wake the child from sleep and may last a few minutes to hours, but resolves quickly with massage or analgesics; pain is never present the following morning (Table 168-3). Pain often follows a day with exercise or other physical activities. Physical findings are normal, and gait is not impaired. Growing pains are generally considered a benign, time-limited condition; there is evidence suggesting that growing pains represent a pain amplification syndrome. Indeed, growing pains persist in a significant percentage of children, with some children developing other pain syndromes such as abdominal pain and headaches. Growing pains are more likely to persist in children with a parent who has a history of a pain syndrome and in children who have lower pain thresholds. Treatment should also focus on reassurance, education, and healthy sleep hygiene. Massage

<table>
<thead>
<tr>
<th>ANATOMICAL REGION</th>
<th>PAIN SYNDROMES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shoulder</td>
<td>Impingement syndrome</td>
</tr>
<tr>
<td>Elbow</td>
<td>Little League elbow, Avulsion fractures, Osteochondritis dissecans</td>
</tr>
<tr>
<td>Arm</td>
<td>Localized hypermobility syndrome, Complex regional pain syndrome</td>
</tr>
<tr>
<td>Pelvis and hip</td>
<td>Avulsion injuries, Legg-Calvé-Perthes syndrome</td>
</tr>
<tr>
<td>Knee</td>
<td>Osteochondritis dissecans, Osgood-Schlatter disease, Sinding-Larsen syndrome</td>
</tr>
<tr>
<td>Leg</td>
<td>Growing pains, Complex regional pain syndrome, Localized hypermobility syndrome</td>
</tr>
<tr>
<td>Foot</td>
<td>Plantar fascitis, Tarsal coalition, Stress fractures</td>
</tr>
<tr>
<td>Spine</td>
<td>Musculoskeletal strain, Spondylolysis, Spondylolysis</td>
</tr>
<tr>
<td>Generalized</td>
<td>Hypermobility syndrome, Juvenile fibromyalgia, Generalized pain syndrome</td>
</tr>
</tbody>
</table>

Musculoskeletal Pain Syndromes

168.2 Small Fiber Polyneuropathy

Kelly K. Anthony and Laura E. Schanberg

Many patients with juvenile onset widespread pain syndromes, as well as patients with pediatric fibromyalgia (see Chapter 168.3), complex regional pain syndrome type I (see Chapter 168.4), and erythromelalgia have evidence of a small fiber polyneuropathy causing dysfunctional or degeneration of small diameter unmyelinated C-fibers and thinly myelinated A-delta fibers that mediate nociception and the autonomic nervous system. Fibromyalgia (see Chapter 168.3) includes chronic widespread pain defined as ≥3 mo duration of axial pain that is often bilateral and also affects the upper and lower extremities. In addition, many patients have associated chronic cardiovascular (dizziness, postural orthostasis syndrome) symptoms, as well as chronic abdominal pain and ileus, headaches, fatigue and erythromelalgia, suggestive of dysautonomia.

There are no typical findings on physical exam or standard laboratory tests. The diagnosis of small fiber polyneuropathy requires distal leg skin immunolabeled biopsy to identify epidermal nociceptive fibers and autonomic function testing to examine cardiovascular, adrenergic, and sudomotor small fiber function.

Treatment of patients with small fiber polyneuropathy and isolated juvenile-onset widespread pain syndrome, or those subsets of patients with small fiber polyneuropathy and fibromyalgia, complex regional pain syndrome, or erythromelalgia is evolving and has included prednisone or intravenous immunoglobulin.

**Bibliography is available at Expert Consult.**

168.3 Fibromyalgia

Kelly K. Anthony and Laura E. Schanberg

Juvenile primary fibromyalgia syndrome (JFPS) is a common pediatric musculoskeletal pain syndrome. Approximately 25-40% of children with chronic pain syndromes can be diagnosed with JFPS. Although specific diagnostic criteria for JFPS have not been determined, children and adolescents with JFPS have diffuse, multifocal, waxing and waning, and at times migratory musculoskeletal pain in at least 3 areas of the body that persists for at least 3 mo in the absence of an underlying condition. Results of laboratory tests are normal, and physical examination reveals at least 5 well-defined tender points (Fig. 168-1). Children and adolescents with JFPS also present with many associated symptoms, including nonrestorative sleep, fatigue, paresthesias, chronic anxiety or tension, chronic headaches, subjective soft-tissue swelling, and pain modulated by physical activity, weather, and anxiety or stress. There is considerable overlap among symptoms associated with JFPS and complaints associated with other functional disorders (e.g., irritable bowel disease, migraines, temporomandibular joint disorder, premenstrual syndrome, mood and anxiety disorders, and chronic fatigue syndrome), raising speculation that these disorders may be part of a larger spectrum of related syndromes.

Although the precise cause of JFPS is unknown, there is an emerging understanding that the development and maintenance of JFPS are related both to biologic and psychological factors. JFPS is an abnormality of central pain processing characterized by disordered sleep physiology, enhanced pain perception with abnormal levels of substance P in cerebrospinal fluid, disordered mood, and dysregulation of hypothalamic–pituitary–adrenal and other neuroendocrine axes resulting in lower tender-point pain thresholds and increased pain sensitivity. Children and adolescents with fibromyalgia often find themselves in a vicious cycle of pain, whereby symptoms build upon one another and contribute to the onset and maintenance of new symptoms (Fig. 168-2). JFPS has a chronic course that can detrimentally affect child health and development. Adolescents with JFPS who do not receive...
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**Bibliography**


Complex regional pain syndrome (CRPS) is characterized by ongoing burning limb pain that is subsequent to an injury, immobilization, or another noxious event affecting the extremity. CRPS1, formerly called reflex sympathetic dystrophy, has no evidence of nerve injury, whereas CRPS2, formerly called causalgia, follows a prior nerve injury. Key associated features are pain disproportionate to the inciting event, persisting allodynia (a heightened pain response to normally non-noxious stimuli), hyperalgesia (exaggerated pain reactivity to noxious stimuli), swelling of distal extremities, and indicators of autonomic dysfunction (i.e., cyanosis, mottling, and hyperhidrosis) (Table 168–4).

The diagnosis requires the following: an initiating noxious event or immobilization; continued pain, allodynia, and hyperalgesia out of proportion to the inciting event; evidence of edema, skin blood flow abnormalities, or sudomotor activity; and exclusion of other disorders. Associated features include atrophy of hair or nails; altered hair growth; loss of joint mobility; weakness, tremor, dystonia; and sympathetically maintained pain.

Although the majority of pediatric patients with CRPS present with a history of minor trauma or repeated stress injury (e.g., caused by competitive sports), a sizeable proportion are unable to identify a precipitating event. Usual age of onset is between 8 and 16 yr, and girls outnumber boys with the disease by as much as 6:1. Childhood CRPS differs from the adult form in that lower extremities, rather than upper extremities, are most commonly affected. The incidence of CRPS in children is unknown, largely because it is often undiagnosed or diagnosed late, with the diagnosis frequently delayed by nearly a year. Left untreated, CRPS can have severe consequences for children including bone demineralization, muscle wasting, and joint contractures.

An evidence-based approach to the treatment of CRPS continues to suggest a multistage treatment approach. Aggressive physical therapy should be initiated as soon as the diagnosis is made and cognitive-behavioral interventions (CBT) added as needed. Physical therapy (PT) is recommended 3-4 times per week, and children may need analgesic premedication at the onset, particularly prior to PT sessions. PT is initially limited to desensitization and then moves to weight-bearing, range-of-motion, and other functional activities. CBT used as an adjunctive therapy targets psychosocial obstacles to fully participating in PT and provides pain coping skills training. Sympathetic and epidural nerve blocks should be attempted only under the auspices of a pediatric pain specialist. The intent of both pharmacologic and adjunctive treatments for CRPS is to provide sufficient pain relief to allow the child to participate in aggressive physical rehabilitation. If CRPS is identified and treated early, the majority of children and adolescents with the disease can be treated successfully with low-dose amitriptyline (10-50 mg orally 30 min prior to bedtime), aggressive PT, and CBT interventions. Opioids and anticonvulsants such as gabapentin can also be helpful. Notably, multiple studies have shown non-invasive treatments, particularly PT and CBT, are at least as efficacious as nerve blocks in helping children with CRPS achieve resolution of their symptoms.

There is growing evidence that some patients with CRPS I have a small fiber polyneuropathy (see Chapter 168.2).

Bibliography is available at Expert Consult.

### 168.4 Complex Regional Pain Syndrome

Kelly K. Anthony and Laura E. Schanberg

Complex regional pain syndrome (CRPS) is characterized by ongoing burning limb pain that is subsequent to an injury, immobilization, or another noxious event affecting the extremity. CRPS1, formerly called reflex sympathetic dystrophy, has no evidence of nerve injury, whereas CRPS2, formerly called causalgia, follows a prior nerve injury. Key associated features are pain disproportionate to the inciting event, persisting allodynia (a heightened pain response to normally non-noxious stimuli), hyperalgesia (exaggerated pain reactivity to noxious stimuli), swelling of distal extremities, and indicators of autonomic dysfunction (i.e., cyanosis, mottling, and hyperhidrosis) (Table 168–4).

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Bibliography is available at Expert Consult.

### 168.5 Erythromelalgia

Laura E. Schanberg

Children with erythromelalgia experience episodes of intense pain, erythema, and heat in their hands and feet (Fig. 168–3). Less commonly involved are the face, ears, or knees. Symptoms may be triggered by exercise and exposure to heat, lasting for hours and occasionally for days. It is more common in girls and in the teenage years and diagnosis is often delayed for years. Although most cases are sporadic, an
**Bibliography**


Bibliography
autosomal dominant hereditary form results from mutations of the SCN9A gene on chromosome 2q31-32, causing a painful channelopathy. Secondary erythromelalgia is associated with an array of disorders, including myeloproliferative diseases, peripheral neuropathy, frostbite, hypertension, and rheumatic disease. Treatment includes avoidance of heat exposure as well as other precipitating situations and the utilization of cooling techniques that do not cause tissue damage during attacks. Nonsteroidal antiinflammatories, narcotics, anesthetic agents (lidocaine patch), anticonvulsants (oxcarbazepine, carbamazepine, gabapentin), and antidepressants, as well as biofeedback and hypnosis may be useful in helping manage pain. Drugs acting on the vascular system (aspirin, sodium nitroprusside, magnesium, misoprostol) may also be somewhat effective. However, a reliably efficacious treatment is not available, resulting in substantial negative impact on physical and mental health.

There is growing evidence that some patients with erythromelalgia have a small fiber polyneuropathy (see Chapter 168.2).

Bibliography is available at Expert Consult.
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RELAPSING POLYCHONDRITE

Relapsing polychondritis (RP) is a rare condition characterized by episodic chondritis causing cartilage destruction and deformation of the ears (sparring the earlobes), nose, larynx and tracheobronchial tree. Antibodies to matrilin-1 and collagen (types II, IX and XI) are present in approximately 60% of patients with RP, suggesting an autoimmune pathogenesis. Patients may experience arthritis, uveitis, and hearing loss due to inflammation near the auditory and vestibular nerves. Children may initially relate episodes of intense erythema over the outer ears. Other dermatologic manifestations such as erythema nodosum, maculopapular rash and purpura may be seen. Cardiac involvement, including conduction defects and coronary vasculitis, has been reported. Severe, progressive, and potentially fatal disease resulting from destruction of the tracheobronchial tree and airway obstruction is unusual in childhood. Diagnostic criteria established for adults are useful guidelines for evaluating children with suggestive symptoms (Table 169-1). The clinical course of RP is variable; flares of disease are often associated with elevations of acute-phase reactants and may remit spontaneously. Although seen more commonly in the adult population, RP may coexist with other inflammatory diseases, such as systemic lupus erythematosus, Sjögren syndrome, and Henoch-Schönlein purpura. The differential diagnosis includes antineutrophilic cytoplasmic antibody–associated vasculitis (granulomatosis with polyangiitis) (see Chapter 167.4) and Cogan syndrome, which is characterized by auditory nerve inflammation and keratitis but not chondritis. Many children respond to nonsteroidal antiinflammatory drugs, but some require corticosteroids or other immunosuppressive agents (aza-thioprine, methotrexate, hydroxychloroquine, colchicine, cyclophosphamide, cyclosporine, and anti–tumor necrosis factor agents), as reported in small series and case reports.

MUCHA-HABERMANN DISEASE/PITYRIASIS LICHENOIDES ET VARIOILIORMIS ACUTA

Pityriasis lichenoides et varioliformis acuta (PLEVA) is a benign, self-limited cutaneous vasculitis characterized by episodes of macules, papules, and papulovesicular lesions that can develop central ulceration, necrosis, and crusting. Different stages of development are usually seen at once. PLEVA fulminans or febrile ulceronecrotic Mucha-Habermann disease is the severe, life-threatening form of PLEVA. Large coalescing ulceronecrotic lesions are seen, and are accompanied by high fever and an elevated erythrocyte sedimentation rate. Systemic manifestations can include interstitial pneumonitis, abdominal pain, malabsorption, arthritis, and neurologic manifestations. There is a male predominance and it occurs more frequently in childhood. The diagnosis is confirmed by biopsy of skin lesions that reveal perivascular and intramural lymphocytic inflammation affecting capillaries and venules in the upper dermis that may lead to keratinocyte necrosis. When disease is severe, corticosteroids have been used with questionable effect, and methotrexate has been reported to induce rapid remission in resistant cases. Cyclosporine and anti–tumor necrosis factor agents have been efficacious in case reports.

SWEET SYNDROME

Sweet syndrome, or acute febrile neutrophilic dermatosis, is a rare entity in children. It is characterized by fever, elevated neutrophil count, and raised, tender erythematous plaques and nodules over the...
HOA can be primary (idiopathic), or secondary. Although rare, secondary HOA is more common in children, and is seen in children with chronic pulmonary disease (cystic fibrosis), congenital heart disease, gastrointestinal disease (malabsorption syndromes, biliary atresia, inflammatory bowel disease), and malignancies (nasopharyngeal sarcoma, osteosarcoma, Hodgkin disease). HOA may precede diagnosis of cardiopulmonary disease or malignancy. The pathogenesis of HOA is unknown; symptoms often improve if the underlying condition is treated successfully. HOA-related pain can be disabling, and in adults management with bisphosphonates has been reported. Evaluation of children presenting with HOA should include a chest radiograph to evaluate for pulmonary disease or intrathoracic mass.

**PLANT THORN SYNOVITIS**

A diagnosis of plant thorn synovitis should be considered in children with monoarticular arthritis nonresponsive to antiinflammatory therapy. Acute or chronic arthritis can occur after a plant thorn or other foreign object penetrates a joint. Unlike septic arthritis, children with plant thorn synovitis are commonly afebrile. The most common organism seen with plant thorn synovitis is *Pantoea agglomerans*, although cultures are often negative. The initial injury may be unknown or forgotten, making diagnosis difficult. Ultrasound or magnetic resonance imaging can be useful in identifying the foreign body. Removal of the foreign body via arthroscopy followed by an antibiotic course is the accepted therapy.

**PIGMENTED VILLONODULAR SYNOVITIS**

Proliferation of synovial tissue is seen in pigmented villonodular synovitis (PVNS). This proliferation is either localized or diffuse, and can affect the joint, tendon sheath or bursa. Macrophages and multinucleated giant cells with brownish hemosiderin are present histologically. It is unclear if the etiology of PVNS is inflammatory or neoplastic in nature. Although findings are not pathognomonic, MRI with contrast is a useful diagnostic tool where PVNS can be seen as a mass or bone erosion. Brown or bloody synovial fluid is seen with arthrocentesis, but the diagnosis is made by tissue biopsy. Surgical removal of the affected tissue is the therapeutic modality, and with diffuse disease, a total synovectomy is recommended.

**Table 169-2** Diagnostic Criteria for Classic Sweet Syndrome

<table>
<thead>
<tr>
<th>MAJOR CRITERIA</th>
<th>MINOR CRITERIA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abrupt onset of painful erythematous plaques or nodules</td>
<td>Pyrexia &gt;38°C (100.4°F)</td>
</tr>
<tr>
<td>Histopathologic evidence of dense neutrophilic infiltrate without evidence of leukocytoclastic vasculitis</td>
<td>Association with underlying hematologic or visceral malignancy, inflammatory disease or pregnancy, or preceded by an upper respiratory or gastrointestinal infection or vaccination</td>
</tr>
<tr>
<td>Excellent response to systemic corticosteroids or potassium iodide</td>
<td>Abnormal laboratory values at presentation (3 of 4): erythrocyte sedimentation rate &gt;20 mm/hr, positive C-reactive protein test result, &gt;8,000 leukocytes/mm³, &gt;70% neutrophils/mm³</td>
</tr>
</tbody>
</table>

*The diagnosis is established by the presence of 2 major criteria plus 2 of the 4 minor criteria.


Hypertrophic osteoarthropathy

Children with chronic disease, especially pulmonary or cardiac disease, can demonstrate clubbing of the terminal phalanges, and have associated periosteal reaction and arthritis. These findings characterize the classic presentation of hypertrophic osteoarthropathy (HOA). HOA...
Bibliography

Laboratory evidence to support the diagnosis of an infectious disease may be based on 1 or more of the following: direct examination of specimens using microscopic or antigen detection techniques, isolation of microorganisms in culture, serologic testing, host gene expression patterns, and molecular detection of an organism, resistance determinant, or virulence factor. Additional important roles of the diagnostic microbiology lab are antimicrobial susceptibility testing to guide in the selection of the most appropriate antimicrobial therapy and supporting hospital infection prevention in the detection and characterization of pathogens associated with nosocomial infections.

SPECIMEN COLLECTION
The success of microbiology cultures, that is, isolation of a pathogen if present, is directly linked to specimen collection techniques. In general, this means collecting the correct specimen type for the disease or condition in question and promptly transporting the specimen to the laboratory for analysis. Although for some conditions swab specimens may be necessary, in general, a swab is a suboptimal specimen. A swab is only able to hold a very small amount of specimen (approximately 100 μL), and using a traditional swab, only a small fraction of organisms that are absorbed onto a swab will be released back into the culture. Flocked swabs, coupled with transport medium, improve organism recovery. However, when possible, fluid or tissue should be submitted to the laboratory for analysis. If anaerobic infection is suspected, the sample should be transported in appropriate medium to preserve viability of anaerobic bacteria. For the recovery of some organism types, such as viruses and Neisseria gonorrhoeae, specific transport media may be required. Considerations specific to the collection of blood cultures will be addressed in the blood culture section.

LABORATORY DIAGNOSIS OF BACTERIAL AND FUNGAL INFECTIONS
Although the scope and availability of molecular methods for detection of bacterial and fungal pathogens is increasing at a rapid pace, the state-of-the-art for the diagnosis of many of these infections is dependent upon microscopic detection of organisms or cultivation of organisms on culture media.

Microscopy
The Gram stain is an extremely valuable diagnostic technique to provide rapid and inexpensive information regarding the absence or presence of inflammatory cells and organisms in clinical specimens. For some specimen types, the presence of inflammatory and epithelial cells is used to judge the suitability of a specimen for culture. For example, the presence of more than 10 epithelial cells per low-power field in a sputum specimen is highly suggestive of a specimen contaminated with oral secretions. In addition, a preliminary assessment of the etiologic agent can be made based upon the morphology (e.g., cocci vs rods) and stain reaction (e.g., Gram-positive isolates are purple; Gram-negative are red) of the microorganisms. However, a negative Gram stain does not rule out infection as 10^4 to 10^5 microorganisms per mL in the specimen are required for detection by this method.

In addition to the Gram stain, many other stains are used in microbiology, both to detect organisms and to help infer their identity. Table 170-1 provides an overview of the most commonly used stains.

Isolation and Identification
The approach to isolation of microorganisms in a clinical specimen will vary depending on the body site and pathogen suspected. For body sites that are usually sterile, such as cerebrospinal fluid, nutrient-rich media such as sheep blood agar and chocolate agar are used to aid in the recovery of fastidious pathogens. In contrast, stool specimens contain abundant amounts of commensal bacteria and thus to isolate pathogens, selective and differential media must be used. Selective media will inhibit the growth of some organisms to aid in isolation of suspect pathogens; differential media rely on growth characteristics or carbohydrate assimilation characteristics to impart a growth pattern that differentiates organisms. MacConkey agar supports growth of Gram-negative rods while suppressing Gram-positive organisms, and a color change in the media from clear to pink distinguishes lactose-fermenting organisms from other Gram-negative rods. Special media, such as Sabouraud dextrose agar and inhibitory mold agar, are used to recover fungi in clinical specimens. Many pathogens, including Bartonella, Bordetella pertussis, Legionella, Mycoplasma, and certain fungal pathogens such as Malassezia furfur, require specialized growth media or incubation conditions. Consultation with the laboratory is advised when these pathogens are suspected.

Once an organism is recovered in culture, additional testing will be performed to identify the isolate. Confirmation of microbial identity has classically been performed using phenotypic tests that rely on the phenotypic properties of an isolate. Some examples include carbohydrate assimilation patterns, indole production, and motility. However, these methods are not able to resolve all organisms to species level and require incubation time. In some instances, sequence based identification, for bacteria usually based on sequence analysis of the bacterial 16S rRNA gene, is used for organism identification (particularly organisms that are difficult to culture).

Matrix-assisted laser desorption-ionization time-of-flight mass spectrometry (MALDI-TOF MS) is a rapid and accurate technique that is based on generating a protein fingerprint of an organism and comparing that fingerprint to a library of known organisms to produce an identification. This method can identify bacteria or yeast growing in culture in a matter of minutes, and the consumable costs for these analyses are minimal.

Blood Culture
The performance of blood cultures is one of the most important functions of the clinical microbiology laboratory. Most blood cultures are performed by collecting blood into bottles of nutrient-rich broth to facilitate the growth of bacteria and yeast. Some blood culture media contain resins or other agents to help neutralize antibiotics that may be present in the patients' blood. Blood culture bottles are then incubated on an automated blood culture incubator that will monitor the blood culture bottle at regular intervals for evidence of growth. Once the instrument detects evidence of microbial growth, it will alarm to
alert the laboratory. Approximately 80% of blood cultures that will ultimately be positive are identified within the 1st 24 hr of incubation. A portion of broth from a blood culture bottle that has signaled positive is then Gram-stained and cultured onto appropriate growth media so that the organism can be isolated and identified. There are numerous pre-analytical variables that can influence the accuracy of blood culture results. In order to facilitate accurate interpretation of a positive blood culture, a minimum of 2 blood cultures drawn from different sites should be collected whenever possible. Growth of an organism that is part of the normal skin flora from a single blood culture raises concern that the isolate resulted from contamination of the culture. To maximize detection of bloodstream infection, up to 4 blood cultures should be collected during a 24 hr period. Proper skin antisepsis is essential prior to blood collection. Chlorhexidine is frequently used for this purpose, but alcohol is also used. If blood is collected through an indwelling line, proper antisepsis prior to collection is also very important. The practice of obtaining blood for culture from intravascular catheters without accompanying peripheral venous blood cultures should be discouraged because it is difficult to determine the significance of coagulase-negative staphylococci and other skin flora or environmental organisms isolated from blood obtained from line cultures. Differential time to positivity of 2 hr or more between paired blood cultures drawn simultaneously from a catheter and peripheral vein is a useful indicator of catheter-related bloodstream infection.

The volume of blood collected is also an important factor in the recovery of bloodstream pathogens, especially as the number of organisms per milliliter of blood in sepsis may be low. The optimal amount of blood to collect from a pediatric patient varies depending on the weight of the child. The Clinical and Laboratory Standards Institute and Cumitech documents provide guidance on the amount of blood that is safe to collect from children of different sizes. Paired collection of aerobic and anaerobic blood culture bottles will result in maximal recovery of pathogens if present.

There are a number of rapid diagnostic assays that can be used directly on positive blood culture broth to identify pathogens commonly associated with bacteremia and some antimicrobial resistance determinants. Most of these rapid diagnostic assays are based on nucleic acid detection techniques. An example of this is the Verigene system, which can identify a number of streptococcal and enterococcal species, as well as mecA and vanA genes, in positive blood culture broth, in approximately 2 hr. MALDI-TOF MS can also be performed on blood culture broth that is positive for growth of microorganisms. These assays can help shorten the interval between a positive blood culture and definitive organism identification, with the goal of early optimization of antimicrobial therapy. Detection of mycobacteria and some filamentous fungi (such as Histoplasma capsulatum and Fusarium) from the bloodstream is maximized using lysis-centrifugation techniques, such as the Isolator system (Wampole, Cranbury, NJ).

**Cerebrospinal Fluid Culture**

Cerebrospinal fluid (CSF) should be transported quickly to the laboratory and then cytocentrifuged to concentrate organisms for microscopic examination. CSF is routinely cultured on blood agar and chocolate agar, which support the growth of common pathogens causing meningitis. If tuberculosis is suspected, cultures for mycobacteria should be specifically requested. Culture of larger volumes of CSF (≥5 mL) significantly improves yield of mycobacteria.

Historically, rapid antigen detection tests for bacterial pathogens such as *Haemophilus influenzae* type b and *Streptococcus pneumoniae* were used to attempt to detect organisms in CSF without the need for culture. These techniques have now been proven to lack sensitivity and, in some cases, specificity. It has been demonstrated that a cyto-spin Gram stain is as sensitive as bacterial antigen tests for detection of microorganisms in CSF. In contrast, the cryptococcal antigen test can be useful when cryptococcal meningitis is suspected. Historically, India Ink preparations were used to detect *Cryptococcus* in CSF,
but this method is insensitive compared to the antigen detection assay.

In the postvaccine era, the epidemiology of infectious meningitis is rapidly changing, and acute bacterial meningitis is now a relatively infrequent event in North America. Many CSF infections are associated with shunts or other hardware, and Propionibacterium and coagulase-negative staphylococci are the organisms most frequently isolated from shunt infections. The laboratory should include media to facilitate the growth of Propionibacterium in CSF specimens received from neurosurgery patients.

Urine Culture

Urine for culture (including colony count) can be obtained by collecting clean-voided midstream specimens, by catheterization, or by suprapubic aspiration. Urine samples collected by placing bags on the perineum are unacceptable for culture because samples are often contaminated. Rapid transport of urine to the laboratory (<2 hr) is imperative, and delay in transport or plating of specimens renders colony counts unreliable. Refrigeration or urine transport devices with boric acid preservative may be used when delay is unavoidable.

The specific colony counts used to define growth in a urine culture as “significant” are somewhat controversial and vary somewhat by laboratory. Urine obtained by suprapubic aspirate is normally sterile, and thus any organism growth is typically considered significant. Urine collected by catheterization is likely to reflect infection if there are ≥10^3 to 10^5 organisms/mL. Clean-voided urine is considered abnormal if ≥10^3 to 10^5 organisms/mL are present.

Genital Culture

N. gonorrhoeae is a fragile organism, and collection and transport in special medium is essential for efficient recovery. Selective agar, such as modified Thayer-Martin medium, should be used to enhance recovery of N. gonorrhoeae in clinical specimens, such as genital, anorectal, and pharyngeal swabs. Antimicrobial resistance is increasing in N. gonorrhoeae, although few clinical laboratories have the ability to perform antimicrobial susceptibility testing for this organism. In pediatric patients, the identification of an organism as N. gonorrhoeae should be confirmed using 2 independent methods.

Specimens for Chlamydia trachomatis culture are obtained by cotton-tipped, aluminum-shafted urethral swabs. Endocervical specimens, using swabs with aluminum or plastic shafts, should be collected by rubbing the swab vigorously against the endocervical wall to obtain as much cellular material as possible. C. trachomatis is an obligate intracellular organism and is cultured by inoculation into cell culture systems, followed by immunofluorescent staining with monoclonal antibody against the organism. Nonculture methods such as enzyme immunoassay (EIA) tests, direct immunofluorescent staining by monoclonal antibodies, and DNA amplification methods are widely used and are more cost-effective than culture.

Although nucleic acid amplification assays (NAAT assays) for N. gonorrhoeae and C. trachomatis are not FDA cleared for use in children, these assays are frequently used in this population to detect these organisms in urine specimens, endocervical and vaginal swabs, and penile swabs. The NAAT assays exhibit superior sensitivity compared to culture-based techniques. Some laboratories take the approach of confirming all NAAT-positive specimens with an alternative NAAT test that detects an alternative genetic target.

Throat and Respiratory Culture

Streptococcal pharyngitis and tonsillitis is a common diagnosis in pediatric patients; vigorous swabbing of the tonsillar area and posterior pharynx can be done to obtain a specimen for detection of group A streptococcus (Streptococcus pyogenes). Rapid antigen detection assays are frequently used when group A streptococci pharyngitis is suspected. Negative rapid antigen assays should be confirmed using culture-based techniques. NAAT assays for detection of group A streptococci are also being used with increasing frequency. Most laboratories screen throat cultures exclusively for the presence of group A streptococci. However, large colony variants of group C and group G streptococci also cause pharyngitis, but are not associated with the same postinfectious sequelae attributed to group A streptococcus; laboratory practices for detecting and reporting group C and group G streptococci are variable and an area of controversy.

In addition to the detection of pathogenic streptococci, the clinical laboratory may query for diphtheria, gonococcal pharyngitis, or infection with Arcanobacterium haemolyticum in throat specimens. The laboratory should be notified if any of these pathogens are suspected to ensure that appropriate methods are used to recover these organisms if present.

Cultures for Bordetella pertussis can be obtained by aspiration or swabbing of the nasopharynx using a Dacron or calcium alginate swab. The aspirate or swab is inoculated onto special charcoal-blood (Regan-Lowe) or Bordet-Gengou media, although molecular assays are now frequently used for detection of B. pertussis in these specimens.

The cause of lower-respiratory-tract disease in children is frequently difficult to confirm microbiologically because of the challenge of obtaining adequate sputum specimens. Gram-stained smears of specimens should be performed to assess the adequacy of sputum samples; specimens with large numbers of epithelial cells (>10 per high-powered field) or with few neutrophils are unsuitable for culture, as there is a lack of correlation between upper respiratory tract flora and organisms causing lower-respiratory tract disease. For patients with cystic fibrosis, special media should be used to detect pathogens important in cystic fibrosis, such as Burkholderia cepacia.

Endotracheal aspirates from intubated patients may be useful if the Gram stain shows abundant neutrophils and bacteria, although pathogens recovered from such specimens might still reflect only contamination from the endotracheal tube or upper airway. Quantitative cultures of bronchoalveolar lavage fluid may be valuable for distinguishing upper respiratory tract contamination from lower tract disease.

If infection with Legionella is suspected, the laboratory should be alerted so that the specimen can be inoculated to special media (such as buffered charcoal yeast extract agar) to facilitate the recovery of this pathogen. The Legionella urinary antigen test is a sensitive and specific, noninvasive method for rapid detection of Legionella pneumophila serogroup 1.

The diagnosis of pulmonary tuberculosis in young children is best made by culture of early-morning gastric aspirates, obtained on 3 consecutive days. Sputum induction for obtaining specimens for mycobacterial culture has also proved useful in young children but requires skilled personnel and containment facilities to prevent exposure of healthcare workers. Cultures for Mycobacterium tuberculosis should be processed only in laboratories equipped with appropriate biologic safety cabinets and containment facilities. NAAT tests for detection of M. tuberculosis in smear-positive respiratory specimens are becoming more widely available.

Detection of Enteric Pathogens

In pediatric patients with diarrheal illnesses, culture of stool for enteric pathogens may be requested. A fresh stool specimen is preferred, but is not always possible to obtain. If there is an unavoidable delay in specimen transport, the specimens should be placed into an appropriate transport medium, such as Cary-Blair. Rectal swabs for enteric culture are also acceptable specimens if the swab is visibly soiled. In general, enteric cultures should be performed on specimens from outpatient patients who have been hospitalized for fewer than 3 days, as nosocomial acquisition of an enteric pathogen is very unusual.

Stool specimens are typically plated on a series of selective and differential media to decrease the overgrowth of normal flora and recover pathogenic organisms if present. The specific pathogens queried vary by laboratory. Most laboratories in North America will routinely culture for Salmonella, Shigella, Campylobacter, and Shiga toxin–producing strains of Escherichia coli. The CDC recommends that all laboratories use an agar-based medium for recovery of E. coli O157 in addition to an assay for detection of Shiga toxin production for all specimens submitted for enteric culture. Practices surrounding the routine culture for Yersinia enterocolitica, Vibrio cholerae, Edwardsiella, Aeromonas, and Plesiomonas will vary with local epidemiology, and the
laboratory should always be notified if one of these pathogens is specifically suspected.

Clostridium difficile is an important cause of antibiotic-associated diarrhea. C. difficile was long characterized as a nosocomial pathogen of older adults, but community-associated disease is emerging and the incidence and severity of C. difficile infection in children is increasing. Although for many years laboratories relied on EIAs for detection of C. difficile toxins, these assays lack adequate sensitivity. Laboratories use nucleic acid detection methods to aid in the diagnosis of C. difficile. Testing for C. difficile in children <1 yr of age should be discouraged as a result of the high incidence of colonization in this patient population.

Viruses are an important cause of gastroenteritis in pediatric patients. Methods for viral detection will vary but may include antigen detection (e.g., for rotavirus or adenovirus 40/41) or nucleic acid detection methods (such as for norovirus).

In North America, the burden of parasitic gastroenteritis is low. Complete microscopic exams for ova and parasite detection in stool samples is usually of low yield, and antigen detection assays for Cryptosporidium and Giardia, the most commonly encountered agents, are a sensitive and cost-effective method for detection of these pathogens.

Multiplex nucleic acid detection tests for simultaneous detection of a dozen or more enteric pathogens, including bacteria, viruses, and parasites are emerging. It is not completely clear how these assays will be deployed by clinical laboratories.

**Culture of Other Fluids and Tissues**

Abscesses, wounds, pleural fluid, peritoneal fluid, joint fluid, and other purulent fluids are cultured onto solid agar and, in some cases, broth media. Whenever possible, fluid rather than swabs from infected sites should be sent to the laboratory, because culture of a larger volume of fluid can detect organisms present in low concentration. Anaerobic organisms are involved in many abdominal and wound abscesses. These specimens should be collected and transported to the laboratory rapidly in anaerobic transport tubes.

Although Staphylococcus aureus is the most common cause of bone and joint infections, Kingella kingae is an important cause of septic arthritis in children, especially in children <4 yr of age. The detection of K. kingae is maximized by inoculation of synovial fluid into blood culture broth in addition to plating on solid medium, as well as by molecular detection of K. kingae in specimens from young patients with suspected septic arthritis.

**Screening Cultures**

Clinical laboratories may perform surveillance cultures for specific pathogens either to assist infection control in identifying patients requiring contact isolation or for outbreak investigation. Screening cultures for detection of methicillin-resistant S. aureus or vancomycin-resistant enterococci may be routinely performed in certain patient populations. In addition, hospitals with carbapenem-resistant Enterobacteriaceae may screen patients for rectal carriage of these organisms. Chromogenic media are frequently used for this purpose. These media contain proprietary compounds to select for the agent of interest and result in growth of colored colonies to identify pathogens of interest.

**ANTIMICROBIAL SUSCEPTIBILITY TESTING**

Antimicrobial susceptibility tests are generally performed on organisms of clinical significance for which standards and interpretive criteria for susceptibility testing exist. In North America, most laboratories use commercial, automated systems for susceptibility testing. The output from these systems is a minimum inhibitory concentration (MIC) value and interpretation of that value as susceptible, intermediate, or resistant. The next most common technique is Kirby-Bauer disk diffusion, in which a standardized inoculum of the organism is seeded onto an agar plate. Antibiotic-impregnated filter paper disks are then placed on the agar surface. After overnight incubation, the zone of inhibition of bacterial growth around each disk is measured and compared with nationally determined standards for susceptibility or resistance.

A less-commonly used technique is broth or microbroth dilution testing. A standard concentration of a microorganism is inoculated into serially diluted concentrations of antibiotic, and the MIC in μg/mL, the lowest concentration of antibiotic required to inhibit growth of the microorganism, is determined. The E-test is a hybrid of disk diffusion and broth dilution and can be used to determine the MIC of individual antibiotics on an agar plate. It uses a paper strip impregnated with a known continuous concentration gradient of antibiotic that diffuses across the agar surface, inhibiting microbial growth in an elliptic zone. The MIC is read off the printed strip at the point at which the zone intersects the strip. Major advantages of the E-test are reliable interpretation, reproducibility, and applicability to organisms that require special media or growth conditions.

In addition to providing data to guide the treatment of individual patients, laboratories use aggregate susceptibility testing data to generate institution specific antibiogram reports. These reports summarize susceptibility trends for common organisms and can be used to guide empirical therapy prior to the availability of specific susceptibility testing results.

Antimicrobial susceptibility patterns are rapidly changing as microbes evolve new resistance mechanisms. Recommendations for performance standards for antimicrobial susceptibility tests and their interpretation are regularly updated by the Clinical and Laboratory Standards Institute.

**FUNGAL CULTURES**

Special growth media is used to recover fungi, both yeasts and molds, in clinical specimens. As most fungi prefer reduced growth temperatures, and some species grow slowly, fungal cultures are incubated at 30°C (86°F) for 4 wk.

Most yeasts are identified using methods similar to those used for bacteria. In contrast, the identification of filamentous fungi has not changed in nearly a century. The laboratory takes into consideration the growth rate, color, and colony characteristics of an isolate and then prepares the specimen in lactophenol aniline blue for microscopic evaluation. These features in aggregate are used to identify the isolate. In some cases, DNA sequencing is used for fungal identification and MALDI-TOF MS is also emerging for identification of filamentous fungi. All manipulations of filamentous fungi should take place in the biologic safety cabinet to avoid infecting laboratory personnel and prevent laboratory contamination.

Antigen detection assays are also available for some fungal pathogens such as Cryptococcus neoformans and H. capsulatum. Assays to detect galactomannan, a molecule found in the cell wall of Aspergillus, are commercially available and increasingly used to assist in making the diagnosis of invasive aspergillosis in immunocompromised populations.

**POINT-OF-CARE DIAGNOSTICS**

Some assays to detect infections may be performed in the office setting, provided the site is certified as meeting appropriate quality-assurance standards specified by the Clinical Laboratory Improvement Amendments (CLIA) of 1988. These include procedures listed under the category of “provider-performed microscopy” such as wet mounts, potassium hydroxide preparations, pinworm examinations, and urinalysis.

Many pediatric offices perform rapid antigen testing for detection of group A streptococcal pharyngitis. The sensitivity of point of care testing is dependent upon specimen collection technique, the type of kit used and on the concentration of streptococci present in the sample. However, in light of the fact that up to 30% of group A streptococcal rapid antigen tests are falsely negative, it is recommended that all negative results should be confirmed by culture.

Office laboratories licensed to perform waived tests are limited to performing these tests and avoid having to undergo inspections and proficiency testing, although they are still subject to CLIA certification requirements specific to these tests. Gram staining, culture inoculation, and isolation of bacteria are considered moderately to highly complex tests under CLIA specifications. Any office laboratory performing
Gram stains or cultures must comply with the same requirements and inspections for quality assurance, proficiency testing, and personnel requirements as fully licensed microbiology laboratories.

**LABORATORY DETECTION OF PARASITIC INFECTIONS**

Most parasites are detected by microscopic examination of clinical specimens. *Plasmodium* and *Babesia* can be detected in stained blood smears, *Leishmania* can be detected in stained bone marrow smears, and *Entamoeba histolytica*, and *Giardia lamblia* can be detected in stained fecal smears (see Table 170-1). Serologic tests are important in documenting exposure to certain parasites that are not typically found in stool or blood, and thus are difficult to demonstrate in clinical specimens, such as *Trichinella*.

Pinworm is a relatively common parasitic infection in pediatric patients. A diagnosis of pinworm can be made by evaluating a “pinworm prep.” The best time to obtain this specimen is first thing in the morning, before the patient has bathed or had a bowel movement. A piece of clear scotch tape is pressed onto the perianal region of the patient and then the tape is applied to a clear microscope slide. The slide is then examined for recovery of pinworm eggs or worms.

Fecal specimens should not be contaminated with water or urine, because water can contain free-living organisms that can be confused with human parasites, and urine can destroy motile organisms. Mineral oil, barium, and bismuth interfere with the detection of parasites, and specimen collection should be delayed for 7-10 days after ingestion of these substances. Because *Giardia* and many worm eggs are shed intermittently into feces, a minimum of 3 specimens on nonconsecutive days are required to adequately exclude the diagnosis of an enteric parasite. Because many protozoan parasites are easily destroyed, collection kits with appropriate stool preservatives (commonly a 2-vial system with formalin and polyvinyl alcohol fixatives) should be used if delay between time of specimen collection and transport to the laboratory is anticipated.

Ova and parasite examination of fecal specimens includes a wet mount (to detect motile organisms if fresh stool is received), concentration (to improve yield), and permanent staining, such as trichrome, for microscopic examination. *Cryptosporidium*, *Cyclospora*, and *Isospora* are detected by modified acid-fast stain, and microsporidia by a modification of the trichrome stain. In addition, *Cyclospora* and *Isospora* autofluoresce under UV microscopy. The laboratory should be alerted if these parasites are suspected. Detection of certain intestinal parasites, especially *Giardia* and *Cryptosporidium*, can be simplified by using antigen detection tests.

Amebic encephalitis, caused by *Acanthamoeba*, *Balamuthia*, or *Naegleria*, is a rare but devastating and rapidly progressive disease. Special laboratory stains and procedures are required to detect these organisms. The laboratory should be notified if this infection is suspected. Rapid antigen detection tests for *Plasmodium* species are available. The sensitivity and specificity of these tests vary depending on the burden of parasite in the sample, and the specific *Plasmodium* species.

In general, these tests are most sensitive for detecting *Plasmodium falciparum* and least sensitive for detecting *Plasmodium malariae*. These tests are particularly useful for laboratories lacking personnel trained in evaluation of thick and thin smears for malaria, or to provide a rapid preliminary result while awaiting microscopy. All positive and negative rapid malaria assays should be confirmed with blood smear analysis.

*Trichomonas vaginalis* is a sexually transmitted protozoan parasite that can also be transmitted on household fomites. Infected individuals may be asymptomatic or may have mild inflammation or severe inflammation and discomfort. *Trichomonas* may be detected using a wet mount, but this method is insensitive. Rapid antigen assays are available. Culture-based detection or nucleic acid amplification techniques are the most sensitive way to make the diagnosis.

**SEROLOGIC DIAGNOSIS**

Serologic tests are primarily used in the diagnosis of infectious agents that are difficult to culture in vitro or detect by direct examination, such as *Bartonella*, *Francisella*, *Legionella*, *Borreliia* (Lyme disease), *Treponema pallidum*, *Mycoplasmia, Rickettsia*, some viruses (HIV, Epstein-Barr virus [EBV], hepatitis A virus), and parasites (Toxoplasma, *Trichinella*).

Antibody tests may be specific for immunoglobulin (Ig) G or IgM or can measure antibody response regardless of immunoglobulin class. In very general terms, the IgM response occurs earlier in the illness, generally peaking at 7-10 days after infection, and usually disappears within a few weeks, but for some infections (e.g., hepatitis A, West Nile Virus) it can persist for months. The IgG response peaks at 4-6 wk and often persists for life. Because the IgM response is transient, the presence of IgM antibody in most cases correlates with recent infection. Methods for IgM antibody detection are difficult to standardize, however, and false-positive results commonly occur with some tests. The presence of IgG antibody can indicate new seroconversion or past exposure to the pathogen. To confirm a new infection using IgG testing, it is essential to demonstrate either seroconversion or a rising IgG titer. A 4-fold increase in a convalescent titer obtained 3-4 wk following the acute titer is considered diagnostic in most situations. In neonates, interpretation of serologic tests is very difficult because of passive transfer of maternal IgG that can persist for 6-18 mo after birth.

Context is extremely important in the interpretation of serologic findings. Important considerations are the ability of the host to mount an immune response, the background rate of seropositivity (especially for IgG detection assays), and, for some diseases, the antibody titer. In addition, interpretation of some serologic assays, such as those used to diagnose Lyme disease, are problematic because of lack of specificity of the immunoassays. A confirmatory immunoblot (Western blot) is required for all positive and equivocal EIA results for Lyme disease.

**LABORATORY DIAGNOSIS OF VIRAL INFECTIONS**

Viral diseases are extremely important in pediatrics, and diagnostic virology has long been important to pediatric practice, especially in the inpatient setting.

**Specimens**

Specimens for viral diagnosis are selected on the basis of knowledge of the site that is most likely to yield the suspected pathogen. When evaluating patients with acute viral infections, specimens should be collected early in the course of infection when viral shedding tends to be maximal. Swabs should be rubbed vigorously against mucosal or skin surfaces to obtain as much cellular material as possible and sent in viral transport media that contain antibiotics to inhibit bacterial growth. Rectal swabs should contain visible fecal material. “Flocked” swabs have been shown to provide more material for the laboratory with consequent improvement in the performance of diagnostic tests. Fluids and respiratory secretions should be collected in sterile containers and promptly delivered to the laboratory. All specimens should be transported on ice if delay is anticipated. Freezing specimens, especially at −20°C (−4°F), can result in a significant decrease in culture sensitivity. Consultation with the laboratory is recommended, because some commercial diagnostic test kits used by laboratories may require specific collection devices.

Laboratory diagnosis of viral infections may be by electron microscopy, antigen detection, virus isolation in culture, serologic testing, or molecular techniques to detect viral nucleic acids. In the past few years, molecular tests have emerged as the primary methods for detecting viral infections, with some virology laboratories abandoning the use of viral culture altogether. Serologic testing still has a role, especially for arboviral infections such as West Nile, acute EBV infections, HIV, hepatitis, A to C, and diseases of childhood such as measles, rubella, and mumps. Serology is also uniquely useful for defining immunity to specific viral infections.

**Antigen Detection Tests**

Immunofluorescent-antibody (IFA) techniques or other methods, such as EIA, that use antibodies to detect viral antigens directly in clinical specimens to permit rapid identification of viruses, were the mainstay
of the diagnosis of respiratory viral infections but are now being replaced by molecular tests. Smears of cellular material from respiratory secretions stained by immunologic reagents can identify the antigens of respiratory syncytial virus (RSV), adenovirus, influenza A and B viruses, parainfluenza virus types 1-3, and human metapneumovirus within 2-3 hr after the specimen is received. The sensitivity of IFA staining for RSV exceeds that of culture in many laboratories. For influenza A and B, IFA sensitivity approaches that of culture, whereas for parainfluenza viruses and adenoviruses, sensitivity of IFA is lower. Novel influenza strains, such as the one responsible for H1N1 pandemic influenza, may be poorly detected by IFA and other antigen detection techniques and require molecular tests for optimal sensitivity.

Sensitive IFA staining techniques are also commercially available for identifying varicella-zoster virus and herpes simplex virus (HSV). These specific methods have supplanted the Tzanck smear for multicellular giant cells characteristic of varicella-zoster virus or HSV infections. A method for detecting cytomegalovirus (CMV) pp65 antigen in blood of immunocompromised patients is also available but is being replaced by molecular testing. IFA is not useful for detecting viruses in specimens that do not contain an adequate number of infected cells.

Rapid antigen tests usually based on lateral flow immunochromatography have been approved by the FDA for detection of influenzas A and B and RSV. Some of these tests have “waived” status under CLIA, meaning that they can be performed by personnel who are not trained laboratory technologists, with relatively little formal quality control other than controls that are incorporated into the test devices. Some require as little as 10 min to perform. Consequently, these tests can be performed in a doctor’s office or an emergency unit. Sensitivity in children is higher than in adults and is in the range of 50-80%. Rapid antigen tests can be useful in managing patients with acute respiratory infections, provided the caregiver keeps in mind that a negative test does not rule out the presence of a virus such as influenza or RSV does not rule out the presence of concomitant bacterial infection.

In addition to their role in respiratory virus infections, antigen-detection EIA tests are commonly used for the diagnosis of viruses that are difficult to culture, such as rotavirus, enteric adenovirus, and hepatitis B virus. The detection of the p24 antigen of HIV along with HIV antibodies is included in “fourth-generation” EIA tests used for the diagnosis of HIV.

Viral Culture

Viruses require living cells for propagation; the cells used most often are human- or animal-derived tissue culture monolayers, such as human embryonic lung fibroblasts or monkey kidney cells. Historically, in vivo methods such as inoculation of sucking mice were also used, but are rarely used today. Viral growth in susceptible cell culture is usually accomplished by detecting characteristic cytopathic effect that is visible by light microscopy under low magnification in the cultured cells. For some viruses (e.g., influenza, parainfluenza, and mumps viruses), this method is supplemented by hemadsorption, based on the production of virally encoded hemagglutinins on infected cell membranes that cause adherence of erythrocytes to infected cells. The most reliable confirmatory method for viral detection in cell culture involves fluorescein- or enzyme-labeled monoclonal antibody staining of infected cell monolayers. An important technical improvement in respiratory viral cultures is the development of cell culture systems that include more than 1 type of cell (R-Mix, Diagnostic Hybrids/Quidel, San Diego, CA) and employ IFA staining for virus detection. This system provides results in 16-40 hr from the time the specimen is received in the laboratory, compared to 2-10 days for conventional cultures. Cell culture methods are now being steadily replaced by molecular tests, which are faster, may be more sensitive, and have the potential to detect viruses that do not grow readily in cell cultures.

Molecular Diagnostics

Most molecular tests to detect viruses use the polymerase chain reaction (PCR) and other nucleic acid amplification tests. The first application of PCR to become widely accepted was a test to detect HSV DNA in CSF in patients with possible HSV encephalitis. The first FDA-cleared test for this purpose was approved in 2014. Many laboratories still use laboratory-developed tests, whose performance characteristics must be validated as specified by CLIA. The consequence of this situation is that testing is not standardized and the performance characteristics of this testing (sensitivity and specificity) may vary from laboratory to laboratory. At its best, PCR has sensitivity and specificity greater than 95% for HSV encephalitis. PCR is also increasingly used to diagnose mucocutaneous HSV and varicella-zoster virus infections. This testing is more sensitive than virus culture and provides a more rapid turnaround time.

An FDA-cleared test for enterovirus in CSF (GeneXpert, Cepheid, Sunnyvale, CA) provides sensitive detection of enteroviruses with a performance time of approximately 3 hr. Because this testing is simple to perform, some hospital laboratories are able to offer testing at all times, thus maximizing the clinical utility of the test. The parechoviruses, which may cause illnesses similar to those caused by enteroviruses, especially in infants <6 mo of age, must be detected by separate molecular assays. No parechovirus assays are currently approved by the FDA.

FDA-cleared molecular tests for respiratory viruses are increasingly replacing antigen detection and culture. Several FDA-cleared multiplex molecular tests are available for detection of influenza A and B and RSV. As of 2014, 4 multiplex tests that detect larger numbers of respiratory viruses are also available (Table 170-2). Viruses detected by these tests include influenza A and B, RSV, parainfluenza 1-4, human metapneumovirus, adenovirus, rhinovirus/enterovirus, and coronaviruses OC43, 229E, NL63, and OC43. The performance of each test for each of the viral targets must be approved or cleared by the FDA, so the tests vary among one another in the specific virus targets for which they have achieved FDA approval/clearance (Table 170-2). In addition, 1 of the tests (FilmArray) is also cleared for the detection of the bacterial agents B. pertussis, Mycoplasma pneumoniae, and Chlamydia phila pneumoniae. This test is also notable because the performance time is only

<table>
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<th>Table 170-2</th>
<th>Multiplex Assays for the Detection of Respiratory Viruses</th>
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<tr>
<td><strong>TEST</strong></td>
<td><strong>MANUFACTURER</strong></td>
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<tr>
<td>xTag</td>
<td>Luminex, Austin, TX</td>
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<td>FAST</td>
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<tr>
<td>FilmArray</td>
<td>Biofire, Salt Lake City, UT</td>
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<td>eSensor GenMark</td>
<td>GenMark, Salt Lake City, UT</td>
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*Cleared by the FDA as of July, 2013. Other versions that detect additional viruses are available outside of the United States.

1Detects rhinoviruses and enteroviruses but does not distinguish between them.
approximately 1 hr, permitting very rapid turnaround time. A multi-
plex assay for the detection of viruses (norovirus and rotavirus), as well
as important bacterial and parasitic pathogens (xTAG Gastrointestinal
Panel, Luminex, Austin, TX), has been cleared by the FDA and similar
tests are being developed by numerous other companies.

Another important area of application of molecular testing is the
detection of viruses in the blood. FDA-approved assays to detect HIV
and hepatitis C RNAs are essential for the management of these infec-
tions, including the prevention of transmission from mother to infant.
Hepatitis B molecular testing is also increasingly used. In addition,
molecular testing is now widely used for viruses that cause systemic
disease in immunocompromised patients, especially CMV, EBV, HSV,
the BK polyomavirus, and adenovirus. For these viruses, as well as for
HIV and the hepatitisviruses, quantitative testing is required. An FDA-
approved PCR assay for the quantitative measurement of CMV DNA
in plasma is now available. In addition, international standards for
CMV have been developed. This is important because it makes possible
better comparability among different quantitative CMV assays if they
are each referenced to the international standard. Testing for the other
viruses must be carried out using laboratory-developed tests, some-
times with the use of analyte-specific reagents, a class of reagents that
are regulated by the FDA although not incorporated into complete
diagnostic test kits.

Laboratory-developed PCR and other molecular assays are used by
some laboratories for numerous other viruses, including parvovirus
B19; human herpesvirus 6; mumps, measles, and rubella viruses; and
the JC polyomavirus.

Host gene expression patterns in whole blood have been used to
differentiate viral from bacterial infections. This microarray-based
assay may rapidly identify a viral or bacterial profile of host gene
expression reprise, thus greatly shortening the time to diagnosis and
potentially avoiding inappropriate treatment while suggesting indi-
cated therapies.

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From the time of birth, the human infant is exposed to a myriad of microbes found on the mother and in the surrounding environment. Microbes rapidly form assemblages across exposed areas of the body, including the skin and enteral tract. The microbial communities are called the microbiota and make a substantial impact on short- and long-term physiology, including immunologic and metabolic development and function. Together the number of body-associated bacterial cells is estimated to be 10 times greater than the number of human cells in the body. In aggregate, the totality of the microbes, including their microbial genes and environmental interactions, constitute the microbiome, and the microbial genes in the human microbiome are estimated to exceed the number of human genes by at least 100-fold, together making a macroorganism with an inseparable collective physiology. Current evidence indicates that the microbiome evolves over the life span to influence health and disease.

**MEASURING THE MICROBIOME**

Prior knowledge of microbes on and around the human body was based on specific methods to cultivate organisms. Molecular technologies have revolutionized the identification of poorly cultivatable microbes, rare microbes, and microbes in complex communities like those associated with the human body (Fig. 171-1). The development of the polymerase chain reaction and the availability of modern nucleic acid sequencing have improved the sensitivity of detection of many organisms and have also resulted in the discovery of new organisms. Modern sequencing technologies, so-called next-generation sequencing platforms, allow sequencing in high volume and depth, with millions of sequences obtained from a single biologic sample. Three major approaches have utilized next-generation sequencing to understand the composition, diversity, and activity of the microbiome: (1) sequencing species-specific regions of genomes such as ribosomal RNA-encoding tracks and intergenic regions, (2) total DNA sequencing and assembly of sequence fragments into large genome pieces termed metagenomics, and (3) RNA transcript sequencing to decipher the composition and, as a surrogate for functional activity, the transcriptional activity of a microbiome. New bioinformatics tools have allowed the analysis and comparison of the large datasets arising from these methods.

Two additional approaches to measure the microbiome have been rapidly developing as well. First, large-scale measurements of the peptide composition of the microbiota, called proteomics, have been increasingly used to describe the activity of a microbiome sample, as peptides provide information about the composition and function of a microbiome. Second, in a complementary approach called metabolomics, microbiome-derived metabolites are measured using advanced mass spectrometry techniques. Together, proteomics and metabolomics better describe the activity of a microbiome than the nucleotide-sequencing approaches; however, at this point in time, they provide less depth of resolution and specificity of the composition of a microbiome.

Despite the power of these new methodologies to interrogate the microbiome, they do not yet replace cultivation of microbes in many clinical circumstances. Cultivation of organisms still represents the most practical means to differentiate potential pathogenic species from more benign species and to provide key information such as susceptibility to antimicrobials.

**EARLY-CHILDHOOD DEVELOPMENT OF THE MICROBIOME**

In healthy, uncomplicated term deliveries, infants are believed to be sterile until birth. The rupture of the fetal membranes and subsequent delivery is likely the first major exposure to colonizing microbes. Exceptions may be prematurity as a complication of infection of the
fetal membranes and either subclinical or clinical chorioamnionitis, where molecular analyses suggest that in utero exposure to microbes is common. Mode of delivery has a major influence on the early-life microbiome, with vaginally delivered infants becoming acutely colonized with intestinal organisms that reflect the mother’s vaginal tract and infants delivered by cesarian section becoming colonized with intestinal organisms reflective of the maternal skin.

In the term infant delivered by vaginal delivery, the first intestinal microbes, so-called pioneering organisms, include aerobic organisms such as Enterobacteriaceae (e.g., E. coli), Streptococcaceae, and Staphylococcaceae. Some infants have anaerobes in their early colonizing microbiota, including Clostridiaceae and Bacteroidaceae. However, anaerobes are uncommon, likely because of the aerobic environment of the neonatal intestinal tract, the underdeveloped mucus layer, and relatively high intestinal motility. Exclusive breastfeeding has been reported to result in high levels of bifidobacteria and Lactobacillus in the week following the start of feeding. These probiotic organisms have unique capacities to exclude would-be pathogens from colonization by sequestering nutrients and producing antimicrobial factors while stimulating the intestinal epithelium to tighten cellular junctions and express antimicrobial peptides. However, these genera have been notably deficient from some breastfed infant cohorts, particularly within the United States.

The premature infant is more likely to be delivered by cesarian section and will often be colonized with skin-related organisms such as coagulase-negative staphylococci, similar to the term infant delivered through a similar mode of delivery. However, the premature infant may fail to progress through the same stages of expansion and diversification of the microbiome over the 1st wk to mo of life as the term infant. The factors related to the delayed maturation are not fully clear but are predictably related to delayed or limited enteral feeding, normal environmental exposure to the household environment, and exposure to medical interventions such as antimicrobials.

The most significant shift in the intestinal microbiota appears to occur after weaning and the introduction of solid foods. As the infant transitions from breast milk to a solid food diet containing complex plant-derived polysaccharides, the microbiota begins to reshape progressively into a more mature composition beginning to resemble the adult microbiota. A partial transition occurs from aerobic and facultative anaerobes such as streptococci and coliform enterics like E. coli to more strict anaerobes such as Bacteroides spp.; however, more studies are required in large numbers of children to fully understand the developmental stages of maturation and the likeness to the mature, healthy adult state.

Currently, development of the oral and skin microbiomes in childhood is not well understood. Past studies revealed remarkable diversity of the composition of the microbiota within the oral cavity in the presence of full adult dentition, with an estimated 1,000 bacterial species. Even with oral health, there is substantial diversity in the gingiva of different types of teeth, so-called geodiversity, and the diversity changes dramatically with the development of oral disease such as periodontitis. However, the oral microbiome predentition, during tooth eruption and during the transition from primary to secondary dentition is currently poorly understood. Furthermore, the placement and removal of oral hardware for orthodontics is common in childhood and may produce important alterations in the microbiome of the oral cavity.

The adult skin microbiome displays a high degree of geodiversity—differences in composition depending on site and local physiology with major differences in dry and wet skin sites. However, the linkage between skin development in childhood and maturation of the skin microbiome remains a key subject of future study.

Social structure and family interactions likely play a large role in the development of the early life microbiome. Breast milk feeding provides a microbiologic link between mothers and infants, including transmission of probiotic-like organisms such as lactobacilli and bifidobacteria, each of which may have some protective effects including prevention against diarrheal diseases and atopy. Pediatricians have long been aware of the infectious disease risks and benefits of daycare attendance, with examples of shared pneumococcal strains producing otitis media and outbreaks of respiratory syncytial virus infection and associations with reduced atopy, allergy, and possibly asthma. Family contacts are risks for acquisition of methicillin-resistant S. aureus and subsequent disease. Recent studies demonstrate that at least parts of the human microbiome are transmitted between household individuals and domesticated pets such as dogs and cats. For instance, family members share the same strains of E. coli known to produce urinary tract infections in 1 of the household members. There may be differences in the oral microbiota among infants for whom the parents did and did not use the practice of pacifier sucking for cleaning. Thus, development of the microbiome during childhood is a complex process that is just beginning to be understood.

### THE MICROBIOME AND PHYSIOLOGIC DEVELOPMENT

The microbiome has increasingly complex roles in the development of mammalian physiology (Fig. 171-2). These include the development of the enteral tract, the immunologic system, the hematologic system, the metabolic-endocrine system, and the neurologic system. The details of how the microbiome contributes to these developmental processes in humans are still under intense investigation; however, modeling in other mammalian systems predicts that the microbiome will have a critical role.

### Microbiome and Metabolism

Soon after entry into the physical world, the mammalian enteral tract is colonized and the interaction of early pioneering microbes in the enteral tract stimulates the development of the intestinal mucosa. In neonatal and juvenile animal models, delayed or absent intestinal colonization results in incomplete development of the epithelium, flattening of the intestinal crypts, loss of vasculature, and severely reduced enzymatic function, including alkaline phosphatase and glucosidas.

The enteric microbiota has a large number of roles in the physiology of the intestinal tract. In addition to its function in mucosal and systemic immune development as well as development and regeneration of the epithelium, the microbiota plays a role in key aspects of metabolism: (1) the digestion of otherwise indigestible plant polysaccharides; (2) production of vitamins and cofactors; (3) metabolism of xenobiotics, including clinically relevant drugs; and (4) stimulation of local and systemic metabolism, including lipid storage. Germ-free animals lacking the enteric microbiota have limited nutrient extraction and have a failure to thrive phenotype.
Mice born into a sterile environment have been colonized with human fecal microbial communities. Feeding of "humanized" mice diets with and without polysaccharides, akin to the weaning to solid food transition, results in dramatic alterations in central metabolites. “Humanized mice” transitioned from a polysaccharide-rich, low-fat diet to a more “Westernized” diet high in fat and monosaccharides under a blossoming of the phyla Actinobacteria and Firmicutes in the enteric microbiota with a commensurate reduction in Bacteroidetes, similar to observations of increased Firmicutes and reduced Bacteroidetes in obesity.

Common patterns of mature enteric microbiota community composition and predicted function may exist among humans. Sequencing of the fecal microbes from adults across multiple nations revealed 3 common patterns of microbial community compositions, called enterotypes. Significant increases in the proportions of Bacteroides, Prevotella, and Ruminococcus were found as sentinels of the different enterotypes, and these enterotypes could be identified in individuals from multiple continents, including North America, Europe, and Asia. The different enterotypes among infants and children are not well defined, with the possibility that mature, stable enterotypes form in the early postweaning period or after infancy. Breast milk and formula feeding enterotypes have been described, with notable enrichment of enteric Gram-negative bacteria such as E. coli and anaerobic Clostridia spp. among the formula-fed infants.

Microbiome, Inflammation, and Immunity

The organisms that compose the microbiome are critical for early immune programming, the development of immune tolerance, and overall maintenance of immune set points. Cells produce a variety of receptors to recognize microbial ligands, in a process called pattern recognition. In turn, microbes produce intentional and unintentional stimulation of those cellular receptors to activate and repress inflammatory pathways. Classic examples of such regulatory interactions include peptidoglycan on bacteria binding to Toll-like receptor 2 (in complex with Toll-like receptor 3 and Toll-like receptor 6), lipopolysaccharide of Gram-negative bacteria binding to Toll-like receptor 4, and glucans of fungi binding to the dectin receptor. The results of these receptor interactions include the production of chemokines and cytokines, cell differentiation and development, alteration in metabolism, and stimulation of cell death and survival programs, all contingent on the type of cell, the state of the cell, and the magnitude of stimulation.

Microbial stimulation of these microbial recognition systems is so critical in development that animals raised in the absence of microbes have diminished innate immune responses such as antimicrobial peptides at mucosal surfaces, dysregulated proinflammatory and immunologic tolerance responses, and reduced T- and B-cell populations. Following restoration of normal colonization weeks after being sterile, animals have long-term aberrant cytokine responses with hyperactive proinflammatory responses to stimuli, demonstrating the long-lasting consequences of altering early microbial acquisition. Different early life colonization patterns also correlate with long-term immune development. In a Scandinavian study, children with persistent early life E. coli colonization had higher sustained memory B-cell (CD3+CD20+CD27+) levels by 1.5 yr of life compared to children with lower levels of E. coli colonization, even despite abundant colonization with prototypical probiotic bacteria Lactobacillus spp.

Microbiome-Neurobiologic Connections

Emerging studies are demonstrating a gut–brain axis that may be altered by the composition and activity of the enteric microbiome. Investigations in animal models have shown that the microbiome alters the hypothalamic-pituitary-adrenal system. Germ-free mice have exaggerated stress–anxiety behavior accompanied by elevated corticosterone and adrenocorticotropic levels compared with conventionally colonized, pathogen-free mice. Functional MRI has shown that the ingestion of 5 strains of probiotic-like bacteria alters brain activity in humans, resulting in decreased brain responses to emotional attention tasks in sensory and emotional input regions of the brain. Although the mechanism underlying these changes can only be inferred, the tractus solitarius and thus the vagus nerve appear to mediate the enteral tract–brain connection.

Another mechanism through which the enteric microbiome may alter brain activity is by the metabolites it produces. Administration of fermented milk with probiotic like organisms, most notably Bifidobacterium animals subsp. lactis, to monozygotic human twins and to mice did not dramatically change the intestinal microbiome composition but did alter its transcriptional profiles, with a shift to increased carbohydrate fermentation to fatty acids, thought to attenuate sad emotional behavior in humans.

CONTRIBUTIONS OF MICROBIOME TO DISEASE

Studies demonstrate that some microbial communities may act in concert to exert negative health effects, whereas other communities may be restorative or resistant to disease. A number of examples of this concept of altered microbial communities, also termed dysbiosis, are provided in the sections to follow.

Microbiome of Premature Birth

While the etiology of premature birth is multifactorial, inflammatory conditions including subclinical and clinically overt infections of the mother and/or fetus have been proposed to be instigators of premature birth. Inflammatory biomarker profiling highlights this point, as women who proceed to preterm birth have increased angiotensin, interleukin 8, and tumor necrosis factor receptor 1, along with a number of race-specific alterations in additional cytokines and chemokines. Prior work reported that women experiencing preterm birth have increased vaginal colonization with Gardnerella spp. and Lactobacillus crispatus. There may be a lower diversity in microbiota of the posterior vaginal fornix of women experiencing preterm birth. A meta-analysis of early treatment of vaginosis with clindamycin prior to 22 wk of pregnancy demonstrated a reduction in spontaneous preterm birth at <37 wk, consistent with an association between dysbiosis of the pregnancy-associated microbiota and preterm birth.

Traditionally, the amniotic cavity and the fetus have been presumed to be sterile prior to the rupture of the fetal membranes and birth. However, several reports identify evidence for bacterial DNA in meconium with 2 predominant meconium types regardless of mode of delivery: (1) dominated by Enterobacteriaceae, and (2) dominated by Leuconostocaceae, Enterococcaceae, and Streptococcaceae. Furthermore, data indicate that the amniotic fluid in subclinical and clinically apparent chorioamnionitis has evidence of vaginal-derived microbes present, including poorly or noncultivable organisms such as Mycoplasma spp., Ureaplasma spp., Bacteroides spp., Fusobacterium, Neisseria spp., and Leptotrichia amnionii. A correlation exists between the burden of intraamniotic organisms and the degree of prematurity. Microbial invasion of the amniotic space may lead to induction of inflammatory pathways through innate immune microbial pattern recognition receptors such as the Toll-like receptors. The result may be the induction of labor and physiologic stress on the fetus and mother. Exposure to microbial factors may have consequences on lung and intestinal development, setting the stage for postnatal pathologic including necrotizing enterocolitis. Beyond the acute threat to the maternal-fetal dyad, chorioamnionitis may not produce the long-term neurodevelopmental consequences it once was thought to cause, with formerly premature infants born to women with chorioamnionitis having similar cognitive and neuropsychiatric outcomes even to age 18 yr as infants not exposed to chorioamnionitis.

Changes in the Microbiome with Necrotizing Enterocolitis

Necrotizing enterocolitis (NEC) is a devastating disease of the neonatal intestine that disproportionately affects severely premature infants who weigh less than 1,500 g at birth. The pathologic steps in NEC include intestinal inflammation with loss-of-barrier function, microbial invasion of the bowel, and eventual death of the affected bowel. Years of research implicated specific organisms as the cause of NEC in case
series; however, none of the proposed specific etiologies proved to be common to all cases of NEC and, instead, appeared to be the emergent organisms after serious intestinal pathology had ensued.

Contemporarily, a model of dysbiosis of the early life intestinal microbiome has been favored in the pathogenesis of NEC. Epidemiologic studies in very-low-birthweight infants have demonstrated an association of cephalosporins and duration of antibiotic exposure with the development of NEC, consistent with the idea that shifts in the microbiota predispose to or incite NEC. Studies demonstrate decreased diversity of the microbiota preceding and during NEC. The NEC microbiota at the time of clinical symptoms resembles the microbiota 72 hr prior to onset but not the microbiota 1 wk prior to onset of symptoms, suggesting that a shift in the intestinal microbiota begins well in advance of the appearance of NEC. Some differences in early colonization following birth may portend an increased risk for NEC.

**Microbiome and Allergic Disorders**

Given the role of the microbiome in the development and modulation of innate and adaptive immune responses, considerable interest has been given to its role in the development and exacerbation of allergic conditions such as atopic dermatitis.

The microbiome of the skin has been studied prior to, during, and following treatment of flares of atopic dermatitis. Flares result in the loss of diversity of bacteria on the affected area, and treatment induces new diversity. *S. aureus* and *Staphylococcus epidermidis* increase prior to and during atopic flares, whereas *Streptococcus* spp. and *Corynebacterium* spp. increase immediately preceding and during clinical improvement. In mice, oral treatment of infant animals with nonabsorbable antibiotics increases serum immunoglobulin (Ig) E, increases clinical symptoms such as itching, and produces atopic-like features. These data suggest that atopic dermatitis is influenced by the local skin microbiome and more distant microbiomes such as in the intestinal tract, also suggesting why the administration of oral probiotics such as *Lactobacillus* spp. may decrease atopic dermatitis with an accompanying shift in the T-cell Th1/Th2 balance and increased interferon-γ, which are part of immune tolerance.

The respiratory tract is a common site of allergic disease, and infections have long been associated with allergic exacerbations of the respiratory tract. Traditional teaching is that the lower respiratory tract is sterile; however, studies of the airway microbiome in healthy and asthmatic children and adults indicate that this teaching is incorrect. Measured through careful bronchoscopic sampling and cytology brushings, the Airways have a diverse microbiota during good health.

Measurement of the microbiota in the lower respiratory tract of healthy and asthmatic children indicates significant differences. Past culture-based studies indicate that early life colonization of the neonatal respiratory tree by *H. influenzae*, *Moraxella catarrhalis*, and *S. pneumoniae* is associated with an increased risk for childhood asthma. These same organisms also are closely associated with exacerbations of asthma. *M. pneumoniae* has been proposed as a major bacterial inducer of childhood asthma exacerbations when infection is identified. The employment of culture-independent measurements of lower airway microbiota composition (see Fig. 171-1) indicates that children with asthma are more likely to have higher levels of Proteobacteria, including *H. influenzae*, as well as Firmicutes such as *Staphylococcus* spp. and *Streptococcus* spp. Remarkably, healthy children are more likely than age-matched asthmatic children to have lower airway Bacteroidetes, particularly *Prevotella* spp., a group of anaerobic bacteria. The association of healthy Airways with a lower respiratory tree anaerobic bacterial population is surprising because the high oxygen tension environment has been assumed to be toxic to anaerobes. This study indicates that the airway environment is significantly different than previously understood, and the potentially protective attributes of a native health-associated microbiota needs to be studied to determine if these associations are also causal.

**Airway Microbiome of Cystic Fibrosis**

Cystic fibrosis is characterized by progressive airway disease and inflammation with acute exacerbations accompanied by loss of pulmonary function. Cystic fibrosis has long been known to have an age-dependent change in lower airway colonization, which starts in early childhood with *S. aureus* and *H. influenzae* and progressively shifts toward more intrinsically multidrug-resistant organisms, including the notoriously persistent and treatment-refractory bacteria *Pseudomonas aeruginosa* and *B. cepacia* complex. Culture-independent molecular analysis of the lung-associated microbiota in cystic fibrosis has revealed far more complex microbial communities than previously expected and has demonstrated an association with patient age and disease severity. In addition to the presence of a variety of previously unexpected airway organisms such as anaerobes and mycobacteria, disease severity is inversely related to the lower airway microbial community diversity with less advanced disease associated with greater species richness and evenness. In contrast, the loss of diversity, including the shift from less complex microbial communities to those dominated by *P. aeruginosa*, is strongly correlated with disease severity, and levels of *H. influenzae*, the early childhood colonizer, have a negative correlation with disease severity. Although antibiotics decrease the rate of progressive lung function, they also decrease the community diversity, thus suggesting a balance between a diverse microbiota and reducing the dominance of certain organisms such as *P. aeruginosa*.

**Microbiome During Antibiotic-Associated Diarrhea and Clostridium difficile Colitis**

Treatment with oral and parenteral antibiotics results in a rapid and significant alteration of the intestinal microbiota. Studies of normal individuals taking ciprofloxacin demonstrated dramatic but individualized responses to the antibiotic, with significant reductions in bacteria outside the expected spectrum of the antibiotic, emphasizing the intraindependence of microbial community members on one another for their stability in the community as a whole. Furthermore, the response to ciprofloxacin among subjects varied by individual, suggesting different degrees of stability of the microbiota and resilience under stress such as antibiotics. In general, with the exception of some rare members of the community, the community was largely restored within 4 wk after the completion of the antibiotic course.

Some antibiotics, such as amoxicillin-clavulinate, for which antibiotic-associated diarrhea is a well-known adverse event, produce a loss of *Clostridium* and *Bacteroides*, known to be important in the production of short-chain fatty acids (SCFA) and the metabolism of otherwise undigestible carbohydrates. Together, their loss may decrease the metabolic integrity of the intestinal epithelium that uses SCFA for energy while resulting in a high osmotic environment in which fluid is drawn into the intestinal lumen. Antibiotic-associated diarrhea may result from these combined effects.

One of the most serious complications from antibiotic exposure is the development of *C. difficile*-associated diarrhea (CDAD), which has high associated morbidity and even mortality. Microbiologic surveys suggest that *C. difficile* is a common constituent of the developing microbiota early in life with less prevalence over the life span. Over 30% of infants are colonized with *C. difficile* in the 1st mo of life, continuing until approximately 6 mo of age. By 1 yr of age, colonization ranges between approximately 15% and 70% and then declines through to adulthood, when carriage is estimated to be <3%. Although *C. difficile* has been found within the vaginal microbiota of pregnant women, vaginal delivery has not been associated with increased rates of neonatal *C. difficile* colonization, with vaginal and cesarian delivery having rates of colonization at 30% and 37%, respectively. CDAD has been reported to result in 35-45 hospitalizations per 10,000 pediatric admissions among children 1-9 yr of age.

Although the studies have not yet determined how the intestinal microbiome is altered preceding, during, and with resolution of CDAD in children, molecular studies of the intestinal microbiota in adults provide some details of the consequences of CDAD on the intestinal microbiota. Studies employing deep sequencing of stool from individuals with CDAD and *C. difficile* colonization without disease have revealed depletion of certain bacterial genera accompanying the presence of *C. difficile* colonization. These genera include *Blautia,*
Pseudobutyrylribio, Roseburia, Faecalibacterium, Anaerostipes, Subdoligranulum, Ruminococcus, Streptococcus, Dorea, and Coprococcus. The relationship of cause and effect and the events triggering the transition from colonization to symptomatic disease remain unknown. Similar to the studies of antibiotic-associated diarrhea, these studies also demonstrate a reduction in butyrate-producing Clostridium spp., which are proposed to be important for producing butyrate as an energy source for the intestinal epithelium and its robust integrity.

Although antibiotics such as metronidazole and vancomycin have been employed to treat CDAD, traditional treatment does not eliminate recurrent CDAD to the extent that might be expected. To address this problem, fecal transplantation or administration of feces from healthy donors to CDAD recipients is effective in treating CDAD and, more importantly, superior to these antibiotics in reducing the likelihood of recurrent disease. Accompanying clinical resolution is repletion of Bacteroidetes and Clostridium clusters IV and XIVa with a matched decrease in Proteobacteria. Most of the experience with fecal transplantation has been gained from adults with only a single published pediatrics report, although research studies are underway.

Microbiome and Association with Inflammatory Bowel Disease

Crohn disease and ulcerative colitis are chronic inflammatory diseases of the enteric tract and are believed to be the result of the intersection of host susceptibility and a dysbiosis, an alteration in the intestinal microbiota. Twin-twin studies indicate concordance rates in monzygotic twins of 10–15% in ulcerative colitis and 30–35% in Crohn disease, thus demonstrating a genetic component for each disease while highlighting environmental factors that likely induce and drive disease progression. More than 150 single-nucleotide polymorphisms are associated with these diseases, revealing potential defects in handling microbes, including those involved in barrier function, innate immunity, autophagy, adaptive immunity, and metabolism and cellular homeostasis.

In inflammatory bowel disease (IBD), the microbiota undergoes a shift in association with the disease throughout the intestinal tract. Although considerable heterogeneity has been described, IBD is often demonstrated to be accompanied by a decrease in bacteroides, clostridia, bifidobacteria, and Firmicutes. Reciprocally, outgrowths of E. coli and other Enterobacteriaceae are described. Increased sulfatemetabolizers have been described with IBD as well. Antibiotics along with biologic therapies such as antibodies directed at neutralizing tumor necrosis factor have been employed to manage the IBD dysbiosis and inflammatory reaction. Trials of fecal transplantation are underway to determine if a noninflammatory microbiota from a healthy donor may mitigate IBD symptoms and progression.

Microbiome of Obesity

Obesity and the metabolic syndrome are associated with notable changes in the intestinal microbiome in terms of composition and metabolic function, ultimately resulting in greater energy extraction from the diet. “Typical” changes in the microbiome include an increase in the ratio of the phyla Firmicutes : Bacteroidetes. Additional work has indicated that Prevotellaceae, a family within the Bacteroidetes phylum, may be specifically increased with obesity. However, there remains considerable debate about obesity-specific changes in the microbiome, as studies other than those mentioned previously have demonstrated decreased Firmicutes : Bacteroidetes ratios in the fecal microbiota from obese individuals compared to lean controls. Further studies show that proportions of phyla-level groups may be less important than changes in Firmicutes subgroups that produce butyrate, a known fatty acid substrate easily acquired and utilized by the intestinal epithelium, and thus ready calories for the host.

The intestinal microbiome benefits the host in important ways, including enhancing caloric extraction from indigestible substrates such as polysaccharides in the diet. The microbiome produces degradative enzymes to break down these substrates where enzymes with comparable functions, such as some glycosyl hydrolases, are not encoded in the human genome. Molecular studies indicate that the intestinal microbiome may also interact with the intestinal epithelium in such a way as to alter general energy homeostasis and fat storage. For instance, the intestinal microbiome may produce SCFA that, in turn, alter endocrine peptide expression such as glucagon-like peptide 1 and peptide YY, which alter glucose homeostasis and satiety, respectively. Furthermore through the production of SCFA and ketones, the microbiota may alter sympathetic tone. Certain microorganisms are known to suppress others to induce fasting-induced adipose factor (also called angioptin-like protein 4), a lipoprotein lipase inhibitor of intestinal, hepatic, and adipose origins. Colonization with a diverse microbiota suppresses fasting-induced adipose factor expression, and dietary supplementation of a Western diet with Lactobacillus paracasei further suppressed otherwise high fasting-induced adipose factor expression. Mice fed a Western diet developed adiposity, which was transferable to recipient lean mice following transplantation with the obese mice microbiota. Reciprocally, obese mice treated with antibiotics experienced less insulin resistance, lower fasting glycemic indices, and improved glucose tolerance compared to untreated counterparts, further implicating the microbiome in these physiologic changes.

Microbiome During Malnutrition

Malnutrition is a leading cause of morbidity and mortality across the world. In its most severe form, malnutrition may result in kwashiorkor, which is characterized by generalized edema, anorexia, fatty enlarged liver, skin ulcerations, and irritability. Ready-to-use foods are employed to try to restore nutrition in areas with severe food restrictions. Monozygotic and dizygotic twins in Malawi were studied for the alterations in the microbiome in association with moderate to severe malnutrition, including kwashiorkor. Among the twins with discordant degrees of malnutrition on food supplements, the twins with mild preexisting malnutrition had intestinal microbiota that changed significantly over the course of supplementation. In contrast, the twins with preexisting kwashiorkor had microbiota with poor to no change in response to nutritional supplementation. These findings were recapitulated to some extent following transplantation of the twins’ microbiota into previous sterile mice. Those mice receiving the microbiota of Malawian twins with kwashiorkor experienced more dramatic weight loss on a Malawian-type diet and more rapid loss of their weight gain once off ready to use food supplements than did mice transplanted with the feces of more healthy twins. The mice with the transplanted kwashiorkor microbiota had sustained problems with carbohydrate, lipid, and amino acid metabolism despite nutritional supplementation of the Malawian diet. Together these data indicate that severe malnutrition results from the combination of nutritional deficits and a microbiome with altered metabolic capabilities that are not readily restored with contemporary nutritional supplementation treatments.

Therapeutic Manipulation of the Microbiome

Therapeutic manipulation of the microbiome falls into 5 general categories: (1) antimicrobials, (2) prebiotics, (3) probiotics, (4) postbiotics, and (5) fecal transplantation. Brief mention of fecal transplantation was discussed in the sections on C. difficile diarrhea and IBD. Postbiotics are nonviable microbial components or metabolites that may alter the microbiota or produce physiologic changes in the host. Insufficient data exist to warrant a discussion of postbiotic therapeutics here.

Prebiotics

“Prebiotic” is defined as “nondigestible food components that beneficially affect the host by selectively stimulating the growth and/or activity of 1 or a limited number of bacteria in the colon and thereby improving host health.” While antimicrobials deplete portions of the microbiota, prebiotics aim to promote the growth of beneficial organisms such as bifidobacteria and lactobacteria. Typically, prebiotics are carbohydrates such as oligosaccharides that may be selectively metabolized by constituents of the microbiota. They may not only stimulate outgrowth of desirable organisms but also may be catabolized to beneficial end products such as SCFA, which may, in turn, be utilized as
energy substrates by the intestinal epithelium. Prebiotic oligosaccharides are naturally found in breast milk and have been used as supplements to human breast milk and formula.

Administration of prebiotics to term infants has demonstrated the expected outgrowth of bacteria; however, clinically significant benefits from prebiotic supplementation have not been clearly established. Treatment of term infants with fructooligosaccharides increases fecal bifidobacteria but without a change in infant growth, despite some infants having increased SCFA in the fecal mass. A systematic review of the topic provided a similar conclusion.

Preterm infants have low to absent levels of bifidobacteria and lactobacilli in their intestinal tracts, despite full breast milk nutrition. Prebiotic supplementation has been proposed as a means to increase these bacterial populations in the preterm infant intestinal tract. Among the proposed benefits may be a decrease in NEC. However, appropriately powered, randomized trials have not been performed to demonstrate the validity of this hypothesis.

**Probiotics**

Probiotics are viable organisms that have health benefits following administration. Nearly all probiotics are isolates from the human microbiota, although they may not necessarily reside in the individual taking them for therapeutic purposes. Alternatively, probiotics may be administrated to increase the levels of an organism already present within the microbiota. Generally, probiotics have been administrated orally or as vaginal suppositories.

Multiple bacterial and fungal genera and species have been studied for probiotic effects. Common bacterial genera include bifidobacteria, lactobacilli, streptococci, enterococci, and *E. coli*. Fewer nonbacterial organisms, have been studied for probiotic effects. *Saccharomyces boulardii* is related to baker’s yeast (*Saccharomyces cerevisiae*) but was isolated for specific beneficial effects.

These probiotic organisms should not be confused with more pathogenic strains within their genera and species. Most probiotics have been isolated on the basis of being associated with healthy states. For instance, bifidobacteria and lactobacilli are common to breast milk and stool among infants with low rates of diarrheal diseases and allergy. With the exception of individuals with significant immunodeficiencies, severely compromised mucosal barriers, and central line catheters, where many of these organisms may adhere to the catheter plastic with otherwise benign transient translocation from the intestinal tract, these bacterial probiotics have proven to be relatively safe even with the administration of billions of colony forming units. The most common adverse events associated with probiotics include abdominal cramping, nausea, fever, soft stools, flatulence, and taste disturbance.

Although bacterial probiotics have been administered widely to humans, evidence for their efficacy is limited to a small number of conditions. Probiotics have consistently shown efficacy for specific conditions, including antibiotic-associated diarrhea, prevention and reduction of atopy in high risk children, and reductions in duration and recurrence of *C. difficile* infection. Trials indicate a reduction in NEC among preterm infants. Probiotics may reduce the risk for respiratory infections and recurrent UTI while reducing the symptoms and frequency of flares in IBD.

Antibiotic-associated diarrhea is reduced in frequency and duration. Metaanalysis indicated a relative risk of antibiotic-associated diarrhea with probiotic administration of 0.58 (95% confidence interval [CI], 0.05-0.68) among combined studies using *Lactobacillus, Bifidobacterium, Saccharomyces, Streptococcus, Enterococcus, and/or Bacillus*. Administration of combinations of organisms has not generally resulted in greater efficacy.

Metaanalysis specifically for the efficacy of probiotics in decreasing the incidence of CDAD demonstrated moderate evidence for the practice. In an analysis of more than 1,800 trials, including many in the pediatric population, probiotics reduced CDAD by 64% with a relative risk of 0.36 (95% CI, 0.26-0.51). A pediatric subgroup was analyzed across relevant studies, revealing benefit in pediatric patients and a well child subgroup (relative risk 0.37; 95% CI 0.23-0.60). A number of probiotics were used, including different *Lactobacillus* strains and *S. boulardii*.

More than 15 trials have been performed to study the effect of probiotic administration during pregnancy and to infants to prevent atopic dermatitis. Metaanalysis suggests a modest benefit from probiotic administration to prevent the development of atopic dermatitis. Trials have primarily involved the administration of *Lactobacillus rhamnosus*. Studies included administration to the pregnant mother, or the infant, or both. The overall relative risk of 0.79 (95% CI, 0.71-0.88) was generally consistent regardless of the treatment of the mother or child, or both. The duration was generally ≥6 mo; however, duration did not appear to significantly alter the effect. The RR was similar for the prevention of IgE- and non-IgE–associated atopic dermatitis.

*Bibliography is available at Expert Consult*. 
Bibliography


Immunization is one of the most beneficial and cost-effective disease-prevention measures available. As a result of effective and safe vaccines, smallpox has been eradicated, polio is close to worldwide eradication, and measles and rubella are no longer endemic in the United States, although cases of vaccine-preventable diseases, including measles, rubella, and pertussis, continue to occur in the United States. For most diseases of childhood preventable by vaccination, incidence of most vaccine-preventable diseases of childhood has been reduced by ≥99% from the annual morbidity prior to development of the corresponding vaccine (Table 172-1a), with newer vaccines not achieving quite the same percentage decrease (Table 172-1b). An analysis of effective prevention measures recommended for widespread use by the U.S. Preventive Services Task Force reported that childhood immunization received a perfect score, based on clinically preventable disease burden and cost-effectiveness.

Immunization is the process of inducing immunity against a specific disease. Immunity can be induced either passively through administration of antibody-containing preparations or actively by administering a vaccine or toxoid to stimulate the immune system to produce a prolonged humoral and/or cellular immune response. As of 2015, infants, children, and adolescents in the United States routinely are immunized against 16 diseases: diphtheria, tetanus, pertussis, poliomyelitis, H. influenzae type b (Hib) disease, hepatitis A, hepatitis B, measles, mumps, rubella, rotavirus, varicella, pneumococcal disease, meningococcal disease, influenza, and human papillomavirus (HPV) infection.

**PASSIVE IMMUNITY**

Passive immunity is achieved by administration of preformed antibodies to induce transient protection against an infectious agent. Products used include:
- Immunoglobulin (Ig) administered intramuscularly (IM)
- Specific or hyperimmune immunoglobulin preparations administered IM
- Intravenous immunoglobulin (IVIG)
Comparison of 20th Century Annual Morbidity and Current Morbidity: Vaccine-Preventable Diseases

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</tbody>
</table>


1 Haemophilus influenzae type b (Hib) <5 yr of age. An additional 10 cases of Hib are estimated to have occurred among the 185 reports of H. influenzae (<3 yr of age) with unknown serotype.

Specific or hyperimmunoglobulin preparations administered IV
- Subcutaneous (SC) human immunoglobulin, which has been licensed to treat patients with primary immunodeficiencies
- Antibodies of animal origin
- Monoclonal antibodies

Passive immunity also can be induced naturally through transplacental transfer of maternal antibodies (IgG) during gestation. Maternally derived transplacental antibodies can provide protection during an infant's first year of life and longer during breastfeeding. Protection for some diseases can persist for as long as 1 year after birth, depending on the quantity of antibody transferred and the time until levels fall below those considered protective.

The major indications for passive immunity are to provide protection to immunodeficient children with B-lymphocyte defects who have difficulties making antibodies, for people exposed to infectious diseases or who are at imminent risk of exposure where there is not adequate time for them to develop an active immune response to a vaccine, and for people with an infectious disease as part of specific therapy for that disease (Table 172-2).

**Intramuscular Immunoglobulin**

Immunoglobulin is a sterile antibody-containing solution, usually derived through cold ethanol fractionation of large pools of human plasma from adults. Antibody concentrations reflect the infectious disease exposure and immunization experience of plasma donors. Immunoglobulin contains 15–18% protein, is predominantly IgG, and is administered IM. IV use of human intramuscular immunoglobulin is contraindicated. Immunoglobulin is not known to transmit infectious agents, including viral hepatitis and HIV.

The major indications for immunoglobulin are:
- Replacement therapy for children with antibody deficiency disorders
- Measles prophylaxis
- Hepatitis A prophylaxis

For replacement therapy, the usual dose of intramuscular immunoglobulin is 100 mg/kg (equivalent to 0.66 mL/kg) monthly. The usual interval between doses is 2-4 wk depending on trough IgG serum concentrations and clinical response. In practice, IVIG has replaced intramuscular immunoglobulin for replacement therapy. Intramuscular immunoglobulin can be used to prevent or modify measles if administered to susceptible children within 6 days of exposure (usual dose: 0.5 mL/kg of body weight; maximum dose: 15 mL). The recommended dose of IVIG is 400 mL/kg. Data suggest that measles vaccine, if given within 72 hr of measles exposure, will provide protection in some cases. Measles vaccine and immunoglobulin should not be administered at the same time.

Two methods are available for postexposure prophylaxis against hepatitis A. In people 12 mo through 40 yr of age, hepatitis A immunization is preferred over immunoglobulin for postexposure prophylaxis and for protection of people traveling to areas where hepatitis A is endemic. Immunoglobulin may be administered to children <12 mo of age and people >40 yr of age for prophylaxis of hepatitis A and for postexposure prophylaxis for people traveling internationally to hepatitis A–endemic areas (0.06 mL/kg). In children <12 mo of age, adults >40 yr of age, and susceptible children and adults with underlying immunodeficiencies or chronic liver disease, immunoglobulin is preferred over hepatitis A immunization.

The most common adverse reaction to immunoglobulin is pain and discomfort at the injection site and, less commonly, flushing, headache, chills, and nausea. Serious adverse events are rare and include chest pain, dyspnea, anaphylaxis, and systemic collapse. Immunoglobulin should not be administered to people with selective IgA deficiency. Patients with selective IgA deficiency can produce antibodies against the trace amounts of IgA in immunoglobulin preparations and develop reactions after repeat doses. These reactions can include fever, chills,
Infectious Diseases

**Table 172-2 Immunoglobulin and Animal Antisera Preparations**

<table>
<thead>
<tr>
<th>PRODUCT</th>
<th>MAJOR INDICATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immunoglobulin for intramuscular injection</td>
<td>Replacement therapy in primary immunodeficiency disorders</td>
</tr>
<tr>
<td></td>
<td>Hepatitis A prophylaxis</td>
</tr>
<tr>
<td></td>
<td>Measles prophylaxis</td>
</tr>
<tr>
<td>Intravenous immunoglobulin (IVIG)</td>
<td>Replacement therapy in primary immune-deficiency disorders</td>
</tr>
<tr>
<td></td>
<td>Kawasaki disease</td>
</tr>
<tr>
<td></td>
<td>Pediatric HIV infection</td>
</tr>
<tr>
<td></td>
<td>Hypogammaglobulinemia in chronic B-lymphocyte lymphocytic leukemia</td>
</tr>
<tr>
<td></td>
<td>Immune-mediated thrombocytopenia</td>
</tr>
<tr>
<td></td>
<td>Hematopoietic cell transplantation in adults to prevent graft-versus-host disease and infection</td>
</tr>
<tr>
<td></td>
<td>May be useful in a variety of other conditions</td>
</tr>
<tr>
<td>Hepatitis B immunoglobulin (IM)</td>
<td>Postexposure prophylaxis</td>
</tr>
<tr>
<td></td>
<td>Prevention of perinatal infection in infants born to hepatitis B surface antigen-positive mothers</td>
</tr>
<tr>
<td>Rabies immunoglobulin (IM)</td>
<td>Postexposure prophylaxis</td>
</tr>
<tr>
<td>Tetanus immunoglobulin (IM)</td>
<td>Wound prophylaxis</td>
</tr>
<tr>
<td></td>
<td>Treatment of tetanus</td>
</tr>
<tr>
<td>Varicella-zoster immunoglobulin (IM) or IVIG</td>
<td>Postexposure prophylaxis of susceptible people at high risk for complications from varicella</td>
</tr>
<tr>
<td>Cytomegalovirus IVIG</td>
<td>Prophylaxis of disease in seronegative transplant recipients</td>
</tr>
<tr>
<td>Subcutaneous immunoglobulin</td>
<td>Treatment of patients with primary immunodeficiencies</td>
</tr>
<tr>
<td>Vaccinia immunoglobulin (IV)</td>
<td>Prevent or modify serious adverse events following smallpox vaccination caused by vaccinia replication</td>
</tr>
<tr>
<td>Botulism IVIG human</td>
<td>Treatment of infant botulism</td>
</tr>
<tr>
<td>Diphtheria antitoxin, equine</td>
<td>Treatment of diphtheria</td>
</tr>
<tr>
<td>Heptavalent botulinum antitoxin against all 7 (A-G) botulinum toxin types</td>
<td>Treatment of food and wound botulism</td>
</tr>
<tr>
<td>Palivizumab (monoclonal antibody) (IM)</td>
<td>Prophylaxis for infants against respiratory syncytial virus (see Chapter 260)</td>
</tr>
</tbody>
</table>


...and a shock-like syndrome. Because these reactions are rare, testing for selective IgA deficiencies is not recommended.

**Intravenous Immunoglobulin**

IVIG is a highly purified preparation of immunoglobulin antibodies prepared from adult plasma donors using alcohol fractionation and is modified to allow IV use. IVIG is more than 95% IgG, and is tested to ensure minimum antibody titers to *Corynebacterium diphtheriae*, hepatitis B virus, measles virus, and poliovirus. Antibody concentrations against other pathogens vary widely among products and even among lots from the same manufacturer. Liquid and lyophilized powder preparations are available. IVIG does not contain thimerosal.

Not all IVIG products are approved by the FDA for all indications. The major recommended indications for IVIG for which there is approval by the FDA are:

- Replacement therapy for primary immunodeficiency disorders
- Kawasaki disease to prevent coronary artery abnormalities and shorten the clinical course
- Replacement therapy for prevention of serious bacterial infections in children infected with HIV
- Prevention of serious bacterial infections in people with hypogammaglobulinemia in chronic B-lymphocyte leukemia
- Immune-mediated thrombocytopenia to increase platelet count
- Prophylaxis of infection following bone marrow transplantation

IVIG may be helpful for patients with severe toxic shock syndrome, Guillain-Barré syndrome, and anemia caused by parvovirus B19. IVIG is used for many other conditions based on clinical experience. IVIG may be used for varicella postexposure if varicella-zoster immune globulin is not available.

Reactions to IVIG range from 1-15%. Some of these reactions appear to be related to the rate of infusion and can be mitigated by decreasing the rate. Such reactions include fever, headache, myalgia, chills, nausea, and vomiting. More serious reactions rarely have been reported, including anaphylactoid events, thromboembolic disorders, aseptic meningitis, and renal insufficiency. Renal failure occurs mainly in patients with preexisting renal dysfunction.

Specific immunoglobulin preparations are derived from donors with high titers of antibodies to specific agents and designed to provide protection against those agents (see Table 172-2).

**Subcutaneous Immunoglobulin**

Subcutaneous administration of immunoglobulin is safe and effective in children and adults with primary immune deficiency disorders. Smaller doses administered less frequently (weekly) result in less fluctuation of serum IgG concentrations over time. Systemic reactions are less frequent than with IVIG and the most common adverse effects of subcutaneous immunoglobulin are injection-site reactions. There are no data on administration of intramuscular immunoglobulin by the subcutaneous route.

**Hyperimmune Animal Antisera Preparations**

Animal antisera preparations are derived from horses. The immunoglobulin fraction is concentrated using ammonium sulfate, and some products are further treated with enzymes to decrease reactions to foreign proteins. As of 2014, 2 equine antisera preparations are available for humans:

- Diphtheria antitoxin, which can be obtained from the CDC (http://www.cdc.gov/diphtheria/dat.html) and is used to treat diphtheria.
- Heptavalent botulinum antitoxin, which is available from the CDC (770-488-7100) for use in adults with botulism. This product contains antitoxin against all 7 (A-G) botulinum toxin types.

Great care must be exercised before administering animal-derived antisera because of the potential for severe allergic reactions. Due caution includes testing for sensitivity before administration; desensitization, if necessary; and treating potential reactions, including febrile events, serum sickness, and anaphylaxis. For infant botulism, IVIG (BabyBIG), a human-derived antitoxin, is licensed and should be used.

**Monoclonal Antibodies**

Monoclonal antibodies are antibody preparations produced against a single antigen. They are mass-produced from a hybridoma, created by fusing an antibody-producing B lymphocyte with a fast-growing immortal cell such as a cancer cell. Palivizumab is a monoclonal antibody that is used for prevention of severe disease from respiratory syncytial virus among children 24 mo of age and younger with chronic lung disease (also called bronchopulmonary dysplasia), with a history of premature birth or with congenital heart lesions or neuromuscular diseases. The American Academy of Pediatrics (AAP) has
developed specific recommendations for use of palivizumab (see Chapter 260). Respiratory syncytial virus–IVIG, a hyperimmunoglobulin formulated for intravenous administration, is no longer produced in the United States. Monoclonal antibodies also are used to prevent transplant rejection and to treat some types of cancer and autoimmune diseases. Monoclonal antibodies against interleukin 2 and tumor necrosis factor α are being used as part of the therapeutic approach to patients with a variety of malignant and autoimmune diseases.

Serious adverse events associated with palivizumab primarily are rare cases of anaphylaxis and hypersensitivity reactions. Adverse reactions to monoclonal antibodies directed at modifying the immune response, such as antibodies against interleukin 2 or tumor necrosis factor, can be more serious, and include cytokine release syndrome, fever, chills, tremors, chest pain, immunosuppression, and infection with various organisms, including mycobacteria.

ACTIVE IMMUNIZATION

Vaccines are defined as whole or parts of microorganisms administered to prevent an infectious disease. Vaccines can consist of whole inactivated microorganisms (e.g., polio and hepatitis A), parts of the organism (e.g., acellular pertussis, HPV, and hepatitis B), polysaccharide capsules (e.g., pneumococcal and meningococcal polysaccharide vaccines), polysaccharide capsules conjugated to protein carriers (e.g., Hib, pneumococcal, and meningococcal conjugate vaccines), live-attenuated microorganisms (measles, mumps, rubella, varicella, rotavirus, and live-attenuated influenza vaccines), and toxoids (tetanus and diphtheria) (Table 172-3). A toxoid is a modified bacterial toxin that is made nontoxic but is still able to induce an active immune response against the toxin.

Immunizing agents can contain a variety of other constituents besides the immunizing antigen. Suspending fluids may be sterile water or saline but could be a complex fluid containing small amounts of proteins or other constituents derived from the biologic system used to grow the immunobiologic. Preservatives, stabilizers, and antimicrobial agents are used to inhibit bacterial growth and to prevent degradation of the antigen. Such components can include gelatin, 2-phenoxethanol, and specific antimicrobial agents. Preservatives are added to multidose vials of vaccines, primarily to prevent bacterial contamination on repeated entry of the vial. In the past, many vaccines for children contained thimerosal, a preservative containing ethyl mercury. Beginning in 1999, removal of thimerosal as a preservative from vaccines for children was begun as a precautionary measure in the absence of any data on harm from the preservative. This objective was accomplished by switching to single-dose packaging. Vaccines in the recommended schedule for young children that contain thimerosal as a preservative are some preparations of influenza vaccine. The thimerosal content in U.S.-licensed vaccines currently being manufactured can be found at http://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/VaccineSafety/ucm096228.htm#pres. Adjuvants are used in some vaccines to enhance the immune response. In the United States, the only adjuvants currently licensed by the FDA to be part of vaccines are aluminum salts and arsenate (AsO₄), an adjuvant that contains aluminum hydroxide and monophosphoryl lipid A. Vaccines with adjuvants should be injected deeply into muscle masses to avoid local irritation, granuloma formation, and necrosis associated with SC or intracutaneous administration.

Vaccines can induce immunity by stimulating antibody formation, cellular immunity, or both. Protection induced by most vaccines is thought to be mediated primarily by B lymphocytes, which produce antibodies. Such antibodies can inactivate toxins, neutralize viruses and prevent their attachment to cellular receptors, facilitate phagocytosis and killing of bacteria, interact with complement to lyse bacteria, and prevent adhesion to mucosal surfaces by interacting with the bacterial cell surface.

Most B-lymphocyte responses require the assistance of CD4 helper T lymphocytes. These T-lymphocyte–dependent responses tend to induce high levels of functional antibody with high avidity, mature over time from primarily an IgM response to a long-term persistent IgG response, and induce immunologic memory that leads to enhanced responses upon boosting. T-lymphocyte–dependent vaccines, which include protein moieties, induce good immune responses even in young infants. In contrast, polysaccharide antigens induce B-lymphocyte responses in the absence of T-lymphocyte help. These T-lymphocyte–independent vaccines are associated with poor immune responses in children <2 yr of age, short-term immunity, and absence of an enhanced or booster response on repeat exposure to the antigen. With some polysaccharide vaccines, repeat doses actually are associated with reduced responses, as measured by antibody concentrations, compared to 1st doses (i.e., hyporesponsive). To overcome problems of plain polysaccharide vaccines, polysaccharides have been conjugated, or covalently linked, to protein carriers, converting the vaccine to a T-lymphocyte–dependent vaccine. In contrast to plain polysaccharide vaccines, conjugate vaccines induce higher-avidity antibody, immunologic memory leading to booster responses on repeat exposure to the antigen, long-term immunity, and herd protection by decreasing carriage of the organism (Table 172-4). As of 2014 in the United States, there were licensed conjugate vaccines to prevent Hib, pneumococcal, and meningococcal diseases.

Serum antibodies may be detected as soon as 7–10 days after injection of antigen. Early antibodies are usually of the IgM class that can fix complement. IgM antibodies tend to decline as IgG antibodies increase. The IgG antibodies tend to peak approximately 1 mo after vaccination and with most vaccines persist for some time after a primary vaccine course. Secondary or booster responses occur more rapidly and result from rapid proliferation of memory B and T lymphocytes.

Assessment of the immune response to most vaccines is performed by measuring serum antibodies. Although detection of serum antibody at levels considered protective after vaccination can indicate immunity, loss of detectable antibody over time does not necessarily mean susceptibility to disease. Some vaccines induce immunologic memory, leading to a booster or anamnestic response on exposure to the microorganism, with resultant protection from disease. In some instances, cellular immune response is used to evaluate immune status. For some vaccines (e.g., acellular pertussis), there is no accepted serologic correlate of protection.

Live-attenuated vaccines routinely recommended for children and adolescents include measles, mumps, and rubella (MMR); MMR and varicella (MMRV); rotavirus; and varicella. In addition, a cold-adapted, live-attenuated quadrivalent influenza vaccine (LAIV) is available for people 2 through 49 yr of age who do not have conditions that place them at high risk for complications from influenza. Live-attenuated vaccines tend to induce long-term immune responses. They replicate, often similarly to natural infections, until an immune response inhibits reproduction. Most live vaccines are administered in 1 or 2 dose schedules. The purpose of repeat doses, such as a 2nd dose of the MMR or MMRV vaccine, is to induce an initial immune response in people who failed to respond to the 1st dose. Influenza vaccines, including LAIV, are recommended to be administered yearly to provide protection against changes in circulating influenza strains.

The remaining vaccines in the recommended schedule for children and adolescents are inactivated vaccines. Inactivated vaccines tend to require multiple doses to induce an adequate immune response and are more likely to need booster doses to maintain that immunity than live-attenuated vaccines. However, some inactivated vaccines appear to induce long-term immunity, perhaps lifelong immunity, after a primary series, including hepatitis B vaccine and inactivated polio vaccine (IPV).

VACCINATION SYSTEM IN THE UNITED STATES

Vaccine Development

Basic scientific knowledge about an organism, its pathogenesis, and the immune responses thought to be associated with protection are financed primarily through government sponsorship of academic research and research conducted by private industry (Fig. 172-1). Private industry usually assumes the lead role for guiding potential
### Table 172-3 Currently* Available Vaccines in the United States by Type

<table>
<thead>
<tr>
<th>PRODUCT</th>
<th>TYPE</th>
<th>PRODUCT</th>
<th>TYPE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anthrax vaccine adsorbed</td>
<td>Cell-free filtrate of components including protective antigen</td>
<td>Japanese encephalitis vaccine</td>
<td>Inactivated whole virus that is purified</td>
</tr>
<tr>
<td>Bacille Calmette-Guérin (BCG) vaccine</td>
<td>Live-attenuated mycobacterial strain used to prevent tuberculosis in very limited circumstances</td>
<td>Measles, mumps, rubella (MMR) vaccine</td>
<td>Live-attenuated viruses</td>
</tr>
<tr>
<td>Diphtheria and tetanus toxoids and acellular pertussis (DTaP) vaccine</td>
<td>Toxoids of diphtheria and tetanus and purified and detoxified components from Bordetella pertussis</td>
<td>Meningococcal conjugate vaccine against serogroups A, C, W135, and Y (MCV4)</td>
<td>Polysaccharide from each serogroup conjugated to diphtheria toxoid or CRM 197</td>
</tr>
<tr>
<td>DTaP–hepatitis B–inactivated polio vaccine (DTaP-HepB-IPV)</td>
<td>DTaP with hepatitis B surface antigen (HBsAg) produced through recombinant techniques in yeast with inactivated whole polioviruses</td>
<td>Meningococcal conjugate vaccine against serogroups C and Y and Hib conjugate vaccine</td>
<td>Polysaccharide from each serogroup conjugated to diphtheria toxoid and Hib polysaccharide conjugated to tetanus toxoid</td>
</tr>
<tr>
<td>DTaP with IPV and Hib (DTaP-IPV/Hib)</td>
<td>DTaP with inactivated whole polioviruses and Hib polysaccharide conjugated to tetanus toxoid</td>
<td>Meningococcal polysaccharide vaccine against serogroups A, C, W135, and Y (MPSV4)</td>
<td>Polysaccharides from each of the serogroups</td>
</tr>
<tr>
<td>DTaP and inactivated polio vaccine (DTaP-IPV)</td>
<td>DTaP with inactivated whole polioviruses</td>
<td>Pneumococcal conjugate vaccine (13 valent) (PCV13)</td>
<td>Pneumococcal polysaccharides conjugated to a nontoxic form of diphtheria toxin CRM197</td>
</tr>
<tr>
<td>Hib conjugate vaccine (Hib)</td>
<td>Polysaccharide conjugated to either tetanus toxoid or meningococcal group B outer membrane protein</td>
<td>Pneumococcal polysaccharide vaccine (23 valent) (PPSV23)</td>
<td>Pneumococcal polysaccharides of 23 serotypes responsible for 85-90% of bacteremic disease in the United States</td>
</tr>
<tr>
<td>Hepatitis A vaccine (HAV)</td>
<td>Inactivated whole virus</td>
<td>Poliomyelitis (inactivated, enhanced potency) (IPV)</td>
<td>Inactivated whole virus</td>
</tr>
<tr>
<td>Hepatitis A–hepatitis B vaccine (HAV-HBV)</td>
<td>Combined hepatitis A and B vaccine</td>
<td>Rabies vaccines (human diploid and purified chick embryo cell)</td>
<td>Inactivated whole virus</td>
</tr>
<tr>
<td>Hepatitis B vaccine (HBV)</td>
<td>HBsAg produced through recombinant techniques in yeast</td>
<td>Rotavirus vaccines (RVS and RV1)</td>
<td>Bovine rotavirus pentavalent vaccine (RVS) live reassortment attenuated virus, and human live-attenuated virus (RV1)</td>
</tr>
<tr>
<td>Hepatitis B–Hib vaccine (Hib-HBV)</td>
<td>Combined hepatitis B–Hib vaccine; the Hib component is polysaccharide conjugated to meningococcal group B outer membrane protein</td>
<td>Smallpox vaccine</td>
<td>Vaccinia virus, an attenuated poxvirus that provides cross-protection against smallpox</td>
</tr>
<tr>
<td>Human papillomavirus vaccine (bivalent) (HPV2), (quadrivalent) (HPV4), and 9-valent (HPV9)</td>
<td>The L1 capsid proteins of HPV types 6, 11, 16, and 18 to prevent cervical cancer and genital warts (HPV4) and types 16 and 18 to prevent cervical cancer (HPV2); HPV9 also contains types 31, 33, 45, 52, and 58.</td>
<td>Tetanus and diphtheria toxoids, adsorbed (Td, adult use)</td>
<td>Tetanus toxoid plus a reduced quantity of diphtheria toxoid compared to diphtheria toxoid used for children &lt;7 yr of age</td>
</tr>
<tr>
<td>Influenzavirus vaccine inactivated (IIV)</td>
<td>Available either as trivalent (A/H1N1, A/H3N2, and B) split and purified inactivated vaccines containing the hemagglutinin (H) and neuraminidase (N) of each type or as quadrivalent preparations (which include representative strains from 2 B-lymphocyte clades in addition to the 2 influenza A strains in trivalent inactivated influenza vaccine)</td>
<td>Tetanus and diphtheria toxoids adsorbed plus acellular pertussis (Tdap) vaccine</td>
<td>Tetanus toxoid plus a reduced quantity of diphtheria toxoid plus acellular pertussis vaccine to be used in adolescents and adults and in children 7 through 9 yr of age who have not been appropriately immunized with DTaP</td>
</tr>
<tr>
<td>Influenzavirus vaccine live, intranasal (LAIV)</td>
<td>Live-attenuated, temperature-sensitive, cold-adapted trivalent vaccine containing the H and N genes from the wild strains reassorted to have the 6 other genes from the cold-adapted parent, only available as quadrivalent preparation</td>
<td>Typhoid vaccine (polysaccharide)</td>
<td>Vi capsular polysaccharide of Salmonella typhi</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Typhoid vaccine (oral)</td>
<td>Live-attenuated Ty21a strain of S. typhi</td>
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<tr>
<td></td>
<td></td>
<td>Varicella vaccine</td>
<td>Live-attenuated Oka strain</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Yellow fever vaccine</td>
<td>Live-attenuated 17D strain</td>
</tr>
</tbody>
</table>

*As of January 2015.

Data from Centers for Disease Control and Prevention: U.S. vaccine names. [http://www.cdc.gov/vaccines/about/terms/USvaccines.html](http://www.cdc.gov/vaccines/about/terms/USvaccines.html)
vaccine candidates through preclinical testing in humans into human clinical trials. There are 3 phases of prelicensure clinical trials: phase I, generally involving <100 participants to gauge safety and dosing; phase II, involving several hundred or more participants to refine safety and dosing; and phase III or pivotal trials that can involve thousands or tens of thousands of participants. Data from phase III trials form the major basis for licensure. Following successful clinical development, the vaccine sponsor applies to the FDA for vaccine licensure. Estimates for the cost of development for each vaccine range to $800 million or more. Following licensure by the FDA, recommendations for use are made by the Advisory Committee on Immunization Practices (ACIP) and postlicensure monitoring is performed on hundreds of thousands to millions of people to monitor vaccine safety and effectiveness.

Vaccine Production

Vaccine production is primarily a responsibility of private industry. Many of the vaccines recommended routinely for children are produced by only 1 of the vaccine manufacturers. Only Hib, hepatitis B, HPV, rotavirus, MCV4 (meningococcal conjugate vaccine against serogroups A, C, W135, and Y), diphtheria and tetanus toxoids and acellular pertussis (DTaP), and tetanus and diphtheria toxoids and acellular pertussis (Tdap) vaccines for adolescents and adults have multiple manufacturers. IPV as an IPV-only vaccine has only 1 manufacturer, but IPV also is available in combination products DTaP–hepatitis B–IPV, DTaP–IPV/Hib, and DTaP–IPV from different manufacturers. Influenza vaccine for children 2 yr of age or younger is produced by fewer manufacturers (see http://www.cdc.gov/flu/protect/vaccine/vaccines.htm for available influenza vaccines). MMR, MMRV, varicella, pneumococcal conjugate vaccine (13 valent) (PCV13), and tetanus and diphtheria (Td) vaccines also are produced by single manufacturers.

**Vaccine Policy**

There are 2 major committees that make vaccine policy recommendations for children: the Committee on Infectious Diseases (COID) of the AAP (the Red Book Committee) and the ACIP of the CDC. Annually, the AAP, the ACIP, and the American Academy of Family Physicians issue a harmonized childhood and adolescent immunization schedule (http://www.cdc.gov/vaccines/schedules/index.html). The COID consists primarily of academic pediatric infectious disease specialists with liaisons from practicing pediatricians, professional organizations, and government agencies including the FDA, CDC, National Institutes of Health, and National Vaccine Program Office. Recommendations of the COID must be approved by the AAP Board of Directors. The ACIP consists of 15 voting members who are academic infectious disease experts (for both children and adults), family physicians, state and local public health officials, nurses, and 1 consumer representative. The ACIP also has representatives from 29 liaison organizations, including major medical societies, professional organizations, managed care, and others, as well as 8 ex officio government entities that deal with vaccines. Only ACIP members vote on vaccine recommendations. Since October 2011, the ACIP has used the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) process to develop evidence-based vaccine recommendations. The ACIP recommendations, available at http://www.cdc.gov/vaccines/acip/recs/index.html, are official only after adoption by the CDC director, which leads to publication in the Morbidity and Mortality Weekly Report (MMWR Morb Mortal Wkly Rep). The AAP recommendations are published in the Red Book and in issues of Pediatrics.
Vaccine Financing

Approximately 50% of vaccines routinely administered to children and adolescents <19 yr of age are purchased through a contract negotiated by the federal government with licensed vaccine manufacturers. There are 3 major sources of funds that can purchase vaccines through this contract.

The greatest portion comes from the Vaccines for Children (VFC) program (http://www.cdc.gov/vaccines/programs/vfc/index.html), a federal entitlement program established in 1993. The VFC program covers children on Medicaid, children without any insurance (uninsured), and Native Americans and Alaska Natives. In addition, children who have insurance but whose insurance does not cover immunization (underinsured) can be covered through VFC but only if they go to a federally qualified health center (http://www.cms.gov/center/fqhc.asp). In contrast to other public funding sources that require approval of discretionary funding by legislative bodies, VFC funds are immediately available for new recommendations provided the ACIP votes the vaccine and the recommendation for its use into the VFC program, the federal government negotiates a contract, and the Office of Management and Budget apportions funds. The VFC program can provide free vaccines to participating private providers for administration to children eligible for coverage under the program.

The second major federal funding source is the Section 317 Discretionary Federal Grant Program to states and selected localities. These funds must be appropriated annually by Congress, but in contrast to VFC, they have not had eligibility requirements for use. The third major public source of funds is state appropriations. The VFC program itself does not cover vaccine administration costs. Medicaid covers the administration fees for children enrolled in that program. Parents of other children eligible for VFC must pay administration fees out of pocket, although there is a stipulation in the law that no one eligible for the program can be denied vaccines because of inability to pay the administration fee. The Affordable Care Act states that all vaccines recommended by ACIP and included in the immunization schedules must be provided by qualified insurance programs with no copay and no deductible.

Vaccine Safety Monitoring

Monitoring vaccine safety is the responsibility of the FDA, CDC, and vaccine manufacturers. A critical part of that monitoring depends on reports provided to the Vaccine Adverse Event Reporting System. Adverse events following immunization can be reported by completing a Vaccine Adverse Event Reporting System form that can be obtained from http://www.vaers.hhs.gov, or by calling 1-800-822-7967. Individual Vaccine Adverse Event Reporting System case reports may be helpful in generating hypotheses about whether vaccines are causing certain clinical syndromes, but in general they are not helpful in evaluating the causal role of vaccines in the adverse event. This is because most clinical syndromes that follow vaccination are similar to syndromes that occur in the absence of vaccination, which constitute background rates. For causality assessment, epidemiologic studies are often necessary, comparing the incidence rate of the adverse event after vaccination with the rate in the unvaccinated. A statistically significant higher rate in the vaccinated would be consistent with causation.

The Vaccine Safety Datalink consists of inpatient and outpatient records of some of the largest managed-care organizations in the United States and facilitates causality evaluation. In addition, the clinical immunization safety assessment network has been established to advise primary care physicians on evaluation and management of adverse events (http://www.cdc.gov/vaccinesafety/Activities/CISA.html).

The Institute of Medicine (IOM) has reviewed independently a variety of vaccine safety concerns and published reports (available at http://www.iom.edu/Reports.aspx?Search=vaccine%20safety) summarizing its findings. From 2001 through 2004, the IOM released 8 reports concluding that the body of epidemiologic evidence did not show an association with vaccines and autism. In 2011, the IOM released a report entitled “Adverse Effects of Vaccines: Evidence and Causality” (http://www.iom.edu/Reports/2011/Adverse-Effects-of-Vaccines-Evidence-and-Causality.aspx), in which the IOM Committee reviewed a list of reported adverse effects associated with 8 vaccines to evaluate the scientific evidence, if any, of an event–vaccine relationship. For the purposes of the report, the committee developed 158 causality conclusions and assigned each relationship between a vaccine and an adverse health problem to 1 of 4 causation categories. The committee concluded that available evidence convincingly supported a causal relationship between MMR, varicella-zoster, influenza, hepatitis B, meningococcal, and tetanus-containing vaccines and anaphylaxis. Additionally, evidence favored rejection of a vaccine–adverse event relationship, including MMR vaccine and autism, inactivated influenza vaccines and asthma episodes, as well as Bell palsy, and MMR and DTap and type 1 diabetes mellitus. For the majority of cases (135 vaccine–adverse event pairs), the evidence was inadequate to accept or reject a causal relationship because of rarity of the events. Overall, the committee concluded that few health problems are caused by or clearly associated with vaccines.

In 2013, the IOM released a report entitled “Childhood Immunization Schedule and Safety: Stakeholder Concerns, Scientific Evidence, and Future Studies” (http://www.iom.edu/Reports/2013/The-Childhood-Immunization-Schedule-and-Safety.aspx). The IOM committee uncovered no evidence of major safety concerns associated with adherence to the recommended childhood immunization schedule. For more information on IOM reports, see http://www.iom.edu/.

The National Vaccine Injury Compensation Program, established in 1988, is designed to compensate people injured by vaccines in the childhood and adolescent immunization schedule. The program is funded through an excise tax of $0.75 per disease prevented per dose. As of 2013, all of the routinely recommended vaccines that protect children against 16 diseases are covered by this program. The National Vaccine Injury Compensation Program was established to provide a no-fault system. There is a table of related injuries and time frames. All people alleging injury from covered vaccines must first file with the program. If the injury meets the requirements of the table, compensation is automatic. If not, the claimant has the responsibility to prove causality. If compensation is accepted, the claimant cannot sue the manufacturer or physician administering the vaccine. If the claimant rejects the judgment of the compensation system, the claimant can enter the tort system, which is uncommon. Information on the National Vaccine Injury Compensation Program is available at http://www.hrsa.gov/vaccinecompensation, or by calling 1-800-338-2382. All physicians administering a vaccine covered by the program are required by law to give the approved Vaccine Information Statement to the child’s parent or guardian at each visit before administering vaccines. Information on the Vaccine Information Statement can be obtained from http://www.cdc.gov/vaccines/hcp/vis/index.html.

Vaccine Delivery

To ensure potency, vaccines should be stored at recommended temperatures before and after reconstitution. A comprehensive resource for providers on vaccine storage and handling recommendations and best practice strategies is available at http://www.cdc.gov/vaccines/recs/storage/default.htm. Expiration dates should be noted, and expired vaccines should be discarded. Lyophilized vaccines often have long shelf lives. However, the shelf life of reconstituted vaccines generally is short, ranging from 30 min for varicella vaccine to 8 hr for MMR vaccine.

All vaccines have a preferred route of administration, which is specified in package inserts and in AAP and ACIP recommendations. Most inactivated vaccines, including DTap, hepatitis A, hepatitis B, Hib, inactivated influenza vaccine (IIV), HPV, PCV13, MCV4, and Tdap, are administered IM. In contrast, MPV54 and the commonly used live-attenuated vaccines, MMR, MMRV, and varicella, should be dispensed by the SC route and rotavirus vaccine is administered orally. IPV and PPS23 (pneumococcal polysaccharide vaccine) can be given IM or SC. One influenza vaccine, LAIV, is administered intranasally, and another influenza vaccine by the intradermal route. For IM injections, the anterolateral thigh muscle is the preferred site for infants and young children. The recommended needle length varies depending on
age and size: \( \frac{3}{8} \) inch for newborn infants, 1 inch for infants 2 through 12 mo of age, and 1-1.25 inches for older children. For adolescents and adults, the deltoid muscle of the arm is the preferred site for IM administration with needle lengths of 1-1.25 inches depending on the size of the patient. Most IM injections can be made with 23-25 gauge needles. For SC injections, needle lengths generally range from \( \frac{3}{8} \) to \( \frac{1}{2} \) inches with 23-25 gauge needles.

Other areas dealing with various aspects of immunization are important for pediatricians and other healthcare providers. Table 172-5 lists websites providing information in these areas.

**RECOMMENDED IMMUNIZATION SCHEDULE**

All children in the United States should be vaccinated against 16 diseases (Figs. 172-2 and 172-3) (annually updated schedule available at [http://www.cdc.gov/vaccines/schedules/index.html](http://www.cdc.gov/vaccines/schedules/index.html)).

Hepatitis B vaccine is recommended in a 3 dose schedule starting at birth. The birth dose, as well as hepatitis B immunoglobulin, is critical for infants born to mothers who are hepatitis B surface antigen (HBsAg)–positive or whose hepatitis B immune status is unknown, but the recommendation is to administer hepatitis B vaccine to all newborns before hospital discharge.

The DTaP series consists of 5 doses administered at 2, 4, 6, and 15 through 18 mo of age, and 4 through 6 yr of age. The 4th dose of DTaP may be administered as early as 12 mo of age, provided 6 mo has elapsed since the 3rd dose. The 5th (booster) dose of DTaP vaccine is not necessary if the 4th dose was administered at 4 yr of age or older. One dose of an adult preparation of Tdap is recommended for all adolescents at 11 through 12 yr of age. Adolescents 13 through 18 yr of age who missed the 11 through 12 yr of age Tdap booster dose should receive a single dose of Tdap if they have completed the diptheria, tetanus, and pertussis (DTP)/DTaP series. Tdap may be given at any interval following the last Td. Table 172-6 lists preparations in which DTaP is combined with other vaccines.

There are 3 licensed preparations of single-antigen Hib vaccines. The vaccine conjugated to tetanus toxoid (PRP-T) is given in a 4 dose series at 2, 4, 6, and 12 through 15 mo of age, and the Hib vaccine conjugated to meningococcal outer membrane protein (PRP-OMP) is recommended in a 3 dose series at 2, 4, and 12 through 15 mo of age. The 3rd Hib vaccine is licensed as a booster for children 15 mo through 4 yr of age. There are several vaccines in which Hib is a component, in addition to single-antigen Hib conjugate vaccines (Table 172-7).

Influenza vaccine is recommended for all children beginning at 6 mo of age, with a minimum age of 6 mo for IIVs and 24 mo of age for LAIVs. Various influenza vaccine preparations are FDA licensed for different age groups (see [http://www.cdc.gov/flu/protection/vaccine/vaccines.htm](http://www.cdc.gov/flu/protection/vaccine/vaccines.htm) and [http://aapredbook.aappublications.org/site/news/vaccstatus.xhtml](http://aapredbook.aappublications.org/site/news/vaccstatus.xhtml)). Children 6 mo of age through 8 yr of age being vaccinated for the first time should receive 2 doses at least 4 wk apart. If such children only received a single dose of IIV the prior season, they need 2 doses the following season. For additional guidelines, follow dosing instructions in the influenza statement, which is updated annually by the CDC. Influenza vaccine usually is given in October or November, although there are benefits even when administered as late as February or March because influenza seasons most commonly peak in February. People 9 yr of age and older should receive 1 dose of influenza vaccine annually.

IPV should be administered at 2, 4, and 6 through 18 mo of age with a booster dose at 4 through 6 yr of age. The final dose in the series should be administered on or after 4 yr of age and at least 6 mo after the previous dose. The final dose in the IPV series should be administered at 4 yr of age or older regardless of the number of previous doses, and the minimal interval from dose 3 to dose 4 is 6 mo. For catch-up vaccine recommendations, see the recommended childhood immunization schedule at [http://www.cdc.gov/vaccines/schedules/hcp/imz/catchup.html](http://www.cdc.gov/vaccines/schedules/hcp/imz/catchup.html).

MMR should be administered at 12 through 15 mo of age followed by a 2nd dose at 4 through 6 yr of age. Two doses of varicella vaccine should be given, the 1st at 12 through 18 mo of age and the 2nd at 4 through 6 yr of age. MMR and MMRV preparations are available. The quadrivalent MMRV vaccine is preferred in place of separate MMR and varicella vaccines at the 4 through 6 yr old visit. Because of a slight increase in febrile seizures associated with combined MMRV vaccine compared to the separate products, use of MMRV is not preferred over use of separate MMR and varicella vaccines for the initial dose at 12 through 15 mo of age.

Protection against pneumococcal and meningococcal disease can be provided by either conjugated or polysaccharide vaccines. Conjugated vaccines offer several benefits over polysaccharide vaccines (see Table 172-4). PCV13 is recommended as a 4 dose series at 2, 4, 6, and 12 through 15 mo of age. For children 14 through 59 mo of age who have received an age-appropriate series of PCV7, administer a single supplemental dose of PCV13. PPSV23 is recommended for select children with conditions that place them at risk for pneumococcal disease.

A 2 dose series of MCV4 includes a recommended dose for all adolescents at 11 through 12 yr of age and a booster dose at 16 yr of age. If the 1st dose is administered at 13 through 15 yr of age, a booster dose should be administered at 16 through 18 yr of age. No booster dose is needed if the 1st dose is administered at 16 yr of age. In addition, MCV4 should be administered to people 2 mo through 55 yr of age with underlying conditions that place them at high risk of meningococcal disease. People with high-risk conditions should receive 2 doses of MCV4 at 0 and 2 mo followed by booster doses.

Hepatitis A vaccine, licensed for administration to children 12 mo of age and older, is recommended for universal administration to all children at 12 through 23 mo of age and for certain high-risk groups. The 2 doses in the series should be separated by at least 6 mo. Children who have received 1 dose of hepatitis A vaccine before 24 mo of age should receive a 2nd dose 6-18 mo after the 1st dose. For anyone 2 yr of age or older who has not yet received the 2 dose hepatitis A vaccine series, 2 doses of vaccine separated by 6-18 mo may be administered if immunity against hepatitis A infection is desired.

Administer a 3 dose series of HPV vaccine to all adolescents 11 through 12 yr of age. Either HPV4 or HPV2 is recommended in a 3 dose series to females, and only HPV4 in the same schedule is recommended for males. The vaccine series can be started at 9 yr of age. Administer the 2nd dose at 1-2 mo after the 1st dose, and the 3rd dose 6 mo after the 1st dose (at least 24 wk after the 1st dose).

Two rotavirus vaccines are available, RotaTeq (RV5) and Rotarix (RV1). With both vaccines, the 1st dose can be administered as early as 6 wk of age and must be administered by 14 wk 6 days. The final dose in the series must be administered no later than 8 mo of age. The RV5 vaccine is administered in 3 doses at least 4 wk apart. The RV1 vaccine is administered in 2 doses at least 4 wk apart. Immunization should not be initiated for infants 15 wk of age and older as stated in the immunization schedule.

The present schedule, excluding influenza vaccine, can require as many as 34 doses, including 31 that must be administered by injection. Of the doses, 25 are recommended prior to 2 yr of age, including 22 injections. Influenza vaccination, starting at 6 mo of age, can add an additional 20 injections through 18 yr of age. To reduce the injection burdens, several combination vaccines are available (see Table 172-7).

The recommended childhood and adolescent immunization schedule establishes a routine adolescent visit at 11 through 12 yr of age. MCV4, a Tdap booster, and HPV vaccine should be administered during this visit. Influenza vaccine should be administered annually. In addition, the 11 through 12 yr old visit is an opportune time to review all of the immunizations the adolescent has received previously, to provide any doses that were missed, and to review other age-appropriate preventive services. The 11 through 12 yr old visit establishes a critical platform for incorporating other vaccines. Information on the current status of new vaccine licensure and recommendations for use can be obtained at [http://aapredbook.aappublications.org/site/news/vaccstatus.xhtml](http://aapredbook.aappublications.org/site/news/vaccstatus.xhtml) and [http://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM093833](http://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM093833).

For children who are at least 1 mo behind in their immunizations, catch-up immunization schedules are available for children 4 mo

Text continued on p. 1254
**Table 172-5  Vaccine Websites and Resources**

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<th>WEBSITE</th>
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<td>American Academy of Family Physicians (AAFP)</td>
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<td>Every Child by Two (ECBT)</td>
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<td>Families Fighting Flu</td>
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<td>Global Alliance for Vaccines and Immunization (GAVI)</td>
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<td>Health on the Net Foundation (HON)</td>
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<td>Infectious Diseases Society of America (IDSA)</td>
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<td>Institute for Vaccine Safety (IVS), Johns Hopkins Bloomberg School of Public Health</td>
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Figure 172-2 Recommended immunization schedule for persons aged 0 through 18 years—United States, 2015. (From Centers for Disease Control and Prevention. Available at: http://www.cdc.gov/vaccines/schedules/hcp/imz/child-adolescent.html)

This schedule includes recommendations in effect as of January 1, 2015. Any dose not administered at the recommended age should be administered at a subsequent visit, when indicated and feasible. The use of a combination vaccine generally is preferred over separate injections of its equivalent component vaccines. Vaccination providers should consult the relevant Advisory Committee on Immunization Practices (ACIP) statement for detailed recommendations, available online at http://www.cdc.gov/vaccines/hcp/acip-recs/index.html. Clinically significant adverse events that follow vaccination should be reported to the Vaccine Adverse Event Reporting System (VAERS) (http://vu.cdc.gov/vaers/) or by telephone (800-822-7967). Suspected cases of vaccine preventable diseases should be reported to the state or local health department. Additional information, including precautions and contraindications for vaccination, is available from CDC online (http://www.cdc.gov/vaccines/recs/vacc-admin/contraindication.html) or by telephone (800-232-4636).

This schedule is approved by the Advisory Committee on Immunization Practices (http://www.cdc.gov/vaccines/acip/), the American Academy of Pediatrics (http://www.aap.org), the American Academy of Family Physicians (http://www.aafp.org), and the American College of Obstetricians and Gynecologists (http://www.acog.org).

This schedule is approved by the Advisory Committee on Immunization Practices (http://www.cdc.gov/vaccines/acip/), the American Academy of Pediatrics (http://www.aap.org), the American Academy of Family Physicians (http://www.aafp.org), and the American College of Obstetricians and Gynecologists (http://www.acog.org).

NOTE: The above recommendations must be read along with the footnotes of this schedule.

Footnotes — Recommended immunization schedule for persons aged 0 through 18 years—United States, 2015

For further guidance on the use of the vaccines mentioned below, see: http://www.cdc.gov/vaccines/hcp/acip-recs/index.html.

For vaccine recommendations for persons 19 years of age and older, see the Adult Immunization Schedule.

Additional information:
- For contraindications and precautions to use of a vaccine and for additional information regarding that vaccine, vaccination providers should consult the relevant ACIP statement available online at http://www.cdc.gov/vaccines/hcp/acip-recs/index.html.
- For purposes of calculating intervals between doses, 4 weeks = 28 days. Intervals of 4 months or greater are determined by calendar months.
- Vaccine doses administered 4 days or less before the minimum interval are considered valid. Doses of any vaccine administered ≥5 days earlier than the minimum interval or minimum age should not be counted as valid doses and should be repeated as age-appropriate. The repeat dose should be spaced after the invalid dose by the recommended minimum interval. For further details, see MMWR, General Recommendations on Immunization and Reports / Vol. 60 / No. 2, Table 1. Recommended and minimum ages and intervals between vaccine doses available online at http://www.cdc.gov/mmwr/pdf/rr/rr6002.pdf.
- Information on travel vaccine requirements and recommendations is available at http://wwwnc.cdc.gov/travel/destinations/list.

### 1. Hepatitis B (HepB) vaccine. (Minimum age: birth)

**Routine vaccination:**
- **At birth:** Administer monovalent HepB vaccine to all newborns before hospital discharge.
- For infants born to hepatitis B surface antigen (HBsAg) positive mothers, administer HepB vaccine and 0.5 ml hepatitis B immune globulin (HBIG) within 12 hours of birth. These infants should be tested for HBsAg and antibody to HBsAg (anti-HBs) 1 to 2 months after completion of the HepB series at age 9 through 18 months (preferably at the next well-child visit).
- If mother’s HBsAg status is unknown, within 12 hours of birth administer HepB vaccine regardless of birth weight. For infants weighing less than 2,000 grams, administer HBIG in addition to HepB vaccine within 12 hours of birth. Determine mother’s HBsAg status as soon as possible and, if mother is HBsAg positive, also administer HBIG for infants weighing 2,000 grams or more as soon as possible, but no later than 7 days.

### 2. Rotavirus (RV) vaccines. (Minimum age: 6 weeks for both RV1 [Rotarix] and RV5 [RotaTeq])

**Routine vaccination:**
- Administer a series of RV vaccine to all infants as follows:
  - RV1: If Rotarix is used, administer a 2-dose series at 2 and 4 months of age.
  - RV5: If RotaTeq is used, administer a 3-dose series at ages 2, 4, and 6 months.
  - Any dose in the series was RotaTeq or vaccine product is unknown for any dose in the series, a total of 3 doses of RV vaccine should be administered.

**Catch-up vaccination:**
- The maximum age for the first dose in the series is 14 weeks, 6 days; vaccination should not be initiated for infants aged 15 weeks, 0 days or older.
- The maximum age for the final dose in the series is 8 months, 0 days.
- For other catch-up guidance, see Figure 172-3.

### 3. Diphtheria and tetanus toxoids and acellular pertussis (DTaP) vaccine. (Minimum age: 6 weeks. Exception: DTaP-IPV [Kinrix]-4 years)

**Routine vaccination:**
- Administer a 5-dose series of DTaP vaccine at ages 2, 4, 6, 15 through 18 months, and 4 through 6 years. The fourth dose may be administered as early as age 12 months, provided at least 6 months have elapsed since the third dose. However, the fourth dose of DTaP may not be repeated if it was administered at least 4 months after the third dose of DTaP.

**Catch-up vaccination:**
- Administer an additional dose of DTaP vaccine at age 18 months, 0 days or older to an infant or child who did not receive the fourth dose of DTaP vaccine at age 18 months, 0 days or older.

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**Table:**

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Recommended ages</th>
<th>Notes</th>
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| Hepatitis B (HepB) | 0, 1, 6 months | Monovalent HepB vaccine should be used for ages 0 through 12 months. HBIG should be used for doses administered before age 6 weeks.
| Rotavirus (RV) vaccine | 0-2 months | Administer as early as 2 months of age to infants who have not received a birth dose. The third dose should be administered at least 2 months after the second dose and at least 6 months after the first dose. The fourth dose should be administered at least 6 months after the third dose.
| Diphtheria and tetanus toxoids and acellular pertussis (DTaP) vaccine | 0-2 months | Administer an additional dose at age 18 months, 0 days or older to an infant or child who did not receive the fourth dose of DTaP vaccine at age 18 months, 0 days or older. The fifth dose should be administered at least 6 months after the fourth dose. |
3. Diphtheria and tetanus toxoids and acellular pertussis (DTaP) vaccine (cont’d)

Catch-up vaccination:
- Administer 1 dose of DTaP vaccine to all adolescents aged 11 through 12 years.

Routine vaccination:
- For other catch-up guidance, see Figure 172-3.

5. Haemophilus influenzae type b (Hib) conjugate vaccine. (Minimum age: 6 weeks for PRP-T [ActHIB, DTaP-IPV/Hib (Pentacel) and Hib-Mencey (MenHibrix), PRP-OMP [PedvaxHib or COMVAX], 12 months for PRP-T [Hiberix])

Routine vaccination:
- Administer 2- or 3-dose Hib vaccine primary series and a booster dose (dose 3 or 4) depending on vaccine used in primary series) at age 12 through 15 months to complete a full Hib vaccine series.
- The primary series with ActHIB, MenHibrix, or Pentacel consists of 3 doses and should be administered at 2, 4, and 6 months of age. The primary series with PedvaxHib or COMVAX consists of 2 doses and should be administered at 2 and 4 months of age; a dose at age 6 months is not indicated.
- One booster dose (dose 3 or 4 depending on vaccine used in primary series) of any Hib vaccine should be administered at age 12 through 15 months. An exception is Hibermune Hib vaccine. Hibermune should only be used for the booster (final) dose in children aged 12 months through 4 years who have received at least 1 prior dose of Hib-containing vaccine.
- For recommendations on the use of MenHibrix in patients at increased risk for meningococcal disease, please refer to the meningococcal vaccine footnotes and also to MMWR February 28, 2014 / 63(RO1)-11, available at http://www.cdc.gov/mmwr/pdf/wk/mm6332.pdf.
8. Influenza vaccines (cont’d)

For children aged 6 months through 8 years:
- For the 2015–16 season, administer a single dose of influenza vaccine (separated by at least 4 weeks) to children who are receiving influenza vaccine for the first time. Some children in this age group who have been vaccinated previously will also need 2 doses. For additional guidance, follow dosing guidelines in the 2014–15 ACP influenza vaccine recommendations, MMWR August 15, 2014 / 63(32);691–697 [40 pages] available at http://www.cdc.gov/mmwr/pdf/rr/rr6332.pdf.
- For the 2015–16 season, follow dosing guidelines in the 2015 ACP influenza vaccine recommendations.

For persons aged 9 years and older:
- Administer 2 doses of influenza vaccine if the interval between doses is less than 4 weeks.

9. Measles, mumps, and rubella (MMR) vaccine. (Minimum age: 12 months for routine vaccination)

Routine vaccination:
- Administer a 2-dose series of MMR vaccine at ages 12 through 15 months and 4 through 6 years. The second dose may be administered before age 4 years, provided at least 4 weeks have elapsed since the first dose.
- Administer 1 dose of MMR vaccine to infants aged 6 through 11 months before departure from the United States for international travel. These children should be revaccinated with 2 doses of MMR vaccine, the first dose at age 12 through 15 months (12 months if the child remains in an area where disease risk is high), and the second dose at least 4 weeks later.
- Administer 2 doses of MMR vaccine to children aged 12 months and older before departure from the United States for international travel. The first dose should be administered on or after age 12 months and the second dose at least 4 weeks later.

Catch-up vaccination:
- Ensure that all school-aged children and adolescents have had 2 doses of MMR vaccine; the minimum interval between the 2 doses is 4 weeks.

10. Varicella (VAR) vaccine. (Minimum age: 12 months)

Routine vaccination:
- Administer a 2-dose series of VAR vaccine at ages 12 through 15 months and 4 through 6 years. The second dose may be administered before age 4 years, provided at least 3 months have elapsed since the first dose. If the second dose was administered at least 4 weeks after the first dose, it can be accepted as valid.

Catch-up vaccination:
- Ensure that all persons aged 7 through 18 years without evidence of immunity (see MMWR 2007 / 56 [No. RR-4] available at http://www.cdc.gov/mmwr/pdf/rr/rr5604.pdf) have 2 doses of varicella vaccine. For children aged 7 through 12 years, the recommended minimum interval between doses is 3 months; if the second dose was administered at least 4 weeks after the first dose, it can be accepted as valid; for persons aged 13 years and older, the minimum interval between doses is 4 weeks.

11. Hepatitis A (HepA) vaccine. (Minimum age: 12 months)

Routine vaccination:
- Initiate the 2-dose HepA vaccine series at 12 through 23 months; separate the 2 doses by 6 to 18 months.
- Children who have received 1 dose of HepA vaccine before age 24 months should receive a second dose 6 to 18 months after the first dose.
- For any person aged 2 years and older who has not already received the HepA vaccine series, 2 doses of HepA vaccine separated by 6 to 18 months may be administered if immunity against hepatitis A virus infection is needed.

Catch-up vaccination:
- The minimum interval between the two doses is 6 months.

Special populations:
- Administer 2 doses of HepA vaccine to at least 6 months apart to previously unvaccinated persons who live in areas where vaccination programs target older children, or who are at increased risk for infection. This includes persons traveling to or working in countries that have high or intermediate endemicity of hepatitis A and who may have received less than 2 doses of HepA vaccine in the past. It also includes persons with chronic liver disease, and persons who anticipate close personal contact (e.g., household or regular babysitting) with an international adoptee during the first 60 days after arrival in the United States. For children aged 11 through 12 years, either the first dose or the second dose may be administered at least 4 weeks after the first dose.

12. Human papillomavirus (HPV) vaccines. (Minimum age: 9 years for HPV2 [Cervarix] and HPV4 [Gardasil])

Routine vaccination:
- Administer a 3-dose series of HPV vaccine on a schedule of 0, 1-2, and 6 months to all adolescents aged 11 through 12 years. Either HPV4 or HPV2 may be used for females, and only HPV4 may be used for males.
- The vaccine series may be started at age 9 years.
- Administer the second dose 1 to 2 months after the first dose (minimum interval of 4 weeks); administer the third dose 24 weeks after the first dose and 16 weeks after the second dose (minimum interval of 12 weeks).

Catch-up vaccination:
- Administer the vaccine series to females (either HPV2 or HPV4) and males (HPV4) at age 13 through 18 years if not previously vaccinated.
- Use recommended routine dosing intervals (see Routine vaccination above) for vaccine series catch-up.

13. Meningococcal conjugate vaccines. (Minimum age: 6 weeks for Hib-MenCY [MenHibrix], 9 months for MenACYW-D [Menactra], 2 months for MenACWY-CRM [Menveo])

Routine vaccination:
- Administer a single dose of Menactra or Menveo vaccine at age 11 through 12 years, with a booster dose at age 16 years.
- Adolescents aged 11 through 18 years with human immunodeficiency virus (HIV) infection should receive a 2-dose primary series of Menactra or Menveo with at least 8 weeks between doses.
- For children aged 2 months through 18 years with high-risk conditions, see below.

Catch-up vaccination:
- Administer Menactra or Menveo vaccine at age 13 through 18 years if not previously vaccinated.
- If the first dose is administered at age 13 through 15 years, a booster dose should be administered at age 16 through 18 years with a minimum interval of at least 8 weeks between doses.
- If the first dose is administered at age 16 years or older, a booster dose is not needed.
- For other catch-up guidance, see Figure 172-3.

Vaccination of persons with high-risk conditions and other persons at increased risk of disease:
- Children with anatomic or functional asplenia (including sickle cell disease).
- Children with persistent complement component deficiency.
- Men having sex with men; users of injection and non-injection illicit drugs; persons who work at high risk.
- For other catch-up recommendations for these persons, and complete information on use of meningococcal vaccines, including guidance related to vaccination of persons at increased risk of infection, see MMWR March 22, 2013 / 62(9):1–22, available at http://www.cdc.gov/mmwr/pdf/rr/rr6209.pdf.
**FIGURE 172-3. Catch-up immunization schedule for persons aged 4 months through 18 years who start late or who are more than 1 month behind — United States, 2015.**

The figure below provides catch-up schedules and minimum intervals between doses for children whose vaccinations have been delayed. A vaccine series does not need to be restarted, regardless of the time that has elapsed between doses. Use the section appropriate for the child’s age. Always use this table in conjunction with Figure 1 and the footnotes that follow.

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Minimum Age for First Dose</th>
<th>Minimum Interval Between Doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatitis B</td>
<td>Birth</td>
<td>Dose 1 to Dose 2: 6 weeks; Dose 2 to Dose 3: 8 weeks; Dose 3 to Dose 4: 4 weeks; Dose 4 to Dose 5: 6 months</td>
</tr>
<tr>
<td>Rotavirus</td>
<td>6 weeks</td>
<td>6 weeks; 4 weeks; 6 months; 6 months</td>
</tr>
<tr>
<td>Diphtheria, tetanus, and acellular pertussis</td>
<td>6 weeks</td>
<td>4-weeks; 6 weeks; 4-weeks; 4-weeks</td>
</tr>
<tr>
<td>Hemophilus influenzae type b</td>
<td>6 weeks</td>
<td>4-weeks; 6 weeks; 6 weeks; 4-weeks; 4-weeks</td>
</tr>
<tr>
<td>Pneumococcal</td>
<td>6 weeks</td>
<td>4-weeks; 8 weeks (as final dose); 6 months; 6 months</td>
</tr>
<tr>
<td>Inactivated poliovirus</td>
<td>6 weeks</td>
<td>4-weeks; 8 weeks (as final dose); 6 months; 6 months</td>
</tr>
<tr>
<td>Meningococcal</td>
<td>6 weeks</td>
<td>See footnote 13; See footnote 13</td>
</tr>
<tr>
<td>Measles, mumps, rubella</td>
<td>12 months</td>
<td>4-weeks; 8 weeks (as final dose for healthy children); 6 months (as final dose)</td>
</tr>
<tr>
<td>Varicella</td>
<td>12 months</td>
<td>3 months; 0 months; 0 months</td>
</tr>
<tr>
<td>Hepatitis A</td>
<td>12 months</td>
<td>6 months; 6 months; 6 months</td>
</tr>
</tbody>
</table>

**VACCINES RECOMMENDED IN SPECIAL CIRCUMSTANCES**

There are 4 vaccines (PCV13, PPSV23, MCV4, and Hib) recommended for children and adolescents at increased risk for complications from vaccine-preventable diseases or children who have an increased risk for exposure to these diseases, who are outside the age groups for which these vaccines are normally recommended (PPSV23 is not routinely recommended for any age group of children and is only used for children with high-risk conditions; see Table 172-7). Specific recommendations for use of these vaccines in children with various underlying conditions can be found in the recommended immunization schedule.

PCV13 is recommended for all children <5 years of age who have conditions that place them at high risk for pneumococcal disease. This recommendation includes children with sickle cell disease and other hemoglobinopathies, including hemoglobin SS, hemoglobin S-C, or hemoglobin S-β-thalassemia, or children who are functionally or anatomically asplenic; children with HIV infection; and children who have chronic disease (see Table 172-7). Children at high risk for pneumococcal disease also should receive PPSV23 to provide immunity to serotypes not contained in the 13-valent conjugate vaccine. PPSV23 should be administered on or after the 2nd birthday and should follow completion of the PCV13 series by at least 6-8 wk. Two doses of PPSV23 are recommended, with an interval of 5 yr between doses. Immunization of previously unvaccinated children with high-risk conditions who are ≥5 yr of age can be performed with either a dose of PCV13 or a dose of PPSV23.

PCV13 is recommended for people with HIV, children with functional or anatomic asplenia, persistent complement component or properdin deficiencies, and as part of outbreak-control programs. Hib through 18 yr of age (http://www.cdc.gov/vaccines/schedules/hcp/imz/catchup.html). Also available are interactive immunization schedulers for children <6 yr of age at https://www.vaccscheduler.org and for adolescents at http://www.cdc.gov/recs/scheduler/AdolescentScheduler.htm.

**NOTE:** The above recommendations must be read along with the footnotes of this schedule in Fig. 172-2.

**Figure 172-3** Catch-up immunization schedule for persons aged 4 mo through 18 yr who start late or who are more than 1 mo old—United States, 2015. (From Centers for Disease Control and Prevention. Available at: http://www.cdc.gov/vaccines/schedules/downloads/child/catchup-schedule-pr.pdf)
vaccine is recommended for children with certain high-risk conditions (see Table 172-7).

A variety of vaccines are available for children who will be traveling to areas of the world where certain infectious diseases are common in addition to vaccines in the recommended childhood and adolescent schedule (Table 172-8). Vaccines for travelers include typhoid fever, hepatitis A, hepatitis B, Japanese encephalitis, MCV4 or MPS4, rabies, and yellow fever, depending on the location and circumstances of travel. Measles is endemic in many parts of the world. Children 6 months of age should receive a dose of MMR before international travel. However, doses of measles vaccine received before 12 mo of age should not be counted in determining compliance with the recommended 2 dose MMR schedule. Additional information on vaccines for international travel can be found at http://wwwnc.cdc.gov/travel/.

Vaccine recommendations for children with immunocompromising conditions, either primary (inherited) or secondary (acquired), vary according to the underlying condition, the degree of immune deficit, the risk for exposure to disease, and the vaccine (Table 172-9). Immunization of children with immunocompromise poses the following potential concerns: the incidence or severity of some vaccine-preventable diseases is higher, and therefore certain vaccines are recommended specifically for certain conditions; vaccines may be less effective during the period of altered immunocompetence and may need to be repeated when immune competence is restored; and because of altered immunocompetence, some children and adolescents may be

<table>
<thead>
<tr>
<th>VACCINE PRODUCT (MANUFACTURER)</th>
<th>TRADE NAME (YEAR LICENSED)</th>
<th>COMPONENTS</th>
<th>Recommended Ages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hib-HepB†‡ (Merck &amp; Co, Inc.)</td>
<td>Comvax (1996)</td>
<td>PRP-OMP + HibB vaccine</td>
<td>2, 4 mo of age</td>
</tr>
<tr>
<td>MenCY/Hib (GlaxoSmithKline)</td>
<td>Men Hibrix (2013)</td>
<td>MenCY + PRP-T</td>
<td>2, 4, 6 mo of age</td>
</tr>
<tr>
<td>DTaP-IPV/Hib (Sanofi Pasteur)</td>
<td>Pentacel (2008)</td>
<td>DTaP-IPV + PRP-T</td>
<td>2, 4, 6 mo of age</td>
</tr>
<tr>
<td>DTaP-HepB-IPV (GlaxoSmithKline)</td>
<td>Pediarpix (2002)</td>
<td>DTaP + HepB + IPV</td>
<td>2, 4, 6 mo of age</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• booster for 5th dose of DTaP</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• booster for 4th dose of IPV</td>
</tr>
<tr>
<td></td>
<td>Kinrix (2008)</td>
<td>DTaP + IPV</td>
<td>4 through 6 yr of age:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• booster for 5th dose of DTaP</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• booster for 4th dose of IPV</td>
</tr>
<tr>
<td>HepA-HepB (GlaxoSmithKline)</td>
<td>Twinrix (2001)</td>
<td>HepA + HepB</td>
<td>&gt;18 yr of age; 0, 1, and 6 mo schedule</td>
</tr>
<tr>
<td>MMRV (Merck &amp; Co, Inc.)</td>
<td>ProQuad (2005)</td>
<td>MMR + varicella</td>
<td>12 through 15 mo of age</td>
</tr>
</tbody>
</table>

*Dash (-) indicates that products are supplied in their final form by the manufacturer and do not require mixing or reconstitution by user; slash (/) indicates that products are mixed or reconstituted by user.
†If a PRP-OMP vaccine is not administered as both doses in the primary series or if there is uncertainty about which products were administered previously, a 3rd dose of Hib conjugate vaccine is needed to complete the primary series.
‡Preferred for American Indian/Alaska Native children.
DF, diphteria and tetanus toxoids and acellular pertussis vaccine; HepA, hepatitis A vaccine; HepB, hepatitis B vaccine; IPV/Hib, trivalent inactivated polio vaccine and Haemophilus influenzae type b vaccine; MMRV, measles-mumps-rubella and varicella vaccine.


<table>
<thead>
<tr>
<th>VACCINES</th>
<th>CONDITIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCV13 (and PPSV23 in certain conditions)</td>
<td>Immunocompetent children with:</td>
</tr>
<tr>
<td></td>
<td>• Chronic heart disease (particularly cyanotic congenital heart disease and cardiac failure)</td>
</tr>
<tr>
<td></td>
<td>• Chronic lung disease (including asthma if treated with high-dose oral corticosteroid therapy)</td>
</tr>
<tr>
<td></td>
<td>• Diabetes mellitus</td>
</tr>
<tr>
<td></td>
<td>• Cerebrospinal fluid leaks</td>
</tr>
<tr>
<td></td>
<td>• Cochlear implant</td>
</tr>
<tr>
<td></td>
<td>• Anatomic or functional asplenia (including sickle cell disease and other hemoglobinopathies, congenital or acquired asplenia or splenic dysfunction)</td>
</tr>
<tr>
<td></td>
<td>• Immunocompromising conditions: HIV infection; chronic renal failure and nephrotic syndrome; diseases associated with treatment with immunosuppressive drugs or radiation therapy, including malignant neoplasms, leukemias, lymphomas, and Hodgkin disease or solid organ transplantation; congenital immunodeficiency</td>
</tr>
<tr>
<td>MCV4</td>
<td>Anatomic or functional asplenia (including sickle cell disease)</td>
</tr>
<tr>
<td></td>
<td>Persistent complement component deficiency</td>
</tr>
<tr>
<td></td>
<td>Residents of or travelers to countries in African meningitis belt or pilgrims on the Haj</td>
</tr>
<tr>
<td></td>
<td>During outbreaks caused by a vaccine serogroup</td>
</tr>
<tr>
<td>Hib</td>
<td>Anatomic or functional asplenia (including sickle cell disease)</td>
</tr>
<tr>
<td></td>
<td>Immunocompromising conditions: HIV disease; immunosuppressive therapy for malignant neoplasms; immunoglobulin deficiency including immunoglobulin G, subclass deficiency or early complement deficiency; recipients of a hematopoietic stem cell transplant (HSCT)</td>
</tr>
</tbody>
</table>

Table 172-7  Vaccines Recommended for Children and Adolescents with Underlying Conditions or at High Risk
at increased risk for an adverse event following receipt of a live viral vaccine. Live-attenuated vaccines generally are contraindicated in immunocompromised people. The exceptions include MMR, which may be given to a child with HIV infection provided the child is asymptomatic or symptomatic without evidence of severe immunosuppression, and varicella vaccine, which may be given to HIV-infected children if the CD4+ lymphocyte count is at least 15%. MMRV is not recommended in these situations.

Altered immunocompetence is considered a precaution for rotavirus; however, the vaccine is contraindicated in children with severe combined immunodeficiency disease. Inactivated vaccines may be administered to immunocompromised children, although, depending on the immune deficit, their effectiveness might not be optimal. Children with complement deficiency disorders may receive all vaccines, including live-attenuated vaccines. In contrast, children with phagocytic disorders may receive both inactivated and live-attenuated viral vaccines but not live-attenuated bacterial vaccines.

Corticosteroids can suppress the immune system. Children receiving corticosteroids (≥22 mg/kg/day or ≥20 mg/day of prednisone or equivalent) for 14 or more days should not receive live vaccines until therapy has been discontinued for at least 1 mo. Children on the same dose levels but for <2 wk may receive live viral vaccines as soon as therapy is discontinued, although some experts would wait 2 wk after therapy has been discontinued. Children receiving lower doses of corticosteroids may be vaccinated while receiving therapy.

Children and adolescents with malignancy, and those who have undergone solid organ or hematopoietic stem cell transplantation and immunosuppressive or radiation therapy, should not receive live virus and live bacterial vaccines depending on their immune status.

Children who have undergone chemotherapy for leukemia may need to be reimmunized with age-appropriate single doses of previously administered vaccines.

Preterm infants generally can be vaccinated at the same chronologic age as full-term infants according to the recommended childhood immunization schedule. An exception is the birth dose of hepatitis B vaccine. Infants weighing ≥2 kg and who are stable may receive a birth dose. However, hepatitis B vaccination should be deferred in infants weighing <2 kg at birth until 30 days of age, if born to an HBsAg-negative mother. All preterm, low birthweight infants born to HBsAg-positive mothers should receive hepatitis B immunoglobulin and hepatitis B vaccine within 12 hr of birth. However, such infants should receive an additional 3 doses of vaccine starting at 30 days of age (see Fig. 172-2).

Some children have situations that are not addressed directly in current immunization schedules. There are general rules that physicians can use to guide immunization decisions in some of these instances. In general, vaccines may be given simultaneously on the same day, whether inactivated or live. Different inactivated vaccines can be administered at any interval between doses. However, because of theoretical concerns about viral interference, different live-attenuated vaccines (MMR, varicella, LAIV) if not administered on the same day, should be given at least 1 mo apart. An inactivated and a live vaccine may be spaced at any interval from each other.

Immunoglobulin does not interfere with killed vaccines. However, immunoglobulin can interfere with the immune response to measles vaccine and by inference to varicella vaccine. In general, immunoglobulin, if needed, should be administered at least 2 wk after measles vaccine. Depending on the dose of immunoglobulin received, MMR

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**Table 172-8**  Recommended Immunizations for Travelers to Developing Countries*

<table>
<thead>
<tr>
<th>IMMUNIZATIONS</th>
<th>Length of Travel</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BRIEF, &lt;2 WK</td>
</tr>
<tr>
<td>Review and complete age-appropriate childhood and adolescent schedule (see text for details)</td>
<td>+</td>
</tr>
<tr>
<td>• DTaP, poliovirus, pneumococcal, and Haemophilus influenzae type b vaccines may be given at 4-wk intervals if necessary to complete the recommended schedule before departure</td>
<td>+</td>
</tr>
<tr>
<td>• Measles: 2 additional doses given if &lt;12 mo of age at 1st dose</td>
<td>+</td>
</tr>
<tr>
<td>• Rotavirus</td>
<td></td>
</tr>
<tr>
<td>• Varicella</td>
<td></td>
</tr>
<tr>
<td>• HPV</td>
<td></td>
</tr>
<tr>
<td>• Hepatitis B†</td>
<td>+</td>
</tr>
<tr>
<td>• Tdap</td>
<td>+</td>
</tr>
<tr>
<td>• MCV4</td>
<td>+</td>
</tr>
<tr>
<td>Yellow fever‡</td>
<td>+</td>
</tr>
<tr>
<td>Hepatitis A†</td>
<td>+</td>
</tr>
<tr>
<td>Typhoid fever¶</td>
<td>±</td>
</tr>
<tr>
<td>Meningococcal disease∥</td>
<td>±</td>
</tr>
<tr>
<td>Rabies**</td>
<td>±</td>
</tr>
<tr>
<td>Japanese encephalitis‖</td>
<td>±</td>
</tr>
</tbody>
</table>

*See disease-specific chapters in the Red Book for details. For further sources of information, see text.
†If there is insufficient time to complete 6 mo primary series, accelerated series can be given.
‡For regions with endemic infection, see Health Information for International Travel (http://www.cdc.gov/travel).
§Indicated for travelers to areas with intermediate or high endemic rates of hepatitis A virus infection.
∥Recommended for regions of Africa with endemic infection and during local epidemics, and required for travel to Saudi Arabia for the Haj.
**Indicated for people with high risk for animal exposure (especially to dogs) and for travelers to countries with endemic infection.
††For regions with endemic infection (see Health Information for International Travel). For high-risk activities in areas experiencing outbreaks, vaccine is recommended, even for brief travel.

+ , Recommended; ±, consider; DTaP, diphtheria and tetanus toxoids and acellular pertussis.

<table>
<thead>
<tr>
<th>PRIMARY</th>
<th>CATEGORY</th>
<th>SPECIFIC IMMUNODEFICIENCY</th>
<th>CONTRAINDIATED VACCINES*</th>
<th>RISK-SPECIFIC RECOMMENDED VACCINES*</th>
<th>EFFECTIVENESS AND COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>B lymphocyte (humoral)</td>
<td>Severe antibody deficiencies (e.g., X-linked agammaglobulinemia and common variable immunodeficiency)</td>
<td>OPV* Smallpox LAIV BCG Ty21a (live typhoid) YF</td>
<td>Pneumococcal Consider measles and varicella vaccination</td>
<td>The effectiveness of any vaccine will be uncertain if it depends only on the humoral response (e.g., PPSV, MPSV) IVIG interferes with the immune response to measles vaccine and possibly varicella vaccine</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Less-severe antibody deficiencies (e.g., selective IgA deficiency and IgG subclass deficiency)</td>
<td>OPV* BCG YF Other live vaccines appear to be safe</td>
<td>Pneumococcal</td>
<td>All vaccines probably effective Immunogenic response may be attenuated</td>
<td></td>
</tr>
<tr>
<td>T lymphocyte (cell-mediated and humoral)</td>
<td>Complete defects (e.g., SCID, complete DiGeorge syndrome) Partial defects (e.g., most patients with DiGeorge syndrome, Wiskott-Aldrich syndrome, ataxia-telangiectasia)</td>
<td>None</td>
<td>Pneumococcal</td>
<td>Vaccines may be ineffective Effectiveness of any vaccine depends on degree of immune suppression</td>
<td></td>
</tr>
<tr>
<td>Complement</td>
<td>Persistent complement, properdin, or factor B deficiency</td>
<td>Live bacterial vaccines†</td>
<td>Pneumococcal Meningococcal Hb (if not administered in infancy)</td>
<td>All routine vaccines probably effective All inactivated vaccines safe and probably effective</td>
<td></td>
</tr>
<tr>
<td>Phagocytic function</td>
<td>Chronic granulomatous disease, leukocyte adhesion defect, and myeloperoxidase deficiency</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SECONDARY</th>
<th>SPECIFIC IMMUNODEFICIENCY</th>
<th>CONTRAINDIATED VACCINES*</th>
<th>RISK-SPECIFIC RECOMMENDED VACCINES*</th>
<th>EFFECTIVENESS AND COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV/AIDS</td>
<td>OPV* Smallpox BCG LAIV Withhold MMR and varicella in severely immunocompromised persons</td>
<td>Pneumococcal Consider Hib (if not administered in infancy) and meningococcal vaccination</td>
<td>MMR, varicella, rotavirus, and all inactivated vaccines, including inactivated influenza, may be effective†</td>
<td></td>
</tr>
<tr>
<td>Malignant neoplasm, transplantation, immunosuppressive or radiation therapy</td>
<td>Live viral and bacterial, depending on immune status†</td>
<td>Pneumococcal</td>
<td>Effectiveness of any vaccine depends on degree of immune suppression</td>
<td></td>
</tr>
<tr>
<td>Asplenia</td>
<td>None</td>
<td>Pneumococcal Meningococcal Hb (if not administered in infancy)</td>
<td>All routine vaccines probably effective</td>
<td></td>
</tr>
<tr>
<td>Chronic renal disease</td>
<td>LAIV</td>
<td>Pneumococcal Hepatitis B**</td>
<td>All routine vaccines probably effective</td>
<td></td>
</tr>
</tbody>
</table>

*Other vaccines that are universally or routinely recommended should be given if not contraindicated.
†OPV is no longer recommended for routine use in the United States.
‡Live bacterial vaccines: BCG and oral Ty21a Salmonella typhi vaccine.
§Live viral vaccines: MMR, MMRV, OPV, LAIV, YF, zoster, rotavirus, and vaccinia (smallpox). Smallpox vaccine is not recommended for children or the general public.
∥Regarding T-lymphocyte immunodeficiency as a contraindication for rotavirus vaccine, data exist only for SCID.
¶Pneumococcal vaccine is not indicated for children with chronic granulomatous disease beyond age-based universal recommendations for PCV. Children with chronic granulomatous disease are not at increased risk for pneumococcal disease.
★HIV-infected children should receive immunoglobulin after exposure to measles and may receive varicella, measles, and YF vaccine if CD4+ lymphocyte count is greater than 15%. (For YF vaccine, CD4+ T-lymphocyte count between 15% and 24% is a precaution.)
**Indicated based on the risk from dialysis-based bloodborne transmission.
BCG, bacille Calmette-Guérin vaccine; Hib, Haemophilus influenzae type b vaccine; HIV/AIDS, human immunodeficiency virus/acquired immunodeficiency syndrome; IVIG, intravenous immunoglobulin; LAIV, live-attenuated influenza vaccine; MMR, measles, mumps, rubella vaccine; MPSV, quadrivalent meningococcal polysaccharide vaccine; OPV, oral poliovirus vaccine (live); PPSV, pneumococcal polysaccharide vaccine; SCID, severe combined immunodeficiency disease; YF, yellow fever.

should be deferred for as long as 3 through 11 mo. Immunoglobulin is not expected to interfere with the immune response to LAIV or rotavirus vaccines.

**PRECAUTIONS AND CONTRAINDICATIONS**

Observation of valid precautions and contraindications is critical to ensure that vaccines are used in the safest manner possible and to obtain optimal immunogenicity. When a child presents for immunization with a clinical condition considered a precaution, the physician must weigh benefits and risks to that individual child. If benefits are judged to outweigh risks, then the vaccine or vaccines in question may be administered. A contraindication means the vaccine should not be administered under any circumstances.

A general contraindication for all vaccines is anaphylactic reaction to a prior dose. Anaphylactic hypersensitivity to vaccine constituents is also a contraindication. However, if a vaccine is essential, there are desensitizing protocols for some vaccines. The major constituents of concern are egg proteins for vaccines grown in eggs; gelatin, a stabilizer in many vaccines; and antimicrobial agents. The measles and mumps components of MMR are grown in chick embryo fibroblast tissue culture. However, the amount of egg protein in MMR is so small as not to require any special procedures before administering vaccine to someone with a history of anaphylaxis following egg ingestion.

Vaccines usually should be deferred in children with moderate to severe acute illnesses, regardless of the presence of fever, until the child recovers. However, children with mild illnesses may be vaccinated. Studies of undervaccinated children have documented opportunities that were missed because mild illness was used as an invalid contraindication. Complete tables of contraindications and contraindication misperceptions can be found at http://www.cdc.gov/vaccines/recs/vac-admin/contraindications.htm.

**IMPROVING IMMUNIZATION COVERAGE**

Standards for child and adolescent immunization practices have been developed to support achievement of high levels of immunization coverage while providing vaccines in a safe and effective manner and educating parents about risks and benefits of vaccines (Table 172-10).

Despite benefits that vaccines have to offer, many children are underimmunized as a result of not receiving recommended vaccines or not receiving them at the recommended ages. Much of the underimmunization problem can be solved through physician actions. Most children have a regular source of healthcare. However, missed opportunities to provide immunizations at healthcare visits include failure to provide all recommended vaccines that could be administered at a single visit during that visit, failure to provide immunizations to children outside of well-child care when the conditions children may have are not contraindications to immunizations, and referral of children to public health clinics because of inability to pay for vaccines. Simultaneous administration of multiple vaccines generally is safe and effective. When the benefits of simultaneous vaccination are explained, many parents prefer such immunization rather than making an extra visit. Providing all needed vaccines simultaneously should be the standard of practice.

Only valid contraindications and precautions to vaccine administration should be observed. Ideally, immunizations should be provided during well-child visits, but using other visits to administer vaccines if there are no contraindications, particularly if a child is behind in the schedule, is important. There is no good evidence that providing immunizations outside of well-child care ultimately decreases well-child visits.

Financial barriers to immunization should be minimized. Participation in the Vaccines for Children program allows physicians to receive vaccines at no cost for their eligible patients, which helps such patients be immunized in their medical home.

Several interventions have been shown to help physicians increase immunization coverage in their practices. Reminder systems for children before an appointment or recall systems for children who fail to keep appointments have repeatedly been demonstrated to improve coverage. Assessment and feedback is also an important intervention. Many physicians overestimate the immunization coverage among patients they serve and thus are not motivated to make any changes in their practices to improve performance. Assessing the immunization coverage of patients served by an individual physician and feedback of results can be a major motivator for improvement. Often public health departments can be contacted to provide the assessments and feedback. Alternatively, physicians can perform some self-assessments. Review of approximately 60 consecutive charts of 2 yr old children may provide a reasonable estimate of practice coverage. Another approach is to have a staff member review the chart of every patient coming in for a visit and placing immunization needs reminders on the chart for the physician. Electronic medical records can be designed to accomplish this goal.

Some parents refuse, delay, or space out immunizations for their children. Pediatricians should try to open a dialog with such parents to understand reasons for refusal and try to work with them to overcome their concerns over time during the course of visits. Discussion should be based on the reason for refusal and the knowledge of the parent. Pediatricians should refer patients to reputable sources

<table>
<thead>
<tr>
<th>Table 172-10 Standards for Child and Adolescent Immunization Practices</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AVAILABILITY OF VACCINES</strong></td>
</tr>
<tr>
<td>Vaccination services are readily available.</td>
</tr>
<tr>
<td>Vaccinations are coordinated with other healthcare services and provided in a medical home when possible.</td>
</tr>
<tr>
<td>Barriers to vaccination are identified and minimized.</td>
</tr>
<tr>
<td>Patient costs are minimized.</td>
</tr>
<tr>
<td><strong>ASSESSMENT OF VACCINATION STATUS</strong></td>
</tr>
<tr>
<td>Healthcare professionals review the vaccination and health status of patients at every encounter to determine which vaccines are indicated.</td>
</tr>
<tr>
<td>Healthcare professionals assess for and follow only medically accepted contraindications.</td>
</tr>
<tr>
<td><strong>EFFECTIVE COMMUNICATION ABOUT VACCINE BENEFITS AND RISKS</strong></td>
</tr>
<tr>
<td>Parents or guardians and patients are educated about the benefits and risks of vaccination in a culturally appropriate manner and in easy-to-understand language.</td>
</tr>
<tr>
<td><strong>PROPER STORAGE AND ADMINISTRATION OF VACCINES AND DOCUMENTATION OF VACCINATIONS</strong></td>
</tr>
<tr>
<td>Healthcare professionals follow appropriate procedures for vaccine storage and handling.</td>
</tr>
<tr>
<td>Up-to-date, written vaccination protocols are accessible at all locations where vaccines are administered.</td>
</tr>
<tr>
<td>Persons who administer vaccines and staff who manage or support vaccine administration are knowledgeable and receive ongoing education.</td>
</tr>
<tr>
<td>Healthcare professionals simultaneously administer as many indicated vaccine doses as possible.</td>
</tr>
<tr>
<td>Vaccination records for patients are accurate, complete, and easily accessible.</td>
</tr>
<tr>
<td>Healthcare professionals report adverse events following vaccination promptly and accurately to the Vaccine Adverse Event Reporting System (VAERS) and are aware of a separate program, the National Vaccine Injury Compensation Program (VICP). All personnel who have contact with patients are appropriately vaccinated.</td>
</tr>
<tr>
<td><strong>IMPLEMENTATION OF STRATEGIES TO IMPROVE VACCINATION COVERAGE</strong></td>
</tr>
<tr>
<td>Systems are used to remind parents or guardians, patients, and healthcare professionals when vaccinations are due and to recall those who are overdue.</td>
</tr>
<tr>
<td>Office- or clinic-based patient record reviews and vaccination coverage assessments are performed annually.</td>
</tr>
<tr>
<td>Healthcare professionals practice community-based approaches.</td>
</tr>
</tbody>
</table>

Vaccines are used to prevent infectious diseases around the world. However, the types of vaccines in use, the indications and contraindications, and the immunization schedules vary substantially. Most developing countries follow the immunization schedules promulgated by the World Health Organization's Immunization Programme; the latest update is available at http://www.who.int/immunization/policy/Immunization_routine_table2.pdf.

According to this schedule, all children should be vaccinated at birth against tuberculosis with bacille Calmette-Guérin vaccine. Many children also receive a dose of the live-attenuated oral polio vaccine (OPV) at this time. Immunization visits are scheduled for 6, 10, and 14 wk of age when DTP vaccine and OPV are administered. Two doses of measles vaccines are recommended, with the first dose given between 9-12 mo and the second dose between 15-18 mo. Nearly all developing countries have implemented hepatitis B vaccination. Two schedule options may be used, depending on epidemiologic and programmatic considerations. Hepatitis B vaccine can be given at the same time as DTP vaccine doses at 6, 9, and 14 wk of age, often in combination vaccines. To prevent pertussis transmission, the 1st dose should be administered as soon as possible after birth (<24 hr) and at 6 and 14 wk of age. Yellow fever and Japanese encephalitis vaccines are recommended for infants 9 mo of age living in endemic areas. Substantial efforts have been made to incorporate Hib vaccines into all but 3 developing countries that are eligible for support by the GAVI Alliance, often within a DPT-based combination vaccine.

In the past few years, the support from the GAVI Alliance has facilitated the adoption of rotavirus and pneumococcal conjugate vaccines into developing country immunization programs. The increased coverage with these additional vaccines will considerably reduce the global childhood morbidity and mortality caused by pneumonia, meningitis, and diarrheal diseases.

In 1988, the World Health Assembly endorsed the goal of eradicating polio from the world by the end of 2000. Although that goal has not been reached, endemic polio transmission was contained to 3 countries worldwide (Afghanistan, Nigeria, and Pakistan) by the end of 2014. The principal strategy is use of OPV both for routine immunization and in mass campaigns, at least twice per year, during which all children <5 yr of age are targeted for immunization, regardless of prior immunization status. Once termination of wild polio virus transmission is achieved, the goal is to stop use of OPV, which rarely can cause vaccine-associated polio and which is capable of mutating and taking on the phenotypic characteristics of the wild viruses.

Latin American countries have maintained the elimination of indigenous circulation of measles since 2002. The strategy called for attainment of high routine immunization coverage of infants with a dose at 9 mo of age, a 1 time mass campaign targeting all persons 9 mo-14 yr of age regardless of prior immunization status, and follow-up campaigns of children born since the prior campaign, generally every 3-5 yr. While global measles deaths have decreased by 78% worldwide in recent years—from 562,000 deaths in 2000 to 122,000 in 2012—measles is still common in many developing countries, particularly in parts of Africa and Asia. Latin American countries have achieved the elimination of indigenous rubella with strategies consisting of both routine immunization and mass campaigns.

Immunization schedules in the industrialized world are substantially more variable than in the developing world. Immunization recommendations for Canada are developed by the Canadian National Advisory Committee on Immunization but are implemented somewhat differently by each province. The Canadian schedule is similar to the U.S. immunization schedule (http://www.phac-aspc.gc.ca/im/is-cv/index-eng.php), with a few exceptions. A birth dose of hepatitis B vaccine is not specifically recommended as it is in the United States. Conjugate meningococcal vaccine is recommended in a 3 dose series at 2, 4, and 6 mo of age. A single dose is recommended after 12 mo of age if the child has never been immunized or has received <3 doses in infancy. In contrast to the situation in the United States, hepatitis A vaccine is not recommended as a routine pediatric immunization.

There is tremendous variation in vaccines used and the immunization schedules recommended in Europe. European immunization schedules can be reviewed at http://apps.who.int/immunization_monitoring/globalsummary. As an example, the United Kingdom developed an immunization schedule during the late 1980s that includes visits at 2, 3, and 4 mo of age where a combination DTaP-Hib-IPV vaccine is administered. Following evidence that a 3 dose series of Hib vaccine at these ages was insufficient to ensure long-term, high-grade protection, a booster dose was added at 12-13 mo of age. MMR is recommended in a 2 dose schedule at 13 mo and 40 mo of age. During the 2nd MMR visit, a booster of DTaP and IPV is provided. A Td/IPV booster is recommended between 13 and 18 yr of age. PCV13 is recommended at 2, 4, and 12-13 mo of age. The United Kingdom was the first country to use conjugate meningococcal C vaccine (MCV-C) during a massive catch-up campaign for children, adolescents, and young adults. The effectiveness of the vaccine in the 1st yr was 88% or greater, and herd immunity was induced with an approximate two-thirds reduction in the incidence among unvaccinated children. MCV-C is administered at 3, 4, and 12-13 mo of age. In September 2008, HPV vaccine was recommended for girls 12-13 yr old. As of April, 2013, the UK schedule did not include hepatitis B vaccine, varicella vaccine, or influenza vaccine for universal childhood immunization (see http://www.nhs.uk/conditions/vaccinations/pages/vaccination-schedule-age-checklist.aspx). The Japanese immunization schedule in 2013 is substantially different from that in the United States. The Japanese do not use MMR and rely on individual vaccines for measles and rubella or combined MR. Japanese children also are vaccinated routinely against polio with OPV; against diphtheria, tetanus, and pertussis with DTaP; against Japanese encephalitis; and against tuberculosis with bacille Calmette-Guérin. Adults 65 yr of age and older receive annual influenza vaccinations. A law passed in March 2013 made vaccination of children against Hib, pneumococci, and HPV mandatory.

Some children come to the United States having started or completed international immunization schedules with vaccines produced outside of the United States. In general, doses administered in other countries should be considered valid if administered at the same ages as recommended in the United States. For missing doses, age-inappropriate doses, lost immunization records, or other concerns, pediatricians have 2 options: administer or repeat missing or inappropriate doses or perform serologic tests, and if they are negative, administer vaccines.

Bibliography is available at Expert Consult.
Immunization


Bibliography


Chapter 173
Infection Prevention and Control
Michael J. Chusid and Mary M. Rotar

Infection prevention and control are playing an ever more important role in pediatric medicine. To be fully effective, such programs require a functional infrastructure that addresses collaboration with the public health system, widespread immunizations, and use of appropriate techniques to prevent transmission of infection within the general population and within healthcare institutions. The national focus upon preventing nosocomial infection is emphasized by the fact that 5 of the 15 elements of the Joint Commission’s 2013 National Patient Safety Goals related to reduction and prevention of healthcare-associated infections (HAIs). Governmental agencies and insurance providers have reduced or eliminated payment to institutions for expenses associated with certain HAIs and a host of national organizations have been established to monitor and report rates of HAI at healthcare facilities. Ratings of healthcare facilities by periodicals such as Parents Magazine and US News and World Report incorporate institutional HAI rates in their reviews and rankings of facilities.

HAIs or nosocomial infections refer to infections acquired during hospitalization or acquired in other healthcare settings, such as nursing homes or ambulatory surgical care centers. An estimated 3-5% of children admitted to hospitals acquire an HAI. HAI rates are highest in patients undergoing invasive procedures. Infections can also be acquired in emergency departments, physicians’ offices, daycare, and long-term care settings. Medical device-associated infections occur in both the home and hospital. Adequate education of home health providers as well as of families is essential to prevent or minimize device-associated infections as ever-greater numbers of children are sent home from the hospital with intravenous catheters and other medical devices in place.

Factors that increase susceptibility to HAIs include host factors, recent invasive procedures, presence of catheters or other devices, prolonged use of antibiotics, contaminated physical environment, and exposure to other patients, visitors, or healthcare providers with active contagious infections or colonized with invasive microorganisms. Host factors increasing the risk for HAIs include anatomic abnormalities (dermal sinuses, cleft palate, obstructive uropathy), abnormal skin, organ dysfunction, malnutrition, and underlying diseases or comorbidities. Invasive procedures can introduce potential pathogens by breaching normal anatomic host barriers. Intravenous and other catheters provide direct access to sterile anatomic sites for usually minimally pathogenic organisms, as well as adherent surfaces for microbial binding, and can disrupt patterns of normally protective flow of mucus (e.g., nasotracheal tubes and sinus ostia). Antibiotic use can alter the composition of bowel flora and encourage the multiplication and emergence of toxigenic or invasive organisms already present in small numbers in the gut, such as C. difficile and Salmonella.

Transmission of infectious agents occurs by various routes, but by far the most common and important route is via the hands. Medical equipment, toys, and hospital and office furnishings can become microbiologically contaminated and thus have a role in transmission of potential pathogens. Pagers, phones, computer keyboards, and even neckties become easily contaminated. These inanimate objects serve as fomites for bacteria. There is increasing recognition of the importance of the healthcare environment in the acquisition of organisms such as methicillin-resistant S. aureus, vancomycin-resistant enterococci, carbapenem-resistant Enterobacteriaceae, C. difficile, and respiratory syncytial virus. Thermometers and other equipment that come in contact with mucous membranes pose special risks. Some agents are easily disseminated via airborne transmission, such as varicella virus, measles virus, and M. tuberculosis. Food can be contaminated and has been involved in hospital outbreaks of nosocomial infection. The hospital physical environment can also serve as a risk factor for infection, particularly for immunocompromised patients. In particular, rainywater or plumbing leaks are associated with bacterial and fungal infections, new construction or renovation with airborne fungal infection, and contamination of an institution’s potable water supply with bacterial, fungal, and atypical mycobacterial nosocomial infections.

Common causes of HAI in children are seasonal viruses such as rotavirus and respiratory viral agents, staphylococci, and Gram-negative bacilli. Fungi and multidrug-resistant organisms are common causes of infection in immunocompromised children, as well as those requiring intensive care and prolonged hospitalization. Common sites of infection are the respiratory tract, gastrointestinal tract, bloodstream, skin, and urinary tract.

Liberalization of visitation policies and spread of in-hospital animal visitation have increased the likelihood of HAI acquisition. The widespread use of contaminated pharmaceutical products like injectable depot corticosteroids has led to recent large outbreaks of fatal fungal HAIs.

HAIs cause considerable morbidity and occasional mortality of hospitalized children. Infections prolong hospital stays and increase healthcare costs. Surveillance, the initial step in identifying such infections and suggesting methods for prevention, is the responsibility of infection preventionists. Within hospitals, oversight of such surveillance is usually the responsibility of the infection prevention and control committee, a multidisciplinary group that collects and reviews surveillance data, establishes institutional policies, and investigates intrainstitutional infection outbreaks. The chair of the committee is often an infectious disease specialist. Surveillance in outpatient settings and during home care is often less-well defined. Local, state, and federal health departments play important roles in identifying and controlling outbreaks and in establishing public health policy.

HAND HYGIENE
The most important tool in any infection control program is good hand hygiene. Although much attention is directed at the type of cleansing agent employed, the most important aspect of hand washing is placing the hands under water and using friction with or without soap. Studies show that a 15 sec scrub removes the majority of transient flora but does not alter hand permanent flora. A variety of hand gels and rubs can be used in place of hand washing. Waterless hand hygiene products increase hand hygiene compliance and save time; these agents are the preferred agents for routine hand hygiene when hands are not visibly soiled. These products are effective in killing most microbes but do not remove dirt or debris. However, they are ineffective against C. difficile spores, requiring the use of other cleansing products during hospital C. difficile outbreaks. Hands should be cleaned before and after every patient encounter. In hospital hand washing compliance studies, physicians are usually the least-compliant group studied, and compliance programs must pay special attention to this group of caregivers.

STANDARD PRECAUTIONS
Standard precautions, formerly known as universal precautions, are intended to protect healthcare workers from pathogens and should be used whenever there is direct contact with patients. Infected patients are often contagious before symptoms of disease develop. Asymptomatic, infected patients are quite capable of transmitting infectious agents. Standard precautions involve the use of barriers—gloves, gowns, masks, goggles, and face shields—as needed, to prevent transmission of microbes associated with contact with blood and body fluids (Table 173-1).
ISOLATION
Isolation of patients infected with transmissible pathogens decreases the risk of nosocomial transmission of organisms to staff and other patients. The specific type of isolation depends upon the infecting agent and potential route of transmission. Transmission by contact is the most common mode of pathogen transmission and involves direct contact with the patient or contact with a contaminated intermediate object. Contact isolation requires the use of gown and gloves when in contact with the patient or immediately surroundings. Transmission by droplets involves the propulsion of infectious large particles over a short distance (<3 ft), with deposition on another's mucous membranes or skin. Droplet isolation requires the use of gloves and gowns, as well as masks and eye guards, when closer than 3-6 ft to the patient. Airborne transmission occurs by dissemination of evaporated droplet nuclei (≤5 µm) or dust particles carrying an infectious agent. Airborne isolation requires the use of masks and negative-pressure air-handling systems to prevent spread of the infectious agent. In the case of active pulmonary tuberculosis in older children and adults, severe acute respiratory syndrome, or avian influenza, the use of special high-density masks (N-95) or self-contained breathing systems (PAPR) is recommended. Positive-pressure HEPA-filtered air handling systems are used in some institutions for housing seriously immunocompromised patients.

Standard precautions are indicated for all patients and are appropriate for use in the clinic as well as the hospital. Additionally, for hospitalized patients, further transmission-based precautions are indicated for certain infections (Table 173-2). For contact and droplet isolation, single rooms are preferred but not required. Cohorting children infected with the same pathogen is acceptable, but the etiologic diagnosis should be confirmed by laboratory methods before exposing infected children to one another. Transmission-based isolation precautions should be continued for as long as a patient is considered contagious.

The use of isolation techniques in outpatient settings has not been well studied. Professional offices should establish procedures to ensure that proper cleaning, disinfection, and sterilization methods are employed. Many practices and clinics provide separate waiting areas for acquiring infection or developing adverse outcome following infection. Contact with the patient or immediate surroundings. Transmission by droplets involves the propulsion of infectious large particles over a short distance (<3 ft), with deposition on another's mucous membranes or skin. Droplet isolation requires the use of gloves and gowns, as well as masks and eye guards, when closer than 3-6 ft to the patient. Airborne transmission occurs by dissemination of evaporated droplet nuclei (≤5 µm) or dust particles carrying an infectious agent. Airborne isolation requires the use of masks and negative-pressure air-handling systems to prevent spread of the infectious agent. In the case of active pulmonary tuberculosis in older children and adults, severe acute respiratory syndrome, or avian influenza, the use of special high-density masks (N-95) or self-contained breathing systems (PAPR) is recommended. Positive-pressure HEPA-filtered air handling systems are used in some institutions for housing seriously immunocompromised patients.

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The use of isolation techniques in outpatient settings has not been well studied. Professional offices should establish procedures to ensure that proper cleaning, disinfection, and sterilization methods are employed. Many practices and clinics provide separate waiting areas

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Table 173-1  Recommendations for Application of Standard Precautions for Care of All Patients in All Healthcare Settings

<table>
<thead>
<tr>
<th>COMPONENT</th>
<th>RECOMMENDATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hand hygiene</td>
<td>Before and after each patient contact, regardless of whether gloves are used. After contact with blood, body fluids, secretions, excretions, or contaminated items; immediately after removing gloves; before and after entering patient rooms. Alcohol-containing antiseptic hand rubs preferred except when hands are visibly soiled with blood or other proteinaceous materials or if exposure to spores (e.g., Clostridium difficile, Bacillus anthracis) is likely to have occurred; in those cases, soap and water necessary.</td>
</tr>
<tr>
<td>PERSONAL PROTECTIVE EQUIPMENT</td>
<td></td>
</tr>
<tr>
<td>Gloves</td>
<td>For touching blood, body fluids, secretions, excretions, or contaminated items; for touching mucous membranes and nonintact skin. Employ hand hygiene before and after glove use.</td>
</tr>
<tr>
<td>Gown</td>
<td>During procedures and patient-care activities when contact of clothing or exposed skin with blood/body fluids, secretions, or excretions is anticipated.</td>
</tr>
<tr>
<td>Mask, eye protection (goggles), face shield</td>
<td>During procedures and patient-care activities likely to generate splashes or sprays of blood, body fluids, or secretions, such as suctioning and endotracheal intubation, to protect healthcare personnel. For patient protection, use of a mask by the person inserting an epidural anesthesia needle or performing myelograms when prolonged exposure of the puncture site is likely to occur.</td>
</tr>
<tr>
<td>Soiled patient-care equipment</td>
<td>Handle in a manner that prevents transfer of microorganisms to others and to the environment. Wear gloves if equipment is visibly contaminated. Perform hand hygiene.</td>
</tr>
<tr>
<td>ENVIRONMENT</td>
<td>Develop procedures for routine care, cleaning, and disinfection of environmental surfaces, especially frequently touched surfaces in patient care areas.</td>
</tr>
<tr>
<td>Textiles (linens) and laundry</td>
<td>Handle in a manner that prevents transfer of microorganisms to others and the environment.</td>
</tr>
<tr>
<td>PATIENT CARE</td>
<td>Do not recap, bend, break, or handle used needles; if recapping is required, use a 1-handed scoop technique only. Use needle-free safety devices when available, placing used sharps in puncture-resistant container. Use a sterile, single-use, disposable needle and syringe for each injection. Single-dose medication vials preferred when medications may be administered to more than 1 patient. Use mouthpiece, resuscitation bag, or other ventilation devices to prevent contact with mouth and oral secretions. Prioritize for single-patient room if patient is at increased risk for transmission, is likely to contaminate the environment, is unable to maintain appropriate hygiene, or is at increased risk for acquiring infection or developing adverse outcome following infection. Instruct symptomatic persons to cover nose/mouth when sneezing or coughing; use tissues with disposal in no-touch receptacles. Employ hand hygiene after soiling of hands with respiratory secretions. Wear surgical mask if tolerated or maintain spatial separation (&gt;3 ft if possible).</td>
</tr>
</tbody>
</table>

Table 173-2  Clinical Syndromes or Conditions Warranting Empiric Transmission-Based Precautions in Addition to Standard Precautions Pending Confirmation of Diagnosis

<table>
<thead>
<tr>
<th>CLINICAL SYNDROME OR CONDITION†</th>
<th>POTENTIAL PATHOGENS‡</th>
<th>EMPIRIC PRECAUTIONS (ALWAYS INCLUDES STANDARD PRECAUTIONS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DIARRHEA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute diarrhea with a likely infectious cause in an incontinent or diapered patient</td>
<td>Enteric pathogens†</td>
<td>Contact precautions (pediatrics and adult)</td>
</tr>
<tr>
<td>Meningitis</td>
<td>Neisseria meningitidis</td>
<td>Droplet precautions for 1st 24 hr of antimicrobial therapy; mask and face protection for intubation</td>
</tr>
<tr>
<td></td>
<td>Enteroviruses</td>
<td>Contact precautions for infants and children</td>
</tr>
<tr>
<td></td>
<td>Mycobacterium tuberculosis</td>
<td>Airborne precautions if pulmonary infiltrate</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Airborne precautions plus contact precautions if potentially infectious draining body fluid present</td>
</tr>
<tr>
<td>RASH OR EXANTHEMS, GENERALIZED, ETIOLOGY UNKNOWN</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Petechial/ecchymotic with fever (general)</td>
<td>Neisseria meningitides</td>
<td>Droplet precautions for 1st 24 hr of antimicrobial therapy</td>
</tr>
<tr>
<td>If positive history of travel to an area with an ongoing outbreak of VHF in the 10 days before onset of fever</td>
<td>Ebola, Lassa, Marburg viruses</td>
<td>Droplet precautions plus contact precautions, with face/eye protection, emphasizing safety sharps and barrier precautions when blood exposure likely. Use N-95 or higher respiratory protection when aerosol-generating procedure performed</td>
</tr>
<tr>
<td>Vesicular</td>
<td>Varicella-zoster, herpes simplex, variola (smallpox), vaccinia viruses</td>
<td>Airborne plus contact precautions</td>
</tr>
<tr>
<td></td>
<td>Vaccinia virus</td>
<td>Contact precautions only if herpes simplex, localized zoster in an immunocompetent host or vaccinia viruses likely</td>
</tr>
<tr>
<td>Maculopapular with cough, coryza, and fever</td>
<td>Rubeola (measles) virus</td>
<td>Airborne precautions</td>
</tr>
<tr>
<td>RESPIRATORY INFECTIONS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough/fever/upper lobe pulmonary infiltrate in an HIV-negative patient or a patient at low risk for human immunodeficiency virus (HIV) infection</td>
<td>M. tuberculosis, respiratory viruses, Streptococcus pneumoniae, Staphylococcus aureus (MSSA or MRSA)</td>
<td>Airborne precautions plus contact precautions</td>
</tr>
<tr>
<td>Cough/fever/pulmonary infiltrate in any lung location in an HIV-infected patient or a patient at high risk for HIV infection</td>
<td>M. tuberculosis, respiratory viruses, S. pneumoniae, S. aureus (MSSA or MRSA)</td>
<td>Airborne precautions plus contact precautions</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Use eye/face protection if aerosol-generating procedure performed or contact with respiratory secretions anticipated</td>
</tr>
<tr>
<td></td>
<td></td>
<td>If tuberculosis is unlikely and there are no AIIRs and/or respirators available, use droplet precautions instead of airborne precautions</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tuberculosis more likely in HIV-infected individual than in HIV-negative individual</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Airborne plus contact precautions plus eye protection</td>
</tr>
<tr>
<td></td>
<td></td>
<td>If SARS and tuberculosis unlikely, use droplet precautions instead of airborne precautions</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Contact plus droplet precautions; droplet precautions may be discontinued when adenovirus and influenza have been ruled out</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Airborne precautions plus contact precautions</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Use eye/face protection if aerosol-generating procedure performed or contact with respiratory secretions anticipated</td>
</tr>
<tr>
<td></td>
<td></td>
<td>If tuberculosis is unlikely and there are no AIIRs and/or respirators available, use droplet precautions instead of airborne precautions</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tuberculosis more likely in HIV-infected individual than in HIV-negative individual</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Airborne plus contact precautions plus eye protection</td>
</tr>
<tr>
<td></td>
<td></td>
<td>If SARS and tuberculosis unlikely, use droplet precautions instead of airborne precautions</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Contact plus droplet precautions; droplet precautions may be discontinued when adenovirus and influenza have been ruled out</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Airborne precautions plus contact precautions</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Use eye/face protection if aerosol-generating procedure performed or contact with respiratory secretions anticipated</td>
</tr>
<tr>
<td></td>
<td></td>
<td>If tuberculosis is unlikely and there are no AIIRs and/or respirators available, use droplet precautions instead of airborne precautions</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tuberculosis more likely in HIV-infected individual than in HIV-negative individual</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Airborne plus contact precautions plus eye protection</td>
</tr>
<tr>
<td></td>
<td></td>
<td>If SARS and tuberculosis unlikely, use droplet precautions instead of airborne precautions</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Contact plus droplet precautions; droplet precautions may be discontinued when adenovirus and influenza have been ruled out</td>
</tr>
<tr>
<td>SKIN OR WOUND INFECTION</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abscess or draining wound that cannot be covered</td>
<td>S. aureus (MSSA or MRSA), group A streptococcus</td>
<td>Contact precautions</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Add droplet precautions for the 1st 24 hr of appropriate antimicrobial therapy if invasive Group A streptococcal disease is suspected</td>
</tr>
</tbody>
</table>

*Infection control professionals should modify or adapt this table according to local conditions. To ensure that appropriate empiric precautions are implemented always, hospitals must have systems in place to evaluate patients routinely according to these criteria as part of their preadmission and admission care.

†The organisms listed under the column “Potential Pathogens” are not intended to represent the complete, or even most likely, diagnoses, but rather possible etiologic agents that require additional precautions beyond Standard Precautions until they can be ruled out.

‡These pathogens include enterohemorrhagic Escherichia coli O157:H7, Shigella spp., hepatitis A virus, noroviruses, rotavirus, Clostridium difficile.

AIIR, airborne infection isolation rooms; MRSA, methicillin-resistant Staphylococcus aureus; MSSA, methicillin-susceptible Staphylococcus aureus; SARS, severe acute respiratory syndrome; SARS-CoV, severe acute respiratory syndrome-associated coronavirus; VHF, viral hemorrhagic fever.

Common Surgical Procedures for Which Perioperative Prophylactic Antibiotics Are Recommended

Infection


Additional measures

Other preventive measures include aseptic technique, catheter care, prudent use of antibiotics, isolation of contagious patients, periodic cleaning of the environment, disinfection and sterilization of medical equipment, reporting of infections, safe handling of needles and other sharp instruments, and establishment of employee health services. Aseptic technique must be used for all invasive procedures, including catheter placement and manipulation. The use of barrier techniques at the time of intravenous catheter placement has reduced the rate of catheter-related bloodstream infections by half. Appropriately catheter use also includes limiting the duration and number of catheters employed, scrubbing catheter hubs periodically, and removing catheters as soon as they become unnecessary.

Surgical prophylaxis

Surgical antibiotic prophylaxis should be employed when there is a high risk of postoperative infection or when the consequences of such infection would be catastrophic. The choice of prophylactic antibiotic depends on the surgical site and type of surgery (Table 173-3). A useful classification of surgical procedures based upon infectious risk recognizes 4 preoperative wound categories: clean wounds, clean-contaminated wounds, contaminated wounds, and dirty and infected wounds. Clinical recommendations regarding antibiotic prophylaxis have been made by the American College of Surgeons, the Surgical Infection Society, and the American Academy of Pediatrics.

Clean wounds are uninfected operative wounds where no inflammation is noted at the operative site and respiratory, alimentary, and genitourinary tracts and the oropharynx are not entered. Such wounds are often the result of nonemergent procedures with primary closure or drained via a closed system. Operative incisional wounds after nonpenetrating trauma are included in this category. For clean wounds, prophylactic antimicrobial therapy is not recommended except in patients at high risk for infection and in circumstances in which the consequences of infection would be potentially life threatening, as with implantation of a foreign body such as a prosthetic heart valve or cerebrospinal fluid shunt, open heart surgery for repair of structural defects, and surgery in immunocompromised patients or small infants.

Clean-contaminated wounds are operative wounds in which the respiratory, alimentary, or genitourinary tract is entered under controlled conditions and that do not have unusual bacterial contamination preoperatively. These wounds occur in operations that involve the biliary tract, appendix, vagina, and oropharynx where no evidence of infection or major break in technique is encountered, as well as in urgent or emergency surgery in an otherwise clean procedure. In procedures involving clean-contaminated wounds, the risk for bacterial contamination and infection is variable. Recommendations for pediatric patients derived from data on adults suggest that antibiotic prophylaxis be provided for procedures in children with obstructive jaundice, certain alimentary tract procedures, and urinary tract surgery or instrumentation in the presence of bacteriuria or obstructive uropathy.

Contaminated wounds include open, fresh, and accidental wounds; major breaks in otherwise sterile operative technique; gross spillage from the gastrointestinal tract; penetrating trauma occurring >4 hr earlier; and incisions in which acute nonpurulent inflammation is encountered.

Dirty and infected wounds include penetrating traumatic wounds >4 hr prior to surgery, those with retained devitalized tissue, and those in which clinical infection is apparent or in which the viscera have been perforated. In contaminated and dirty or infected wound procedures, antimicrobial therapy is indicated and may need to be continued for several days. In these cases, antibiotic therapy is considered therapeutic rather than truly prophylactic.

<table>
<thead>
<tr>
<th>Table 173-3</th>
<th>Common Surgical Procedures for Which Perioperative Prophylactic Antibiotics Are Recommended</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SURGICAL PROCEDURE</strong></td>
<td><strong>LIKELY PATHOGENS</strong></td>
</tr>
<tr>
<td>Clean Wounds</td>
<td>Cardiac surgery (e.g., open heart surgery)</td>
</tr>
<tr>
<td></td>
<td>Vascular surgery</td>
</tr>
<tr>
<td></td>
<td>Neurosurgery</td>
</tr>
<tr>
<td></td>
<td>Orthopedic surgery (e.g., joint replacement)</td>
</tr>
<tr>
<td>Clean Contaminated Wounds</td>
<td>Head and neck surgery involving the oral cavity or pharynx</td>
</tr>
<tr>
<td></td>
<td>Gastrointestinal and genitourinary surgery</td>
</tr>
<tr>
<td>Contaminated Wounds</td>
<td>Traumatic wounds (e.g., compound fracture)</td>
</tr>
<tr>
<td>Dirty Wounds</td>
<td>Appendectomy, penetrating abdominal wounds, colorectal surgery</td>
</tr>
</tbody>
</table>

Prophylactic antibiotics should be administered, preferably intravenously, within an hour prior to skin incision, with the intent of having peak serum concentrations of the drug present in blood and tissues around the time of incision. Adequate plasma and tissue concentration of the antibiotic should be maintained until the incision is closed. Intraoperative antibiotic dosing may be necessary if surgery is prolonged and/or the antibiotic being employed has a short intravascular half-life. Continuation of prophylactic therapy after the procedure is not recommended. In cases of contaminated surgical sites, antibiotics are continued as therapy for infection at the site. For patients undergoing colonic procedures, additional oral antibiotics may be employed and should also be given on the day before surgery.

The selection of antibiotic regimen for prophylaxis is based on the procedure, the likely contaminating organisms, and antibiotic. Because of the variety of antibiotics available, many regimens are acceptable (see Table 173-2).

**EMPLOYEE HEALTH**

Employee health is important in hospital-based infection control because employees are at risk for acquiring infection from patients and infected employees pose a potential risk to patients. This risk is minimized by use of standard precautions and hand hygiene before and after all patient contacts. Within hospitals, employee health services or departments of occupational safety and health manage employee health issues. New employees should be screened for the presence of infectious diseases. Their immunization history should be noted, and necessary immunizations should be offered.

All healthcare workers (medical and nonmedical, paid or volunteer, full time or part time, student or nonstudent, with or without patient care responsibilities) who work within facilities providing healthcare, inpatient or outpatient, should be immune to measles, rubella, and varicella. All workers who are at risk of exposure to blood or body fluids should be immunized against hepatitis B. In pediatric institutions, employees with patient contact should be urged to receive the pertussis booster vaccine. Annual influenza immunization is strongly recommended for all healthcare workers, and institutions are being ranked publicly regarding employee immunization rates as a measure of quality of care. Many healthcare facilities have now made annual influenza vaccination mandatory for employees unless there are legitimate medical reasons for nonimmunization. Such a program reduces staff illness and absenteeism and decreases HAI. Immunizations should be encouraged and should be provided free of charge whenever possible to enhance compliance.

All healthcare workers with duties involving face-to-face contact with patients with suspected or confirmed tuberculosis (including transport staff) should be included in a tuberculosis screening program at the time of hiring and may require periodic retesting if the workplace is determined to be a high-prevalence environment for tuberculosis. Each medical office and hospital must comply with the rules developed by the Occupational Safety and Health Administration. Each office and hospital should have written policies about exclusion of infected and ill staff from direct patient care. Staff should be encouraged to not report for work if they are ill. Regular educational sessions should be performed to ensure that staff are aware of prevention and control methods and that they adhere to such policies.

_Bibliography is available at Expert Consult._
Infectious Diseases

Chapter 174
Childcare and Communicable Diseases
Linda A. Waggoner-Fountain

More than 25 million children <5 yr of age attend a childcare facility. These facilities can include some type of out-of-home care on a routine basis, such as nursery school, preschool, or a full-day program based either in a childcare center or in another person's home. Regardless of the age at entry, children entering daycare are more prone to infections. Exposure to larger groups of children increases a child's probability of getting sick. Childcare facilities can be classified on the basis of size of enrollment, ages of attendees, health status of the children enrolled, and type of setting. As defined in the United States, childcare facilities consist of childcare centers, small and large family childcare homes, and facilities for ill children or for children with special needs. Centers are licensed and regulated by state governments and care for a larger number of children than are cared for in family homes. In contrast, family childcare homes are designated as small (1-6 children) or large (7-12 children), may be full day or part day, and may be designed for either daily or sporadic attendance. Family childcare homes generally are not licensed or registered, depending on state requirements.

Although the majority of children who attend childcare facilities are cared for in childcare home settings, most studies of infectious diseases among children in out-of-home childcare have been conducted among infants (birth to 12 mo of age) and toddlers (13-36 mo of age) who are enrolled in a childcare center. Almost any organism has the potential to be spread and to cause disease in a childcare setting. Epidemiologic studies have established that children in childcare facilities are 2-18 times more likely to acquire a variety of infectious diseases than are children not enrolled in childcare (Table 174-1). Children in childcare facilities are more likely both to receive more courses of antimicrobial agents for longer periods and to acquire antibiotic-resistant organisms. Transmission of infectious agents in group care depends on the age and immune status of the children, season, hygiene practices, crowding, environmental characteristics of the facilities, and characteristics of the pathogen, including its infectivity, survivability in the environment, and virulence. Rates of infection, duration of illness, and risk for hospitalization tend to decrease among children in childcare facilities after the 1st 6 mo of attendance and decline to levels observed among home-bound children after 3 yr of age. Adult caregivers are also at increased risk for acquiring and transmitting infectious diseases, particularly in the 1st yr of contact with children in these settings.

EPIDEMIOLOGY
Infectious illnesses among children in childcare and their contacts occur in several different patterns. With many viral infections, children often are infectious 2-3 days before they exhibit symptoms of illness. Respiratory tract infections and diarrhea are the most common diseases associated with childcare. These infections occur in children, childcare staff, and household contacts, and can spread to the community. Respiratory tract pathogens and enteric pathogens can infect both children and adults in these settings but may have varying degrees of impact, depending on the person's underlying health, previous exposures, and age. Infections caused by hepatitis A virus might not be clinically apparent in young children who attend childcare, but can cause major clinical disease among older children and adult contacts, including childcare staff and household contacts. Other diseases, such as otitis media and varicella, usually affect children rather than adults. Some common infections, such as cytomegalovirus (CMV) and parvovirus B19 infections, can have serious consequences for the fetuses.
Childcare attendance is associated with nasopharyngeal carriage of serotypes of *H. influenzae* and *S. pneumoniae*. The risk for developing otitis media is 2-3 times higher among children in childcare than among children cared for at home. Outbreaks of diarrhea, which occur frequently in childcare centers, usually are caused by enteric viruses such as rotaviruses, caliciviruses including norovirus, enteric adenoviruses, and astroviruses, or by enteric parasites such as *G. lambia* or *Cryptosporidium*. The most common enteropathogens, such as rotavirus and *G. lambia*, are characterized by low infective doses and high rates of asymptomatic excretion among children in childcare. Both enteropathogens such as *Shigella* and *E. coli* O157:H7 and, less commonly, *Campylobacter*, *C. difficile*, and *Bacillus cereus* also have caused outbreaks of diarrhea in childcare settings. *Salmonella* rarely is associated with outbreaks of diarrhea in childcare settings, because person-to-person spread of this organism is uncommon. Outbreaks of hepatitis A in children enrolled in childcare facilities have resulted in community-wide outbreaks. Hepatitis A usually is mild or asymptomatic in young children and often is identified only after symptomatic illness becomes apparent among either older children or adult contacts of children in childcare. Enteropathogens and hepatitis A viruses are transmitted in childcare facilities by the fecal-oral route and only rarely by contaminated food or water. Children in diapers constitute a high risk for the spread of gastrointestinal infections through the fecal-oral route. Enteric illness and hepatitis A are more common in centers that care for children who are not toilet trained and where proper hygienic practices are not followed.

**SKIN DISEASES**

The most commonly recognized skin infections or infestations in children in childcare are impetigo caused by *S. aureus* or group A streptococcus, pediculosis, scabies, tinea capitis, and tinea corporis. Many of these diseases are spread by contact with infected linens, clothing, hairbrushes, and hats and through direct personal contact; they more often affect children >2 yr of age. The magnitude of these infections and infestations in children in childcare is not known. *Parvovirus* B19, which causes fifth disease (erythema infectiosum), is spread through the respiratory route, and outbreaks have occurred in childcare centers. The rash of fifth disease is a systemic manifestation of parvovirus B19 infection; the child is no longer contagious once the rash is present (see Chapter 251). The greatest health hazard is for pregnant women and immunocompromised persons, who are not toilet trained and where proper hygienic practices are not followed.

**INVASIVE ORGANISMS**

Prior to universal immunization, primary *H. influenzae* type b invasive disease was more common among children in childcare, although evidence for increased risk for secondary cases from *H. influenzae* type b in a childcare setting remains less convincing. There is an indication that the risk for primary disease caused by *Neisseria meningitidis* is higher among children in childcare than among children cared for at home. Childcare attendance is associated with nasopharyngeal carriage of penicillin-resistant *S. pneumoniae* and invasive pneumococcal disease, especially among children with a history of recurrent otitis media and use of antibiotics. Secondary spread of *S. pneumoniae* and *N. meningitidis* has been reported, indicating the potential for outbreaks to occur in this setting. Routine use of pneumococcal conjugate vaccine has decreased the incidence of invasive disease and reduced carriage of serotypes of *S. pneumoniae* contained in the vaccine both of pregnant women or for immunocompromised persons. Hepatitis B virus (HBV) transmission has been reported rarely in a childcare setting. Transmission of hepatitis C virus (HCV), hepatitis D virus (HDV), and HIV has never been reported in a childcare setting. Both infections and infestations of the skin and hair may be acquired through contact with contaminated linens or through close personal contact.

**RESPIRATORY TRACT INFECTIONS**

Respiratory tract infections account for the majority of childcare-related illnesses. Children <2 yr of age who attend childcare centers have more upper and lower respiratory tract infections than do age-matched children not in childcare. The organisms responsible for these illnesses are similar to those that circulate in the community and include respiratory syncytial virus, parainfluenza viruses, influenza viruses, adenoviruses, rhinoviruses, coronaviruses, parvovirus B19, and *S. pneumoniae*. The risk for developing otitis media is 2-3 times greater among children who attend childcare centers than among children cared for at home. Most prescriptions for antibiotics for children <3 yr of age in childcare are to treat otitis media. These children also are at increased risk for recurrent otitis media, which further increases use of antimicrobial agents in this population. Pharyngeal carriage of group A streptococcus occurs earlier among children in childcare, although outbreaks of clinical infections with this organism are uncommon. Airborne droplets from the respiratory tract can spread via direct contact with another person’s mucous membranes or by touching surfaces contaminated with secretions. This intimate contact is a routine part of the play and care of young children, regardless of setting. The most common surfaces from which airborne droplets can be spread are the hands; consequently, the most efficient form of infection control in the childcare setting is good hand washing.

**INFECTIONS IN CHILD CARE**

Table 174-1 Infectious Diseases in the Childcare Setting

<table>
<thead>
<tr>
<th>DISEASE</th>
<th>INCREASED INCIDENCE WITH CHILD CARE</th>
</tr>
</thead>
<tbody>
<tr>
<td>RESPIRATORY TRACT INFECTIONS</td>
<td></td>
</tr>
<tr>
<td>Otitis media</td>
<td>Yes</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>Probably</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>Probably</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>Yes</td>
</tr>
<tr>
<td>GASTROINTESTINAL TRACT INFECTIONS</td>
<td></td>
</tr>
<tr>
<td>Diarrhea (rotavirus, calicivirus, astrovirus, enteric adenovirus, <em>Giardia lambia</em>, <em>Cryptosporidium, Shigella, Escherichia coli O157:H7</em>, and <em>Clostridium difficile</em>)</td>
<td>Yes</td>
</tr>
<tr>
<td>Hepatitis A</td>
<td>Yes</td>
</tr>
<tr>
<td>SKIN DISEASES</td>
<td></td>
</tr>
<tr>
<td>Impetigo</td>
<td>Probably</td>
</tr>
<tr>
<td>Scabies</td>
<td>Probably</td>
</tr>
<tr>
<td>Pediculosis</td>
<td>Probably</td>
</tr>
<tr>
<td>Tinea (ringworm)</td>
<td>Probably</td>
</tr>
<tr>
<td>INVASIVE BACTERIA INFECTIONS</td>
<td></td>
</tr>
<tr>
<td><em>Haemophilus influenzae type b</em></td>
<td>No*</td>
</tr>
<tr>
<td><em>Neisseria meningitidis</em></td>
<td>Probably</td>
</tr>
<tr>
<td><em>Streptococcus pneumoniae</em></td>
<td>Yes</td>
</tr>
<tr>
<td>ASEPTIC MENINGITIS</td>
<td></td>
</tr>
<tr>
<td>Enteroviruses</td>
<td>Probably</td>
</tr>
<tr>
<td>HERPSVIRUS INFECTIONS</td>
<td></td>
</tr>
<tr>
<td>Cytomegalovirus</td>
<td>Yes</td>
</tr>
<tr>
<td>Varicella-zoster virus</td>
<td>Yes</td>
</tr>
<tr>
<td>Herpes simplex virus</td>
<td>Probably</td>
</tr>
<tr>
<td>BLOOD-BORNE INFECTIONS</td>
<td></td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>Few case reports</td>
</tr>
<tr>
<td>HIV</td>
<td>No cases reported</td>
</tr>
<tr>
<td>Hepatitis C</td>
<td>No cases reported</td>
</tr>
<tr>
<td>VACCINE-PREVENTABLE DISEASES</td>
<td></td>
</tr>
<tr>
<td>Measles, mumps, rubella, diphtheria, pertussis, tetanus</td>
<td>Not established</td>
</tr>
<tr>
<td>Polio</td>
<td>No</td>
</tr>
<tr>
<td><em>H. influenzae</em> type b</td>
<td>No*</td>
</tr>
<tr>
<td>Varicella</td>
<td>Yes</td>
</tr>
<tr>
<td>Rotavirus</td>
<td>Yes</td>
</tr>
</tbody>
</table>

*Not in the postvaccine era; yes in the prevaccine era.*
in the child and in younger siblings. The use of conjugate meningococcal vaccine in children <2 yr of age is anticipated in the near future and will alter the epidemiology of meningococcal disease in this age group. Outbreaks of aseptic meningitis from echovirus 30 have been reported among children in childcare centers, as well as among their parents and their teachers.

**HERPESVIRUSES**

Studies of CMV infection in childcare centers show that as many as 70% of diapered children continuously shed CMV in urine and saliva after they become infected. CMV-infected children often transmit the virus to other children with whom they have contact, as well as to their care providers and their mothers, at a rate of 8-20% per yr. Transmission occurs as a result of contact with either saliva or urine. The overwhelming majority of primary infection with and reactivation of CMV in otherwise healthy children results in asymptomatic shedding of CMV; nonetheless, this shedding can pose a health risk for previously uninfected pregnant childcare providers or immunocompromised persons (see Chapter 255). Varicella often is transmitted in childcare centers, but routine use of varicella vaccine has reduced this risk. Vaccinated children who become infected with varicella often have mild, atypical symptoms and signs of disease that can result in delayed recognition and spread of infection to susceptible contacts. The role of childcare facilities in the spread of herpes simplex virus, especially during episodes of gingivostomatitis, requires further clarification.

**BLOOD-BORNE PATHOGENS**

Because it is impossible to identify every child who might have a blood-borne infection such as hepatitis B, C, or D, or HIV, it is critical that standard universal precautions be observed routinely to reduce the risk for transmitting these viruses. Transmission of hepatitis B among children in childcare has been documented in a few rare instances, but the risk for transmission, which already was low, declined with implementation of universal immunization of infants with hepatitis B vaccine. Transmission of hepatitis C or D in childcare settings has not been reported.

Issues about HIV in childcare include the potential risk for HIV transmission within the childcare setting and concerns of opportunistic infections of HIV-infected children. No cases of HIV transmission in out-of-home childcare have been reported. Children with HIV infection enrolled in childcare facilities should be monitored for exposure to infectious diseases, and their health and immune status should be evaluated frequently.

Some infections are spread through contact of contaminated blood with either a mucous membrane or an open wound. Although it is theoretically possible, infection is unlikely to spread via toddler biting in a group setting. Most of these bites do not break the skin, and if a bite does break the skin, the mouth of the biter does not stay on the victim long enough for blood to transfer from the victim to the biter. If there are concerns about transmission of hepatitis B, hepatitis C, or HIV infection, it is recommended to check the status of the biter rather than the bite victim as part of the initial evaluation process.

### ANTIBIOTIC USE AND BACTERIAL RESISTANCE

Antibiotic resistance has become a significant problem in childcare facilities, because the incidence of infection by organisms resistant to frequently used antimicrobial agents has increased dramatically. The estimated annual rate of antibiotic use among children in childcare is 2-4 times higher than among age-matched children cared for at home and the mean duration of antibiotic treatment is 4 times longer among children in childcare. This frequency of antibiotic use combined with the propensity for person-to-person transmission of pathogens in a crowded environment has resulted in an increased prevalence of antibiotic-resistant bacteria in the respiratory and intestinal tracts, including *S. pneumoniae*, *H. influenzae*, *M. catarrhalis*, *E. coli* O157:H7, and *Shigella* species. Preliminary data do not demonstrate a difference between meticillin-resistant *S. aureus* and methicillin-susceptible *S. aureus* strains in children in childcare.

### PREVENTION

Written policies designed to prevent or to control the spread of infectious agents in a childcare center should be available and should be reviewed regularly. It is suggested that all programs use a health consultant to help with development and implementation of infection-control policies. Standards for environmental and personal hygiene should include maintenance of current immunization records for both children and staff; appropriate policies for exclusion of ill children and caretakers; targeting of potentially contaminated areas for frequent cleaning; adherence to appropriate procedures for changing diapers; appropriate handling of food; management of pets; and surveillance for and reporting of communicable diseases. Staff whose primary function is preparing food should not change diapers. Strategies for improving adherence to these standards should be implemented. Appropriate and thorough hand hygiene is the most important factor for reducing infectious diseases in the childcare setting. Children at risk for introducing an infectious disease should not attend childcare until they are no longer contagious (Tables 174-2 and 174-3).

In the United States, there are 15 diseases and organisms for which all children should be immunized unless there are contraindications: diphtheria, pertussis, tetanus, measles, mumps, rubella, polio, hepatitides A and B, varicella, *H. influenzae* type b, *S. pneumoniae*, rotavirus, *N. meningitidis*, and influenza. Rates of immunization among children in licensed childcare facilities are high, in part because of laws in almost all states that require age-appropriate immunizations of children who attend licensed childcare programs. Routine vaccination has had a significant beneficial effect on the health of children in childcare settings. Vaccines against *influenza*, *H. influenzae* type b, hepatitis B, rotavirus, varicella, *S. pneumoniae*, and hepatitis A are of particular benefit to children in childcare centers. Influenza vaccination of younger infants reduces influenza infection and secondary sequelae in both children and the adults who care for them in both their home and in childcare settings. Childcare providers should receive all immunizations that are recommended routinely for adults and have a preemployment health evaluation, including a tuberculin skin test. Local public

### Table 174-2 Disease- or Condition-Specific Recommendations for Exclusion of Children in Out-of-Home Childcare

<table>
<thead>
<tr>
<th>CONDITION</th>
<th>MANAGEMENT OF CASE</th>
<th>MANAGEMENT OF CONTACTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>HAV infection</td>
<td>Serologic testing to confirm HAV infection in suspected cases Exclusion until 1 wk after onset of jaundice</td>
<td>If ≥1 case is confirmed in child or staff attendees or ≥2 cases in households of staff or attendees, HAV vaccine or Ig should be administered within 14 days of exposure to unimmunized staff and attendees In centers without diapered children, HAV vaccine or Ig should be given to unimmunized classroom contacts of index case Asymptomatic Ig recipients may return after receipt of Ig</td>
</tr>
<tr>
<td>Impetigo</td>
<td>Exclusion until 24 hr after treatment has been initiated Lesions on exposed skin covered with watertight dressing</td>
<td>No intervention needed unless additional lesions develop</td>
</tr>
<tr>
<td>CONDITION</td>
<td>MANAGEMENT OF CASE</td>
<td>MANAGEMENT OF CONTACTS</td>
</tr>
<tr>
<td>-----------</td>
<td>--------------------</td>
<td>------------------------</td>
</tr>
<tr>
<td>Measles</td>
<td>Exclusion until 4 days after beginning of rash and when the child is able to participate</td>
<td>Immunize exposed children without evidence of immunity within 72 hr of exposure. Children who do not receive vaccine within 72 hr or who remain unimmunized after exposure should be excluded until at least 2 wk after onset of rash in the last case of measles</td>
</tr>
<tr>
<td>Mumps</td>
<td>Exclusion until 5 days after onset of parotid gland swelling</td>
<td>In outbreak setting, people without documentation of immunity should be immunized or excluded. Immediate readmission may occur following immunization. Unimmunized people should be excluded for ≥26 days following onset of parotitis in last case</td>
</tr>
<tr>
<td>Pediculosis capitis (head lice)</td>
<td>Treatment at end of program day and readmission on completion of 1st treatment</td>
<td>Household and close contacts should be examined and treated if infested. No exclusion is necessary</td>
</tr>
<tr>
<td>Pertussis</td>
<td>Exclusion until 5 days of appropriate antimicrobial therapy course have been completed</td>
<td>Immunization and chemoprophylaxis should be administered as recommended for household contacts. Symptomatic children and staff should be excluded until completion of 5 days of antimicrobial therapy course. Untreated adults should be excluded until 21 days after onset of cough</td>
</tr>
<tr>
<td>Rubella</td>
<td>Exclusion until 6 days after onset of rash for postnatal infection</td>
<td>Pregnant contacts should be evaluated</td>
</tr>
<tr>
<td>Salmonella serotype Typhi infection</td>
<td>Exclusion until diarrhea resolves</td>
<td>Stool cultures should be performed for attendees and staff. Infected people should be excluded on the basis of age</td>
</tr>
<tr>
<td>Non-serotype Typhi Salmonella infection</td>
<td>Exclusion until diarrhea resolves. Negative stool culture results not required for non-serotype Typhi Salmonella species</td>
<td>Symptomatic contacts should be excluded until symptoms resolve. Stool cultures are not required for asymptomatic contacts. Antimicrobial therapy is not recommended for asymptomatic infection or uncomplicated diarrhea or for contacts</td>
</tr>
<tr>
<td>Scabies</td>
<td>Exclusion until after treatment given</td>
<td>Close contacts with prolonged skin-to-skin contact should have prophylactic therapy. Bedding and clothing in contact with skin of infected people should be laundered</td>
</tr>
<tr>
<td>Shiga toxin–producing Escherichia coli, including E. coli O157:H7, or Shigella infection</td>
<td>Exclusion until diarrhea resolves and results of 2 stool cultures are negative for these organisms, depending on state regulations</td>
<td>Meticulous hand hygiene; stool cultures should be performed for contacts. Center(s) with cases should be closed to new admissions during E. coli O157:H7 outbreak</td>
</tr>
<tr>
<td>Staphylococcus aureus skin infections</td>
<td>Exclusion only if skin lesions are draining and cannot be covered with a watertight dressing</td>
<td>Meticulous hand hygiene. Cultures of contacts are not recommended</td>
</tr>
<tr>
<td>Streptococcal pharyngitis</td>
<td>Exclusion until 24 hr after treatment has been initiated and the child is able to participate in activities</td>
<td>Symptomatic contacts of documented cases of group A streptococcal infection should be tested and treated if test results are positive</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>For active disease, exclusion until determined to be noninfectious by physician or health department authority. May return to activities after therapy is instituted, symptoms have diminished, and adherence to therapy is documented. No exclusion for latent tuberculosis infection</td>
<td>Local health department personnel should be informed for contact investigation</td>
</tr>
<tr>
<td>Varicella</td>
<td>Exclusion until all lesions have dried and crusted, usually 6 days after onset of rash in immunocompetent people; may be longer in immunocompromised people</td>
<td>Varicella vaccine should be administered by 3-5 days after exposure, and varicella-zoster Ig should be administered up to 96 hr after exposure when indicated</td>
</tr>
</tbody>
</table>

HAV, hepatitis A virus; Ig, immunoglobulin.
health authorities should be notified of cases of reportable communicable disease that occur in children or providers in childcare settings.

**STANDARDS**

Every state has specific standards for licensing and reviewing childcare centers and family childcare homes. The American Academy of Pediatrics, the American Public Health Association, and the National Resource Center jointly publish comprehensive health and safety performance standards that can be used by pediatricians and other healthcare professionals to guide decisions about management of infectious diseases and other health-related matters in childcare facilities (available at [http://cfoc.nrckids.org/](http://cfoc.nrckids.org/)). Specific standards set by all states also are available on this website.

*Bibliography is available at Expert Consult.*

<table>
<thead>
<tr>
<th>SYMPTOM(S)</th>
<th>MANAGEMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Illness preventing participation in activities, as determined by childcare staff</td>
<td>Exclusion until illness resolves and able to participate in activities</td>
</tr>
<tr>
<td>Illness that requires care greater than staff can provide without compromising health and safety of others</td>
<td>Exclusion or placement in care environment where appropriate care can be provided without compromising care of others</td>
</tr>
<tr>
<td>Severe illness suggested by fever with behavior changes, lethargy, irritability, persistent crying, difficulty breathing, progressive rash</td>
<td>Medical evaluation and exclusion until symptoms have resolved</td>
</tr>
<tr>
<td>Rash with fever or behavioral change</td>
<td>Medical evaluation and exclusion until illness is determined not to be communicable</td>
</tr>
<tr>
<td>Persistent abdominal pain (≥2 hr) or intermittent abdominal pain associated with fever, dehydration, or other systemic signs and symptoms</td>
<td>Medical evaluation and exclusion until symptoms have resolved</td>
</tr>
<tr>
<td>Vomiting ≥2 times in preceding 24 hr</td>
<td>Exclusion until symptoms have resolved, unless vomiting is determined to be caused by a noncommunicable condition and child is able to remain hydrated and participate in activities</td>
</tr>
<tr>
<td>Diarrhea or stools containing blood or mucus</td>
<td>Medical evaluation and exclusion until symptoms have resolved</td>
</tr>
<tr>
<td>Oral lesions</td>
<td>Exclusion until child or staff member is considered to be noninfectious (lesions crusted and dry)</td>
</tr>
</tbody>
</table>

Bibliography


Children are traveling internationally with increasing frequency and to more “exotic” destinations that pose unique injury and disease risks. Compared to adults, children are less likely to receive pretravel advice and more likely to be seen by a medical provider or be hospitalized upon return for a travel-related illness. Primary care providers are confronted with the challenge of trying to ensure safe, healthy travel for their patient, whether travel is occurring for purposes of tourism, study abroad, visiting friends and relatives, or volunteerism. Whenever possible, health professionals are encouraged to consult with Travel Medicine specialists, especially when uncertain about pretravel advice, unique travel medicine vaccines (e.g., yellow fever, Japanese encephalitis, typhoid, rabies), and recommendations for malaria medications.

Travel medicine is a unique specialty, and experienced travel medicine practitioners provide specialized guidance on the infectious and noninfectious risks based on age, itinerary, duration, season, purpose of travel, and underlying traveler characteristics (health and vaccination status). A pretravel consultation includes the essential elements of (1) safety and preventive counseling against injuries and diseases; (2) routine, recommended, and required vaccinations, based on individual risk assessment; (3) counseling and medications for self-treatment of traveler’s diarrhea; and (4) when indicated by itinerary, malaria chemoprophylaxis.

In the United States, recommendations and vaccine requirements for travel to different countries are provided by the Centers for Disease Control and Prevention (CDC) and are available online at http://wwwnc.cdc.gov/travel/yellowbook/2014/chapter-3-infectious-diseases-related-to-travel/travel-vaccines-and-malaria-information-by-country. Some travel vaccines and medications may not be recommended based on specifics of travel itinerary, trip duration, or patient characteristics. Alternatively, some vaccinations are not approved for younger children because of lack of data or limited immunologic response, but may still confer potential benefit to the young traveler with off-label vaccine administration. In both scenarios, consultation or referral to a knowledgeable travel medicine practitioner is encouraged, especially if uncertainty exists regarding pretravel recommendations.

THE PEDIATRIC TRAVEL MEDICINE CONSULTATION
Parents of traveling children should seek medical consultation at least 4–6 wk before departure to review the travel itinerary, obtain safety and preventive counseling, ensure adequate vaccinations (routine, recommended, and required), receive necessary medications for chronic health conditions, and obtain important medications for self-treatment of traveler’s diarrhea and, when indicated, malaria chemoprophylaxis with counseling. Preparing a child to travel internationally should begin with an emphasis on the positive aspects of the upcoming trip rather than solely focusing on travel risks and diseases. Subsequent advice, vaccinations, and medications should be emphasized as important measures with the provider goal of keeping the child healthy during travel rather than to discourage traveling.
Pediatric Travelers Visiting Friends and Relatives

Compared to most children traveling internationally, the pediatric visiting-friends-and-relatives (VFR) traveler is a vulnerable population uniquely at risk for travel-related illnesses. VFR travelers may include immigrants, refugees, migrants, students, or displaced persons who are traveling back to their country of origin for purposes of visiting friends and relatives. Pediatric VFR travelers are typically children accompanying their parents or family members back to their ancestral country, where relational, social, and cultural connections remain. Compared to tourist travelers, VFR travelers are more likely to travel for longer durations, visit more remote destinations, travel by higher-risk local transportation modes, experience closer contact with the local population, and utilize fewer insect, food, and water precautions. Adult and pediatric VFR travelers are also less likely to perceive a risk of travel-related illnesses, seek pretravel advice, receive travel immunizations, or use effective malaria prophylaxis upon arrival in the destination country. VFR travel comprises 50-84% of imported malaria in children in the United States (i.e., malaria acquired outside the United States), and pediatric VFR travelers are reported to be 4 times more likely to acquire malaria than tourist travelers. Among all travelers, pediatric VFR travelers remain at higher risk for contracting hepatitis A and having symptomatic illness. Several studies suggest that VFR travelers are at disproportionate risk of acquiring typhoid fever and possibly tuberculosis. Providers should inquire if their foreign-born patients will be traveling internationally and seek opportunities to encourage pretravel consultation for VFR travelers.

SAFETY AND PREVENTIVE COUNSELING TOPOICS

Health and Evacuation Insurance, Underlying Health Conditions, and Medications

Parents should be made aware that their medical insurance policy might not provide coverage for hospitalizations or medical emergencies in foreign countries and is unlikely to cover the high cost of an emergency medical evacuation. Supplemental travel medical insurance and evacuation insurance may be purchased and are especially recommended for prolonged travel itineraries, for remote destinations, and for children with higher-risk preexisting health conditions going to countries where inpatient care at a level comparable to the traveler’s home country may not be available. A list of medical and evacuation insurance providers can be found at the U.S. Department of State’s International Travel advisory website (http://travel.state.gov/travel/cis_pa_tw/cis/cis_1470.html).

Parents of children with medical conditions should take with them a brief medical summary and a sufficient supply of prescription medications for their children, with bottles that are clearly identified by prescription labels. For children requiring care by specialists, an international directory for that specialty can be consulted. A directory of physicians worldwide who speak English and who have met certain qualifications is available from the International Association for Medical Assistance to Travelers (http://www.iamat.org/index.cfm). If medical care is needed urgently when abroad, sources of information include the American embassy or consulate, hotel managers, travel agents catering to foreign tourists, and missionary hospitals.

A travel health kit consisting of prescription medications and nonprescription items, such as acetaminophen, an antihistamine, oral rehydration solution packets, antibiotic ointment, bandages, insect repellent, and sunscreen, is highly recommended for all children. Children with persistent asthma should have bronchodilators and oral steroids prescribed for treatment of any acute asthma exacerbations encountered during overseas travel. Children with a history of angioedema, anaphylaxis, or severe allergies to food or insects should have an epinephrine autoinjector (EpiPen) and antihistamines available for use during travel.

Parents and family members should be aware of the prevalence of counterfeit medication and lack of quality control of medications in many areas of the world, particularly in low- and middle-income countries. Critical medications, including insulin and newly prescribed antimalarials, should be purchased prior to international travel and packed in original prescription containers.

Safety and Injury Prevention

Motor vehicle accidents are a leading cause of traumatic injuries to, hospitalizations of, and deaths of pediatric and adult travelers. Differences in traffic patterns should be emphasized to children, and the use of safety belts should be reinforced. When possible, child safety seats should be taken on the trip. Parents should also be aware of additional risks for small children that may exist overseas, such as open balconies, windows without screens or bars, exposed wires and electrical outlets, paint chips, pest and rodent poison, and stray animals. Water-related activities also are associated with significant injuries in pediatric travelers, and pools and oceanfronts are often unsupervised and without lifeguards at overseas destinations.

Animal Contact

Among travelers, attacks from domestic or stray animals are far more likely to occur than attacks from wild animals. Wounds from animal bites present a risk for bacterial infections, tetanus, and rabies. Dogs are responsible for more than 95% of all rabies transmission in Asia, Africa, and Latin America. Globally, the World Health Organization (WHO) estimates that there are approximately 55,000 human deaths from rabies each year, with the vast majority of cases occurring in South Asia, Southeast Asia, and Africa. Reports of rabies transmission have less commonly occurred following bites from cats and other carnivores, monkeys, and bats. Macaque monkeys, native to Asia and North Africa, can be found in urban centers and tourist sites and pose a risk for rabies and herpes B virus infections following bites and scratches.

Young children are more likely to be bitten and experience more severe facial wounds related to their short stature. As such, they are at higher risk for rabies exposure from dogs and other animals during travel and require greater supervision. Parents should always encourage their children to report bite injuries and to avoid petting, feeding, or handling dogs, monkeys, and stray animals. Before travel, tetanus vaccinations need to be current for all travelers. Children, long-term travelers, expatriates, and all individuals likely to come into contact with animals in a rabies-endemic region (primarily Africa and South and Southeast Asia) should consider preexposure vaccination for rabies before international travel (see “Rabies” below). Bite or scratch wounds should be washed thoroughly and for a prolonged time (15 min) with copious water and soap. Local wound care will substantially reduce the risk of canine and other mammalian rabies transmission. Rabies postexposure vaccination and rabies immunoglobulin should be considered. Antibiotics (amoxicillin–clavulanate) may need to be administered to a child to prevent secondary infections, especially for animal bites involving the hands and head/neck areas.

ROUTINE CHILDHOOD VACCINATIONS REQUIRED FOR PEDIATRIC TRAVEL

Parents should allow 4 or more weeks before departure for optimal administration of vaccines to their children. All children who travel should be immunized according to the routine childhood immunization schedule with all vaccines appropriate for their age. The immunization schedule can be accelerated to maximize protection for traveling children, especially for unvaccinated or incompletely vaccinated children (see Fig. 172-4 in Chapter 172). Routine and catch-up childhood vaccine schedules for healthcare professionals can be found at the CDC website (http://www.cdc.gov/vaccines/schedules/index.html).

Live-attenuated viral vaccines should be administered concurrently or 4 or more weeks apart to minimize immunologic interference. Intramuscular immunoglobulin interferes with the immune response to measles immunization and possibly to varicella immunization. If a child requires measles or varicella immunization, the vaccines should be given either 2 wk before or 3 mo after immunoglobulin administration (longer with higher doses of intravenous immunoglobulin).
Immunoglobulin does not interfere with the immune response to oral typhoid, poliovirus, or yellow fever vaccines.

Vaccine products produced in eggs (yellow fever, influenza) may be associated with hypersensitivity responses, including anaphylaxis in persons with known severe egg sensitivity. Screening by inquiring about adverse effects when eating eggs is a reasonable way to identify those at risk for anaphylaxis from receiving influenza or yellow fever vaccines. Although measles and mumps vaccines are produced in chick embryo cell cultures, children with egg allergy are at very low risk for anaphylaxis with these vaccines.

**Diphtheria-Tetanus-Pertussis**

Children traveling internationally should be fully vaccinated with diphtheria and tetanus toxoids and acellular pertussis (DTaP), having completed the 4th or 5th booster dose by 4-6 yr of age. A single dose of an adolescent/adult preparation of tetanus and diphtheria toxoids and acellular pertussis (Tdap) vaccine is recommended at 11-12 yr of age for those who have completed the recommended primary DTaP (or DTP) series.

Adolescents and adults should receive a single Tdap booster if more than 5 yr have elapsed since the last dose, as a tetanus-containing booster (Td or Tdap) may not be readily available for tetanus-prone wounds during international travel or in remote settings (adventure travel, wilderness).

**Haemophilus influenzae Type B**

*Haemophilus influenzae* type b remains a leading cause of meningitis in children 6 mo to 3 yr of age in many low- and middle-income countries. Before they travel, all unimmunized children <5 yr of age should be vaccinated (see Chapter 172). A single dose of *H. influenzae* type b vaccine should also be administered to unvaccinated or partially vaccinated children who are 5 yr of age or older if they have anatomic or functional asplenia, sickle cell disease, HIV infection, leukemia, malignancy, or other immunocompromising condition. Unvaccinated children who are >5 yr of age do not need vaccination unless they have a high-risk condition.

**Hepatitis A**

Hepatitis A is a routine childhood vaccine in the United States but requires special considerations in the traveling pediatric patient, and protection from hepatitis A in specific children may also involve the provision of immunoglobulin. For this reason, hepatitis A vaccination is covered below in "Specialized Pediatric Travel Vaccinations."

**Hepatitis B**

Hepatitis B is a travel-associated infection. Hepatitis B is highly prevalent throughout much of the world, including areas of South America, sub-Saharan Africa, eastern and southeastern Asia, and most of the Pacific basin. In certain parts of the world, 8-15% of the population may be chronically infected. Disease can be transmitted via blood transfusions not screened for hepatitis B surface antigen, exposure to unsterilized needles, close contact with local children who have open skin lesions, and sexual exposure. Exposure to hepatitis B is more likely for travelers residing for prolonged periods in endemic areas. Partial protection may be provided by 1 or 2 doses, but ideally 3 doses should be given before travel. For unvaccinated adolescents, the 1st 2 doses are 4 wk apart and are followed by a 3rd dose 8 wk later (at least 16 wk after 1st dose).

All unvaccinated children and adolescents should receive the accelerated hepatitis B vaccine series prior to travel. Because 1 or 2 doses provide some protection, hepatitis B vaccination should be initiated even if the full series cannot be completed before travel.

**Influenza and Avian Influenza**

Influenza remains the most common vaccine-preventable disease occurring among pediatric and adult travelers. The risk for exposure to influenza during international travel varies depending on the time of yr, destination, and intermingling of persons from different parts of the world where influenza may be circulating. In tropical areas, influenza can occur throughout the year, whereas in the temperate regions of the Southern hemisphere, most activity occurs from April through September. In the Northern hemisphere, influenza generally occurs from November through March. Seasonal influenza vaccination is strongly recommended for all pediatric and adolescent travelers who do not have a contraindication or severe egg allergy.

Currently, there is no available vaccine effective against avian influenza, the H5N1 virus, which has become an increasing concern worldwide. However, there are precautions for those traveling to endemic areas, which include parts of Asia, Africa, Eastern Europe, and the Middle East (see the CDC's website for a detailed list of countries). Because H5N1 influenza is spread through contact with infected birds, these precautions include avoiding direct contact with birds or surfaces with bird droppings, avoiding poultry farms or bird markets, eating only well-cooked bird meat or products, and washing hands frequently. Human-to-human transmission has been reported but is very rare and has not involved spread past 1 person. Oseltamivir is the antiviral of choice to treat avian influenza, because the virus is resistant to amantadine and rimantadine. Oseltamivir is FDA-approved for children 1 yr of age and older but can also be administered for treatment of influenza during infancy with weight-based dosing (http://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm).

**Measles-Mumps-Rubella**

Measles is still endemic in many low- and middle-income countries and in some industrialized nations. It remains a leading cause of vaccine-preventable death in much of the world. Vaccine status for measles is important for all traveling children, particularly if they are traveling to low- and middle-income countries or areas with measles outbreaks. Measles vaccine, preferably in combination with mumps and rubella vaccines (MMR), should be given to all children at 12-15 mo of age and at 4-6 yr of age, unless there is a contraindication (see Chapter 172.2). In children traveling internationally, the 2nd vaccination can be given as soon as 4 wk after the 1st, to induce immunity among those children who did not respond to the 1st MMR vaccine.

Children between the ages of 6 and 12 mo who are traveling to the low- and middle-income world should be vaccinated with monovalent measles vaccine. If the monovalent vaccine is unavailable, MMR should be used. Early vaccination (i.e., between 6-12 mo of age) will provide some immunity to measles, but antibody response is not durable or lasting. Any MMR vaccine before 12 mo of age does not count toward the routine vaccination schedule; children vaccinated early for purposes of international travel must be revaccinated on or after their 1st birthday with 2 doses, separated by at least 4 wk. Infants <6 mo of age are generally protected by maternal antibodies and should not receive early MMR vaccination prior to travel.

**Pneumococcal Vaccines**

*Streptococcus pneumoniae* is the leading cause of childhood bacterial pneumonia and is among the leading causes of bacteremia and bacterial meningitis in children in low- and middle-income and industrialized nations. Preparing a child to travel internationally includes routine or catch-up vaccination with 13-valent pneumococcal conjugate vaccine (PCV13) and, for children with certain high-risk conditions, use of 23-valent pneumococcal polysaccharide vaccine (PPSV23). A single dose of PCV13 should be administered to previously unvaccinated children 6-18 yr old with underlying high-risk medical conditions: anatomic or functional asplenia (including sickle cell disease), HIV infection, a congenital immunodeficiency or immunocompromising condition, chronic heart or lung disease, chronic renal failure or nephrotic syndrome, diabetes mellitus, cerebrospinal fluid leak, or cochlear implant. The Advisory Committee on Immunization Practices also recommends that high-risk children age 2 yr and older receive the PPSV23 vaccine 8 or more weeks after their last PCV13 dose. Recommendations of the Advisory Committee on Immunization Practices on prevention of pneumococcal disease among infants and children using PCV13 and PPSV23 can be found at http://www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/pneumo.html.
**Polio Vaccine**

Poliomyelitis was eradicated from the Western hemisphere in 1991. Polio remains endemic in 3 countries—Afghanistan, Nigeria, and Pakistan—with additional surrounding countries at risk for importation of polio. A number of countries continue to experience periodic outbreaks of importation polio, particularly countries extending from west Africa to the Horn of Africa. The poliovirus vaccination schedule in the United States is now a 4-dose, all-inactivated poliovirus (IPV) regimen (see Chapter 172). Traveling infants should begin IPV series as early as 6 wk of age. For an accelerated dosing schedule for children, see Figure 172-4 in Chapter 172. Length of immunity conferred by IPV immunization is not known; a single booster dose of IPV is therefore recommended for previously vaccinated adolescents and adults traveling to polio-endemic areas if approximately 10 yr has elapsed since they completed their primary series. Oral poliovirus vaccine is no longer available in the United States.

**Varicella**

All children 12 mo of age and older who have no history of varicella vaccination or chickenpox should be vaccinated unless there is a contraindication to vaccination (see Chapter 172). Infants <6 mo of age are generally protected by maternal antibodies. All children now require 2 doses, the 1st at 12 mo of age and the 2nd at 4-6 yr of age. The 2nd dose can be given as soon as 3 mo after the 1st dose. For unvaccinated children 13 yr of age and older, the 1st and 2nd doses can be separated by 4 wk.

### SPECIALIZED PEDIATRIC TRAVEL VACCINATIONS

Table 175-1 summarizes the dosages and age restrictions of vaccines specifically given to children traveling internationally.

**Cholera**

Cholera is present in many low- and middle-income countries, but the risk for infection among travelers to these countries is extremely low. At present, there is no cholera vaccine available for travelers in the United States, although an effective vaccine is available in other countries. Travelers entering countries reporting cholera outbreaks are at minimal risk of acquiring cholera if they take adequate safe food and water precautions and utilize frequent handwashing. No country or territory currently requires cholera vaccination as a condition for entry.

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**Table 175-1** Travel Vaccinations for Children

<table>
<thead>
<tr>
<th>VACCINE</th>
<th>PRIMARY SERIES</th>
<th>AGE AT VACCINATION</th>
<th>BOOSTER/COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HEPATITIS A</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Havrix, Vaqta</td>
<td>0.5 mL IM</td>
<td>&gt;1 yr</td>
<td>No booster; see text about off-label administration (age 6-11 mo)</td>
</tr>
<tr>
<td>Immunoglobulin (Ig)</td>
<td>&lt; 2 doses: 0.02 mL/kg IM once</td>
<td>Birth</td>
<td>See text about restrictions with live virus vaccinations (i.e., MMR) following lg administration</td>
</tr>
<tr>
<td></td>
<td>&gt; 2 doses: 0.06 mL/kg IM once</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>INFLUENZA</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inactivated</td>
<td>4-35 mo: 0.25 mL IM, 1 or 2 doses</td>
<td>&gt;6 mo</td>
<td>New vaccine yearly</td>
</tr>
<tr>
<td></td>
<td>3-8 yr: 0.5 mL IM, 1 or 2 doses</td>
<td></td>
<td>In children 6 mo-9 yr, 2 doses should be given ≥1 mo apart if no prior vaccination</td>
</tr>
<tr>
<td></td>
<td>&gt;9 yr: 0.5 mL IM once</td>
<td></td>
<td>New vaccine yearly</td>
</tr>
<tr>
<td>Live-attenuated</td>
<td>0.25 mL in each nostril, 1 or 2 doses</td>
<td>&gt;2 yr</td>
<td></td>
</tr>
<tr>
<td><strong>JAPANESE B RABIES</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ixaro (inactive)</td>
<td>1 dose IM</td>
<td>&gt;6-11 mo: 1 dose</td>
<td>See text. MMR at 6-11 mo does not count toward primary series; MMR should be</td>
</tr>
<tr>
<td></td>
<td></td>
<td>recommended if</td>
<td>administered simultaneously with other recommended/required live-virus travel</td>
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<tr>
<td></td>
<td></td>
<td>traveling to measles-</td>
<td>vaccines (yellow fever)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>endemic area</td>
<td></td>
</tr>
<tr>
<td><strong>MEASLES</strong></td>
<td>Recommended schedule: 12-15 mo</td>
<td>&gt;6-11 mo: 1 dose</td>
<td>See text. MMR at 6-11 mo does not count toward primary series; MMR should be</td>
</tr>
<tr>
<td></td>
<td>and 4-6 yr</td>
<td>recommended if</td>
<td>administered simultaneously with other recommended/required live-virus travel</td>
</tr>
<tr>
<td></td>
<td>If &gt;12 mo and traveling internationally,</td>
<td>traveling to measles-</td>
<td>vaccines (yellow fever)</td>
</tr>
<tr>
<td></td>
<td>2nd MMR dose can be administered</td>
<td>endemic area</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4 wk later</td>
<td></td>
<td></td>
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<tr>
<td><strong>MENINGOCOCCAL DISEASE</strong></td>
<td></td>
<td></td>
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<tr>
<td>Conjugate A/C/Y/W-135</td>
<td>0.5 mL IM</td>
<td>9-23 mo</td>
<td>Booster 3 yr after primary series</td>
</tr>
<tr>
<td></td>
<td>2 doses, 3 mo apart</td>
<td></td>
<td>Booster after 3 yr (age 2-6 yr)</td>
</tr>
<tr>
<td></td>
<td>0.5 mL IM once</td>
<td>&gt;2-6 yr</td>
<td>Booster after 5 yr (age &gt;7 yr)</td>
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<tr>
<td></td>
<td></td>
<td>&gt;7 yr</td>
<td>Children with functional/anatomic asplenia receive 2 dose primary series, 2 mo</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>apart; conjugate vaccine recommended over polysaccharide A/C/Y/W-135</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>&lt;4 yr of age: every 2 yr</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>&gt;4 yr of age: every 3-5 yr</td>
</tr>
<tr>
<td>Polysaccharide A/C/Y/W-135</td>
<td>0.5 mL SC once</td>
<td>&gt;2 yr</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>RABIES</strong></td>
<td>Preexposure: 1.0 mL IM × 3 doses,</td>
<td>Any age</td>
<td>See text for follow-up vaccination if bitten</td>
</tr>
<tr>
<td></td>
<td>days 0, 7, and 21 or 28 days</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>TYPHOID</strong></td>
<td>0.5 mL IM once</td>
<td>≥2 yr</td>
<td>Every 2-3 yr</td>
</tr>
<tr>
<td>Intramuscular Vi</td>
<td>4 doses: 1 capsule PO every other day</td>
<td>≥6 yr</td>
<td>Every 5 yr; see text for administration</td>
</tr>
<tr>
<td>Oral Ty21</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>YELLOW FEVER</strong></td>
<td>0.5 mL SC once</td>
<td>&gt;9 mo</td>
<td>Every 10 yr (see text)</td>
</tr>
</tbody>
</table>

**Hepatitis A Vaccination and Preexposure Immunoglobulin**

Hepatitis A virus is endemic in most of the world, and travelers are at risk, even if their travel is restricted to the usual tourist routes. Hepatitis A infection can occur as a result of eating shellfish harvested from sewage-contaminated waters, eating unwashed vegetables or fruits, or eating food prepared by an asymptomatic carrier of hepatitis A virus.

Young children infected with hepatitis A are often asymptomatic but can transmit the infection to older children and adults, who are more likely to develop clinical hepatitis. Few areas carry no risk of this infection, and therefore immunization is recommended for all travelers. Hepatitis A vaccine is recommended in the United States for universal immunization of all children 12 mo of age or older. Administered as 2 doses 6 mo apart. A single dose of hepatitis A vaccine given to travelers will provide adequate protection in most instances. Protective immunity develops within 2 wk after the initial vaccine dose. A combined 3 dose hepatitis A and hepatitis B vaccine (Twinrix, GlaxoSmithKline) is available in the United States but is licensed for use only in adolescents >18 yr of age. Pediatric combination hepatitis A–hepatitis B vaccine (Twinrix-Junior, GlaxoSmithKline) is licensed for use in children 1-18 yr in Canada and Europe.

Children <1 yr of age are at lower risk of clinical hepatitis A infection, especially if they are breastfed or residing in areas with safe water for formula reconstitution. Some experts recommend use of preexposure intramuscular immunoglobulin for children <12 mo who are traveling internationally to higher-risk destinations, particularly low-income destinations or regions where hygienic or sanitary conditions are limited. However, administration of immunoglobulin diminishes the immunogenicity of live-virus vaccines, in particular measles vaccine, that may be needed for infant travelers. Vaccination against measles should occur 2 or more weeks prior to any immunoglobulin administration, and a 3 mo interval is suggested between immunoglobulin administration and subsequent measles immunization.

Providers should be aware that infant travelers 6 mo of age or older who are being considered for preexposure immunoglobulin may also need measles (MMR) vaccination, as measles-endemic countries frequently overlap with higher-risk travel destinations for hepatitis A virus infection. For this reason, and on the basis of vaccine safety data, many travel medicine experts recommend immunization with hepatitis A vaccine rather than administration of intramuscular immunoglobulin to infants 6-11 mo of age who will be traveling to a hepatitis A virus–endemic area. Several studies demonstrate that infants as young as 6 mo old will develop antibodies following hepatitis A vaccine, especially if there are no interfering maternal antibodies from prior maternal vaccination or disease. There is potential for a more durable immune response to the hepatitis A vaccination especially in later infancy, when potential interfering maternal antibody concentrations are lower. If early hepatitis A vaccination is given rather than immunoglobulin to infant travelers (age 6-11 mo), it should not count toward the routine 2 dose vaccine series. Similar to MMR vaccination, an informed decision should be made, with the parents balancing the risk of travel-associated disease and vaccine adverse events with the potential protective benefit to the traveling infant.

**Japanese Encephalitis**

Japanese encephalitis is a disease transmitted by mosquitoes in many areas of Asia, especially in rural farming areas. Although it is a leading cause of vaccine-preventable encephalitis in children in many Asian countries and parts of western Pacific countries, the risk of disease to nonimmune travelers is low. A map showing where Japanese encephalitis transmission occurs can be found at http://wwwnc.cdc.gov/travel/yellowbook/2012/chapter-3-infectious-diseases-related-to-travel/japanese-encephalitis#2473.

Most human infections with Japanese encephalitis virus are asymptomatic, and <1% of individuals develop clinical disease. With symptomatic disease, the fatality rate is 20-30% and the incidence of neurologic or psychiatric sequelae in survivors is 30-50%. The risk of Japanese encephalitis disease for pediatric travelers is unknown, but among all travelers, it is estimated to be less than 1 case per 1 million travelers to Asia. Risk of Japanese encephalitis neurologic disease following mosquito-bite transmission is thought to be higher in children than adults. The disease occurs primarily from June to September in temperate zones and throughout the entire year in tropical zones. Vaccination is recommended for travelers planning visits of longer than 1 mo to rural areas of Asia, where the disease is endemic, especially areas of rice or pig farming. Vaccination is recommended for shorter visits to such areas if the traveler will often be outdoors (e.g., camping or hiking). Risk for infection can be greatly reduced by following the standard precautions to avoid mosquito bites.

The inactivated Vero-cell culture-derived Japanese encephalitis vaccine (Ixiaro) has replaced the older inactivated mouse-brain-derived vaccine (JE-VAX), which is no longer manufactured. Japanese encephalitis (Ixiaro) vaccine efficacy is >95% in adults who receive 2 doses administered 28 days apart. The licensed range for Japanese encephalitis vaccine (Ixiaro) has been extended to include children as young as age 2 mo, with a dose administered on days 0 and 28.

**Meningococcal Vaccines**

There are currently 2 forms of meningococcal vaccine available in the United States: a quadrivalent polysaccharide A/C/Y/W-135 vaccine (Menomune) and 2 quadrivalent conjugate A/C/Y/W-135 vaccines (Menactra, Menveo). A single-dose conjugate quadrivalent A/C/Y/W-135 vaccine, Nimenrix (manufactured by GlaxoSmithKline), is licensed in Canada and Europe for individuals from 12 mo-55 yr of age.

Children traveling to those equatorial countries in sub-Saharan Africa where the incidence of meningococcal disease is highest should receive a Neisseria meningitidis vaccine, especially if travel is prolonged or occurs during the dry season of December to June. Risk is greatest in the “meningitis belt” of sub-Saharan Africa (see the map at http://wwwnc.cdc.gov/travel/yellowbook/2012/chapter-3-infectious-diseases-related-to-travel/meningococcal-disease), with rates of meningococcal disease in endemic regions reaching up to 1,000 cases per 100,000 population per year. Children 9-23 mo of age who are traveling to these equatorial African countries where meningococcal disease is hyperendemic or epidemic should receive a 2 dose series of Menactra brand MCV4, 8-12 wk apart. Conjugate vaccine is preferred in children over the less-effective polysaccharide vaccine (Menomune). Booster doses of conjugate A/C/Y/W-135 should occur every 3-5 yr for travelers returning to endemic areas, depending on age of pediatric traveler. Providers may also wish to consider meningococcal vaccination for other pediatric travelers, especially if there is remote or rural travel to low-income countries with limited healthcare access, as meningococcal outbreaks can occur anywhere in the world. Proof of receipt of quadrivalent meningococcal vaccination is also necessary for individuals traveling to Mecca, Saudi Arabia, for the annual Hajj or Umrah pilgrimages.

Serogroups A and C are most commonly associated with epidemics of meningitis in sub-Saharan Africa, especially in the “meningitis belt” of equatorial Africa during the dry season mo (December to June). Serogroups Y and W-135 have also been found in meningococcal outbreaks. Serogroup B, currently not included in any licensed meningococcal vaccine in the United States, is associated with more sporadic cases of invasive meningococcal disease in industrialized countries, including the United States. Additional vaccine information on meningococcal vaccination regimens and booster intervals can be found at the CDC website (http://www.cdc.gov/vaccines/vpd-vac/mening/#recs).

**Rabies**

Rabies is endemic in many countries in Africa, Asia, and Central and South America. Children are at particular risk because they are less likely to report bites and because facial bites are more common in children. Rabies has the potential for an extended latency period (months) and is uniformly fatal once the clinical symptoms emerge. Preexposure prophylaxis is recommended for ambulatory children with extended travel to high-risk regions, especially expatriate children and younger children traveling to or living in rural areas where enzootic dog rabies is endemic. Rabies preexposure vaccination should also
be considered for adventure travelers (hikers, bikers), individuals likely to come into contact with rabies vectors (i.e., students working with animal or bat conservation), or travelers with itineraries to rabies-endemic regions where timely, effective postexposure prophylaxis might not be available following an animal bite. Most animal bites in a rabies-endemic area should be considered a medical emergency, especially bites from stray dogs, other carnivores, and bats. Immediate wound care washing should be followed by prompt administration of appropriate postexposure rabies prophylaxis at a medical facility. Postexposure prophylaxis is required even for persons who received preexposure vaccination. Algorithms for pre- and postexposure vaccination are the same regardless of patient age.

Numerous rabies vaccine formulations exist around the world. In the United States, 2 rabies vaccines are available: human diploid cell vaccine (HDCV; Imovax, Sanofi Pasteur, SA) and purified chick embryo cell (PCEC; RabAvert, Novartis) vaccine. Preexposure prophylaxis is given either intramuscularly (HDCV or PCEC) as 3 doses (1 mL) on days 0, 7, and 21 or 28. Postexposure prophylaxis is given as 4 doses (1 mL) of HDCV or PCEC vaccine intramuscularly on days 0, 3, 7, and 14 if previously unvaccinated and 2 doses (1 mL) intramuscularly on days 0 and 3 if previously vaccinated. Previously unvaccinated persons should also receive rabies immunoglobulin (RIG, 20 IU/kg), with as much of the dose as possible infiltrated around the wound site at the time of initial postexposure prophylaxis. Previously vaccinated persons should not receive RIG. Unpurified or purified equine RIG preparations are still used in some low- and middle-income countries and are associated with a higher risk for severe reactions, including serum sickness and anaphylaxis. Purified cell culture–derived vaccines are also not always available abroad; travelers should be aware that any rabies vaccines derived from neural tissue carry an increased risk for adverse reactions, often with neurologic sequelae. If rabies prophylaxis is initiated abroad, neutralizing titers should be checked on return and immunization completed with a cell culture–derived vaccine. If rabies prophylaxis cannot be provided abroad, children with high-risk bites (e.g., stray dog) should be emer-
gently transported to a site where they can receive prophylaxis, as the vaccinations should be started as soon as possible after the bite and ideally within 24 hr. Infants and young children respond well to rabies vaccine, and both pre- and postexposure vaccinations can be given at any age, using the same dose and schedule as adults. Individual travel-
ers simultaneously receiving mefloquine or chloroquine may have limited immune reactions to intradermal rabies vaccine and should be vaccinated intramuscularly.

**Tuberculosis**

The risk for tuberculosis in the typical traveler is low. Pre- and post-
travel testing for tuberculosis is controversial, and should be done on
an individualized basis depending on the itinerary, duration, and activi-
ties (i.e., working in a hospital setting). Immunization with bacillus Calmette-Guérin is even more controversial. It has variable efficacy in reducing severe tuberculosis disease in infants and young children, is not available in the United States, and is generally not recommended for pediatric travelers. Infection with *Mycobacterium bovis* can be prevented through avoiding consumption of unpasteurized dairy products.

**Typhoid**

*Salmonella typhi* infection, or typhoid fever, is common in many low-
and middle-income countries in Asia, Africa, and Latin America (see Chapter 198). Typhoid vaccination is recommended for most children 2 yr of age or older who are traveling to the Indian subcontinent, as the incidence of typhoid is 10-100 times higher for travelers to the Indian subcontinent than all other travel destinations. Vaccination should be strongly considered for other travelers to low- and middle-income countries, particularly if they are visiting friends and relatives, lack access to reliable clean water and food, are traveling for a pro-
longed duration, or are adventurous eaters.

Two typhoid vaccines, the intramuscular Vi-polysaccharide vaccine and oral Ty21a strain live-attenuated vaccine, are recommended for use in children in the United States. Both produce a protective response in 50-80% of recipients. Neither vaccination offers meaningful protec-
tion against *Salmonella paratyphi*, another cause of enteric fever. Trav-

erers who have had prior diagnoses of “typhoid fever” should still receive vaccination, as past infection does not confer long-term immunity.

The intramuscular Vi-polysaccharide vaccine is licensed for use in children 2 yr of age and older. It can be given any time before depar-
ture, but it should ideally be administered 2 wk before travel, with a booster needed 2-3 yr later. The oral Ty21a vaccine can only be used in children 6 yr of age or older and is given in 4 doses over a 1 wk period. Enteric-coated capsules are to be swallowed with a cool or room-temperature drink, at least 1 hr before a meal, every other day until the 4 doses are completed. Oral typhoid capsules must remain refrigerated (not frozen). Capsules should never be broken open, as vaccine efficacy is dependent on capsules being swallowed whole in order to get past the acidic stomach contents. The oral vaccine is associ-
ated with an immune response lasting 5-7 yr (depending on national labeling). Antibiotics inhibit the immune response to the oral Ty21a vaccine; the vaccine should not be given within 72 hr of antibiotic treat-
ment, and antibiotics should be avoided until 7 days after complet-
ing the vaccine series. Studies demonstrate that melqofo, chlo-
roquine, and atovaquone-proguanil can be given concurrently with the oral Ty21a vaccine without affecting the immunogenicity of the vaccine. Oral Ty21a vaccine should not be given to immunocompro-
mised children; these children should receive the intramuscular Vi-polysaccharide vaccine.

**Yellow Fever**

Yellow fever (see Chapter 270) is a mosquito-borne viral illness resem-
bling other viral hemorrhagic fevers (see Chapter 271) but with more prominent hepatic involvement. Yellow fever is present in tropical areas of South America and Africa.

Yellow fever vaccination is indicated in children >9 mo of age travel-
ing to an endemic area. Many countries require yellow fever vaccina-
tion by law for travelers arriving from endemic areas, and some African countries require evidence of vaccination from all entering travelers. Current recommendations can be obtained by contacting state or local health departments or the Division of Vector-Borne Infectious Dise-
ases of the CDC (telephone: 404-332-4555; or website: http://wwwn.
cdc.gov/travel/yellowbook/2014/chapter-3-infectious-diseases-
related-to-travel/yellow-fever). Most countries accept a medical waiver for children who are too young to be vaccinated (<6 mo of age) and for persons with a contraindication to vaccination. Children with asymptomatic HIV infection may be vaccinated if exposure to yellow fever virus cannot be avoided.

Yellow fever vaccine (0.5 mL SC), a live-attenuated vaccine (17D strain) developed in chick embryos, is safe and highly effective in children >9 mo of age, but in young infants it is associated with a markedly increased risk for vaccine-associated encephalitis (0.5-
/4,100) and other severe reactions. Yellow fever vaccine should never be given to infants <6 mo of age; infants 6-8 mo of age should be vac-
cinated only in consultation with the CDC or a travel medicine expert to assess the current epidemiology, travel itinerary and duration, and whether the yellow fever virus exposure is greater than vaccine risks. In children >9 mo, adverse effects are rare, although vaccine-associated neurotropic and viscerotropic disease associated with the vaccine have been reported. The risk of these reactions is higher in those with thymus disease, altered immune status, age >60 yr, or multiple sclerosis and in infants <9 mo of age (neurotropic disease). Yellow fever vacci-
nation is generally contraindicated in pregnancy and for nursing mothers, unless extended travel to a yellow fever–endemic area is unavoidable.

Children with immunodeficiency or an immunosuppressed state, a thymic disorder or dysfunction (i.e., DiGeorge syndrome), or a history of anaphylactic reactions to eggs should not receive yellow fever vaccine. Long-lived immunity develops with this vaccine, perhaps even lasting for a lifetime; however, international travel certificates require proof of immunization within 10 yr.
Traveler’s Diarrhea

Ingestion of contaminated food or water makes travel-associated diarrhea the most common health complaint among international travelers. Traveler’s diarrhea, characterized by a 2-fold or greater increase in the frequency of unformed bowel movements, occurs in as many as 40% of all travelers overseas (see Chapter 340.1). Children, especially those <3 yr of age, have a higher incidence of diarrhea, more-severe symptoms, and more-prolonged symptoms than adults, with a reported attack rate of 60% for those <3 yr of age in 1 study.

An important risk factor for traveler’s diarrhea is the country of destination. High-risk areas (attack rates of 25-50%) include low- and middle-income countries of Latin America, Africa, the Middle East, and Asia. Intermediate risk occurs in the Mediterranean, China, and Israel. Low-risk areas include North America, Northern Europe, Australia, and New Zealand. Fecal-oral diarrheal pathogens that children acquire during travel are similar to those acquired by adults and include enterotoxigenic and enterogaugregative Escherichia coli, Campylobacter, Salmonella (nontyphoidal serotypes predominate), and Shigella species. Enteric protozoa are a much less common cause of traveler’s diarrhea than bacterial pathogens—G. lamblia is the most likely protozoal cause of persistent diarrhea. Less-common travel-associated protozoa include Cryptosporidium species, E. histolytica, and Cyclospora. Viral infections, particularly rotavirus infections, may also cause travel-associated diarrhea in children. Clinicians should be aware that not all diarrheal illness in children is food borne or waterborne—febrile children with malaria may also present with vomiting and/or nonbloody diarrhea and may be misdiagnosed as having traveler’s diarrhea.

Guidance on Prevention of Traveler’s Diarrhea

Food and water hygiene remain important measures to reduce the incidence of traveler’s diarrhea in children. However, creating long lists of foods to avoid or offering the popular, simple advice of “Boil it, peel it, cook it, or forget it!” is generally an ineffective method of reducing traveler’s diarrhea. Most studies show that these kinds of dietary directives are difficult to keep and may have little impact on the incidence of traveler’s diarrhea. In adult studies, the risk of developing traveler’s diarrhea appears to be more associated with where you eat rather than what you eat. Eating in a relative’s or friend’s home is generally safer than eating in a restaurant, where restaurant kitchen hygiene and proper refrigeration may be lacking and employee handwashing may be sporadic.

In general, travel medicine providers can provide some common sense food and water advice to family travelers. Boiled or bottled water, hot beverages, and canned or bottled beverages are generally safe to consume. Ice should be avoided. In low- and middle-income countries, tap water is generally unsafe for drinking or brushing teeth. Boiling water for 1 min or longer (or 3 min at altitudes >2000 m) remains a reliable method of disinfecting water. Food that is thoroughly cooked and served hot is almost always safe to eat. Dry foods, such as pastry items, breads, and cookies, are generally safe to eat. Unpasteurized milk or other dairy products (cheese) should always be avoided. Breastfeeding should be encouraged for young children, especially infants <6 mo of age, to reduce exposure to contaminated water/formula. All children should be reminded to wash their hands before eating and after playing around soil or animals. Chemoprophylactic agents for traveler’s diarrhea are not recommended for children.

Management of Traveler’s Diarrhea

Dehydration is the greatest threat presented by a diarrheal illness in a small child. Parents should be made aware of the symptoms and signs of dehydration and should be given instructions on how to administer rehydration solutions. Prepackaged WHO oral rehydration solution packets, which are available at stores or pharmacies in almost all low- and middle-income countries, should be part of a child’s travel kit. Oral rehydration solution should be mixed as directed with bottled or boiled water and given slowly, as tolerated, to the child while symptoms persist.

Antimotility agents such as diphenoxylate (Lomotil) and loperamide (Imodium) should be avoided in infants and young children, and the American Academy of Pediatrics does not recommend their routine use in acute gastroenteritis. Use of antimotility agents may be beneficial in older children and adolescents with afebrile, nonbloody traveler’s diarrhea. In general, antimotility agents should not distract parents from giving frequent oral rehydration solution, as ongoing intestinal fluid losses likely continue despite a decrease in stooling. Bismuth subsalicylate for acute gastroenteritis should be avoided because of concern for toxicity and Reye syndrome.

Presumptive Antibiotic Treatment

Oral rehydration is the mainstay of treatment for pediatric traveler’s diarrhea. However, antibiotics should be prescribed for the pediatric traveler, with parental instructions to start presumptive treatment early in the diarrheal illness. Systemic antibiotics can shorten the duration and severity of diarrheal illness, especially if presumptive antibiotics are initiated immediately after onset of traveler’s diarrhea. For children, the drug of choice is azithromycin (10 mg/kg once daily for up to 3 days, with maximum daily dose of 500 mg). Ciprofloxacin (10 mg/kg per dose twice a day for up to 3 days, maximum dose of 500 mg twice a day) is an alternative for children >1 yr of age, but should not be prescribed for traveler’s traveling to the Indian subcontinent or South-east Asia, where fluoroquinolone resistance is common. Shiga-toxin producing E. coli such as E. coli O157:H7 is an extremely uncommon cause of pediatric traveler’s diarrhea in nonindustrialized countries, and the benefit of presumptive antibiotic therapy in traveling children, even with bloody diarrhea, typically outweighs the low risk of developing hemolytic-uremic syndrome.

Azithromycin is highly effective against most bacterial pathogens that cause traveler’s diarrhea, and is the preferred antibiotic among many travel experts. Azithromycin can be prescribed in powder form that can be reconstituted with safe water into a liquid suspension when needed. In addition, azithromycin 250 mg tablets can be cut to the nearest ½ tablet size to achieve a dosage of approximately 10 mg/kg, and then crushed and mixed with food or water for younger children. Amoxicillin, trimethoprim-sulfamethoxazole (cotrimoxazole), and erythromycin should not be prescribed for self-treatment of traveler’s diarrhea, because of widespread resistance among diarrheal pathogens. Traveler’s diarrhea that results in bloody stools, persistently high fevers, systemic chills and rigors, severe or localizing abdominal pain, or continued fluid losses should prompt additional medical evaluation.

INSECT-BORNE INFECTIONS

Insect-borne infections for which traveling children are most at risk include malaria, dengue, chikungunya, yellow fever, and Japanese encephalitis, depending on the area of travel. Malaria is transmitted by night-biting Anopheles mosquitoes, whereas dengue occurs from mosquito species (Culex, Aedes) that are predominantly active during the day. Families should be encouraged to protect children against daytime and nighttime biting mosquitoes, as many regions of the world in which malaria is found also have diseases transmitted by daytime biting mosquitoes (dengue, chikungunya).

Exposure to insect bites can be reduced by wearing appropriate attire and using insect repellents containing N,N-diethyl-m-toluamide (DEET) or picaridin. The American Academy of Pediatrics recommends avoiding DEET-containing repellants in children <2 mo of age. Rare instances of neurologic events have been reported in very young children with exposure to inappropriate, frequent applications of DEET-containing repellants (>10 times a day) or who licked off DEET. Concentrations of 25-30% DEET need be applied every 4-6 hr as needed, whereas 5-7% DEET provides only 1-2 hr of protection time. DEET concentrations >40-50% do not confer a substantially longer protection time for children and generally should be avoided.

Picaridin is a newer insect repellant in the United States but has been used widely in Europe and Australia for yr. Picaridin is fragrance-free, effective, and generally well tolerated on exposed skin and faces. It has similar efficacy to DEET but with less inhalational or dermal irritation.
Picaredin at concentrations of 20% or higher provides adequate protection against *Anopheles* mosquitoes that have potential to transmit malaria. When applying sunscreen and insect repellent, sunscreen should be applied first followed by DEET or picaridin.

Spraying or treating clothing with permethrin, a synthetic pyrethroid, is a safe and effective method of further reducing insect bites in children. Permethrin can be applied to directly to clothing, bed nets, shoes, and hats, and should be allowed to fully dry before use. As an insecticide, permethrin should never be applied to skin. Permethrin-treated garments retain both repellency and insecticidal activity, even with repeated laundering. Clothing will eventually need to be retreated to maintain repellency, according to the product label. Bed nets, particularly permethrin-impregnated bed nets, also decrease the risk of insect bites, and their use is highly recommended in malarial areas.

**Malaria Chemoprophylaxis**

Malaria, a mosquito-borne infection, is the leading parasitic cause of death in children worldwide (see Chapter 288). Of the 4 *Plasmodium* species that infect humans, *Plasmodium falciparum* causes the greatest morbidity and mortality. Each yr, more than 8 million U.S. citizens visit parts of the world where malaria is endemic (sub-Saharan Africa, Central and South America, India, Southeast Asia, Oceania). Children accounted for 15-20% of imported malaria cases in a WHO study in Europe. Given the major resurgence of malaria and increased travel among families with young children, physicians in industrialized countries are increasingly required to give advice on prevention, diagnosis, and treatment of malaria. Risk factors for severe malaria and death include inadequate adherence to chemoprophylaxis, delay in seeking medical care, delay in diagnosis, and nonimmune status, but the case fatality rate of imported malaria remains <1% in children from non-endemic countries. The CDC maintains updated information at http://www.cdc.gov/malaria/travelers/index.html, as well as a malaria hotline for physicians (770-488-7788). It is important to check this updated information, because recommendations for prophylaxis and treatment are often modified owing to changes in the risk for developing malaria in different areas of the world, changing *Plasmodium* resistance patterns, and the availability of new antimalarial medications.

Avoidance of mosquitoes and barrier protection from mosquitoes are an important part of malaria prevention for travelers to endemic areas. The *Anopheles* mosquito feeds from dusk to dawn. Travelers should remain in well-screened areas, wear clothing that covers most of the body, sleep under a bed net (ideally one impregnated with permethrin), and use insect repellents with DEET during these hours. Parents should be discouraged from taking a young child on a trip that will entail evening or nighttime exposure in areas endemic for *P. falciparum*.

Chemoprophylaxis is the cornerstone of malaria prevention for non-immune children and adults who travel to malaria-endemic areas but it is not a replacement for other protective measures. Travelers often do not take malaria prophylaxis as prescribed or at all. They are more likely to use prophylactic antimalarial drugs if their physicians provide appropriate recommendations and education before departure. However, in 1 survey, only 14% of persons who sought medical advice obtained correct information about malaria prevention and prophylaxis. Families with children visiting friends and relatives are particularly less likely to take malaria prophylaxis or seek pretravel medical advice.

Resistance of *P. falciparum* to the traditional chemoprophylactic agent, chloroquine, is widespread, and in most areas of the world other agents must be used (Table 175-2). Factors that must be considered in choosing appropriate chemoprophylaxis medications and dosing schedules include age of the child, travel itinerary (including whether the child will be traveling to areas of risk within a particular country and whether chloroquine-resistant *P. falciparum* is present in the country), vaccinations being given, allergies or other known adverse reactions to antimalarial agents, and the availability of medical care during travel.

Children traveling to areas with chloroquine-resistant *P. falciparum* can be given mefloquine, atovaquone-proguanil, or doxycycline (if >8 yr of age) as malaria prophylaxis. For trips shorter than 4 wk, atovaquone-proguanil is the preferred medication, because it is given for only a short period before and after travel. Atovaquone-proguanil or doxycycline is also indicated for travel of any duration to western Cambodia and the Thailand–Cambodia and Thailand–Myanmar borders because of mefloquine resistance in these areas. For periods of travel longer than 4 wk to all other areas with chloroquine-resistant *P. falciparum*, mefloquine is the preferred medication because it can be taken weekly.

Mefloquine is FDA-approved only for children weighing more than 15 kg, but the CDC recommends mefloquine prophylaxis for all children regardless of weight because the risk for acquiring severe malaria outweighs the risk for potential mefloquine toxicity. Adults taking mefloquine prophylaxis have a 10-25% incidence of sleep disturbance and dysphoria and, less frequently, more serious neuropsychiatric symptoms. These side effects appear to be less common in children. Other potential side effects of mefloquine therapy include nausea and vomiting. The lack of a liquid or suspension formulation can make chloroquine and mefloquine administration difficult. For children who cannot take tablets, parents should take a chloroquine or mefloquine prescription to a compounding pharmacy, which can pulverize the tablets and place exact dosages into gel capsules. Parents can then open the gel capsules and sprinkle the powder into food. “Disguising” these medications, which have a bitter taste, is important; chocolate syrup has been used successfully as a vehicle for the medication. Persons with depression, neuropsychiatric disorders, seizure disorders, and cardiac conduction defects should not take mefloquine.

Atovaquone-proguanil fixed combination (Malarone) is an effective and safe chemoprophylaxis for travelers to chloroquine-resistant malaria-endemic areas, but it is fairly expensive. Adverse effects are infrequent and mild (abdominal pain, vomiting, and headache) and infrequently result in discontinuation of the medication. Atovaquone-proguanil prophylaxis must be taken every day with food, so it is better suited for prophylaxis during short periods of exposure. Recent data allow dosing down to 5 kg of body weight, although the use of atovaquone-proguanil at a weight between 5 and 10 kg is considered off-label.

Daily doxycycline is an alternative chemoprophylaxis regimen for chloroquine-resistant *P. falciparum* malaria that is considerably less expensive than atovaquone-proguanil. Doxycycline has been used extensively and is highly effective, but it cannot be used in children <8 yr of age owing to the risk of permanent tooth staining, and adverse effects (nausea, vomiting, photosensitivity, vaginal candidiasis) are not uncommon. Persons given doxycycline prophylaxis should be warned to decrease exposure to direct sunlight to minimize the possibility of photosensitivity. Primaquine has also been used successfully as chemoprophylaxis, especially in areas of high prevalence of *Plasmodium vivax* and *Plasmodium ovale*, but there are limited data about its use in nonimmune children. Primaquine prophylaxis for children should only be given in consultation with the CDC or a travel medicine specialist. Chloroquine, chloroquine-proguanil, and azithromycin do not provide adequate protection for children traveling to a chloroquine-resistant malaria-endemic area.

In areas of the world where *P. falciparum* remains fully chloroquine-sensitive (Haiti, the Dominican Republic, Central America north of the Panama Canal, and some countries in the Middle East), weekly chloroquine is the drug of choice for malaria chemoprophylaxis. Updated information on chloroquine susceptibility and recommended malaria prophylaxis is available at http://wwwnc.cdc.gov/travel/yellowbook/2014/chapter-3-infectious-diseases-related-to-travel/malaria.

On leaving an area endemic for *P. vivax* or *P. ovale* after a prolonged visit (usually >3 mo), travelers should consider terminal prophylaxis with primaquine (0.5 mg/kg base) daily, up to a maximum dose of 30 mg base or 52.6 mg salt, for 14 days, to eliminate extraerythrocytic forms of *P. vivax* and *P. ovale* and prevent relapses. Screening for
Table 175-2  Chemoprophylaxis of Malaria for Children

<table>
<thead>
<tr>
<th>AREA</th>
<th>DRUG</th>
<th>DOSAGE (ORAL)</th>
<th>ADVANTAGES</th>
<th>DISADVANTAGES</th>
<th>BEST USE</th>
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<tbody>
<tr>
<td>Chloroquine-resistant area</td>
<td>Mefloquine*†</td>
<td>weight &lt;10 kg: 4.6 mg base (5 mg salt)/kg/wk weight 10-19 kg: ( \frac{1}{2} ) tab/wk weight 20-30 kg: ( \frac{1}{4} ) tab/wk weight 31-45 kg: ( \frac{1}{4} ) tab/wk weight &gt;45 kg: 1 tab/wk (228 mg base)</td>
<td>Once-weekly dosing</td>
<td>Bitter taste No pediatric formulation Side effects of sleep disturbance, vivid dreams</td>
<td>Children going to malaria-endemic area for 4 wk or more Children unlikely to take daily medication</td>
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<tr>
<td></td>
<td></td>
<td>2 mg/kg daily (max: 100 mg)</td>
<td></td>
<td>Inexpensive</td>
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<tr>
<td></td>
<td>Doxycycline‡</td>
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<td></td>
<td></td>
<td>Cannot give to children &lt;8 yr old Daily dosing Must take with food or causes stomach upset Photosensitivity</td>
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<tr>
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<td>Atovaquone/proguanil§ (Malarone)</td>
<td>Pediatric tabs: 62.5 mg atovaquone/25 mg proguanil Adult tabs: 250 mg proguanil/100 mg proguanil weight 5-8 kg: ( \frac{1}{4} ) pediatric tab once daily (off-label) weight 9-10 kg: ( \frac{1}{4} ) pediatric tab once daily (off-label) weight 11-20 kg: 1 pediatric tab once daily weight 21-30 kg: 2 pediatric tabs once daily weight 31-40 kg: 3 pediatric tabs once daily weight &gt;40 kg: 1 adult tab once daily</td>
<td>Pediatric formulation Generally well tolerated</td>
<td>Expensive Can cause stomach upset</td>
<td>Children going to malaria-endemic area for &lt;4 wk</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chloroquine-susceptible area</td>
<td>Chloroquine phosphate</td>
<td>5 mg base/kg/wk (max: 300 mg base)</td>
<td>Once-weekly dosing</td>
<td>Inexpensive Generally well tolerated</td>
<td>Best medication for children traveling to areas with Plasmodium falciparum or Plasmodium vivax that is chloroquine susceptible</td>
</tr>
<tr>
<td>Drugs used for chloroquine-resistant areas can also be used in chloroquine-susceptible areas</td>
<td></td>
<td></td>
<td></td>
<td>Inexpensive</td>
<td></td>
</tr>
</tbody>
</table>

*Chloroquine and mefloquine should be started 1-2 wk prior to departure and continued for 4 wk after last exposure.
†Mefloquine resistance exists in western Cambodia and along the Thailand–Cambodia and Thailand–Myanmar borders. Travelers to these areas should take doxycycline or atovaquone-proguanil. See text for precautions about mefloquine use.
‡Doxycycline should be started 1-2 days prior to departure and continued for 4 wk after last exposure. Do not use in children <8 yr of age or in pregnant women.
§Atovaquone-proguanil (Malarone) should be started 1-2 days prior to departure and continued for 7 days after last exposure. Should be taken with food or a milky drink. Not recommended in pregnant women, children who weigh <5 kg, and women breastfeeding infants who weigh <5 kg. Contraindicated in individuals with severe renal impairment (creatinine clearance <30 mL/min).

glucose-6-phosphate dehydrogenase deficiency is mandatory before primaquine treatment, because primaquine is contraindicated in glucose-6-phosphate dehydrogenase–deficient persons because it can cause severe hemolysis in these persons.
Small amounts of antimalarial drugs are secreted into breast milk. The amounts of transferred drug are not considered to be either harmful or sufficient to provide adequate prophylaxis against malaria. Prolonged infant exposure to doxycycline via breast milk is not advisable.
Self-treatment of presumptive malaria during travel remains controversial. It should never be substituted for seeking appropriate medical care, but it can be considered in special circumstances such as travel to remote areas, intolerance of prophylaxis, or refusal of chemoprophylaxis by the traveler. Self-treatment medication should be different than the prescribed chemoprophylaxis. The CDC or a travel medicine specialist should be consulted if self-treatment medication is being considered for a traveler.

**THE RETURNING TRAVELER**
Posttravel evaluations are part of travel medicine and continuing care. Physicians unfamiliar with diseases that occur in low- and middle-income countries often misdiagnose the cause of illness in a child returning from travel abroad. Among returning patients identified from GeoSentinal sites who were ill, the common disorders included, in descending order of frequency, malaria, giardiasis, dengue fever, campylobacteriosis, cutaneous larva migrans, enteric fever, spotted
Patterns of Illness Among Returning International Travelers

<table>
<thead>
<tr>
<th>SYSTEMIC FEBRILE ILLNESS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malaria</td>
</tr>
<tr>
<td>Dengue</td>
</tr>
<tr>
<td>Enteric fever (typhoid/paratyphoid)</td>
</tr>
<tr>
<td>Chikungunya virus</td>
</tr>
<tr>
<td>Spotted fever rickettsia</td>
</tr>
<tr>
<td>Hepatitis A</td>
</tr>
<tr>
<td>Acute HIV</td>
</tr>
<tr>
<td>Leptospirosis</td>
</tr>
<tr>
<td>Measles</td>
</tr>
<tr>
<td>Infectious mononucleosis</td>
</tr>
<tr>
<td>Respiratory causes (pneumonia, influenza)</td>
</tr>
<tr>
<td>Undetermined fever source</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ACUTE DIARRHEA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Campylobacter</td>
</tr>
<tr>
<td>Shigella spp.</td>
</tr>
<tr>
<td>Salmonella spp.</td>
</tr>
<tr>
<td>Diarrheagenic Escherichia coli (enterotoxigenic E. coli, enteroadherent E. coli—not tested for by routine stool culture methods)</td>
</tr>
<tr>
<td>Giardiasis (acute, persistent, or recurrent)</td>
</tr>
<tr>
<td>Entamoeba histolytica</td>
</tr>
<tr>
<td>Cryptosporidium spp.</td>
</tr>
<tr>
<td>Cyclospora cayetanensis</td>
</tr>
<tr>
<td>Presumed viral enteritis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>DERMATOLOGIC MANIFESTATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rash with fever (dengue)</td>
</tr>
<tr>
<td>Arthropod-related dermatitis (insect bites)</td>
</tr>
<tr>
<td>Cutaneous larva migrants (Ancylostoma braziliense)</td>
</tr>
<tr>
<td>Bacterial skin infections—pyoderma, impetigo, ecthyma, erysipelas</td>
</tr>
<tr>
<td>Myiasis (tumbu and botfly)</td>
</tr>
<tr>
<td>Scabies</td>
</tr>
<tr>
<td>Tungiasis</td>
</tr>
<tr>
<td>Superficial mycosis</td>
</tr>
<tr>
<td>Animal bite</td>
</tr>
<tr>
<td>Leishmaniasis</td>
</tr>
<tr>
<td>Rickettsial diseases</td>
</tr>
<tr>
<td>Marine envenomation/dermatitis</td>
</tr>
<tr>
<td>Photoallergic and phytophotodermatitis</td>
</tr>
</tbody>
</table>

Thick and thin blood smears need to be performed for diagnosis if malaria is clinically suspected. If results are negative initially, 2 or more additional smears should be done 12-24 hr after the initial smear. Rapid malaria antigen tests (Binax Now) are FDA-approved and sensitive for diagnosing falciparum malaria. Treatment should be initiated immediately once the diagnosis is confirmed or empirically if presentation is severe with suspected malaria. Treatment should be determined in consultation with a pediatric infectious disease specialist and the CDC, which has updated information on the drugs of choice, which are similar to those for adults (see Chapter 288 for more details on malaria infection). Great caution should be used with young children, nonimmune patients, and pregnant patients with falciparum malaria, and hospitalization of these patients should be strongly considered until reliable improvement is observed.

Enteric (typhoid) fever should be considered in children with persistent or recurrent fevers following return from the Indian subcontinent. Multiple blood cultures and a stool culture may both be necessary to diagnosis enteric fever. Dengue is another cause of fever and systemic illness in ill travelers, particularly when returning from Southeast Asia, the Caribbean, Central and South America, or the Indian subcontinent. Many bacterial and protozoal causes of acute traveler’s diarrhea may also result in fever and systemic symptoms in children. Additional travel-associated febrile, diarrheal, and dermatologic illnesses exist, of which the most common etiologies can be found in Table 175-3.

Bibliography is available at Expert Consult.
Bibliography


DEFINITION
Fever is defined as a rectal temperature ≥38°C (100.4°F), and a value >40°C (104°F) is called hyperpyrexia. Body temperature fluctuates in a defined normal range (36.6-37.9°C [97.9-100.2°F] rectally), so that the highest point is reached in early evening and the lowest point is reached in the morning. Any abnormal rise in body temperature should be considered a symptom of an underlying condition.

PATHOGENESIS
Body temperature is regulated by thermosensitive neurons located in the preoptic or anterior hypothalamus that respond to changes in blood temperature as well as by cold and warm receptors located in skin and muscles. Thermoregulatory responses include redirecting blood to or from cutaneous vascular beds, increased or decreased sweating, regulation of extracellular fluid volume via arginine vasopressin, and behavioral responses, such as seeking a warmer or cooler environmental temperature.

Three different mechanisms can produce fever: pyrogens, heat production exceeding loss, and defective heat loss.

The first mechanism involves endogenous and exogenous pyrogens that raise the hypothalamic temperature set point. Endogenous pyrogens include the cytokines interleukins 1 and 6, tumor necrosis factor α, and interferons β and γ. Stimulated leukocytes and other cells produce lipids that also serve as endogenous pyrogens. The best-studied lipid mediator is prostaglandin E2, which attaches to the prostaglandin receptors in the hypothalamus to produce the new temperature set point. Along with infectious diseases and drugs, malignancy and inflammatory diseases can cause fever through the production of endogenous pyrogens. Some substances produced within the
body are not pyrogens but are capable of stimulating endogenous pyrogens. Such substances include antigen–antibody complexes in the presence of complement, complement components, lymphocyte products, bile acids, and androgenic steroid metabolites.

Exogenous pyrogens or substances that come from outside the body include mainly infectious pathogens and drugs. Microbes, microbial toxins, or other products of microbes are the most common exogenous pyrogens and stimulate macrophages and other cells to produce endogenous pyrogens. Endotoxin is one of the few substances that can directly affect thermoregulation in the hypothalamus as well as stimulate endogenous pyrogen release.

Many drugs cause fever, and the mechanism for increasing body temperature varies with the class of drug. Drugs that are known to cause fever include vancomycin, amphotericin B, and allopurinol.

Heat production exceeding heat loss is the second mechanism that leads to fever, with examples including salicylate poisoning and malignant hyperthermia. Defective heat loss is the third mechanism of fever genesis; for example, in children with ectodermal dysplasia or victims of severe heat exposure.

**ETIOLOGY**

The causes of fever can be organized into 4 main categories: infectious, inflammatory, neoplastic, and miscellaneous. Self-limited viral infections (common cold, gastroenteritis) and uncomplicated bacterial infections (otitis media, pharyngitis, sinusitis) are the most common causes of acute fever. The body temperature rarely rises above potentially lethal levels (42°C [107.6°F]) in the neurologically intact child unless extreme hyperthermic environmental conditions are present or other extenuating circumstances exist, such as underlying malignant hyperthermia or thyrotoxicosis.

The pattern of the fever can provide clues to the underlying etiology. Viral infections typically are associated with a slow decline of fever over a wk, whereas bacterial infections are often associated with a prompt resolution of fever after effective antimicrobial treatment is employed. Although administration of antimicrobial agents can result in a very rapid elimination of bacteria, if tissue injury has been extensive, the inflammatory response and fever can continue for days after all microbes have been eradicated.

Intermittent fever is an exaggerated circadian rhythm that includes a period of normal temperatures on most days; extremely wide fluctuations may be termed septic or hectic fever. Sustained fever is persistent and does not vary by more than 0.5°C (0.9°F)/day. Remittent fever is persistent and varies by more than 0.5°C (0.9°F)/day. Relapsing fever is characterized by febrile periods that are separated by intervals of normal temperature; tertian fever occurs on the 1st and 3rd days (malaria caused by *Plasmodium vivax*), and quartan fever occurs on the 1st and 4th days (malaria caused by *Plasmodium malariae*). Diseases characterized by relapsing fevers (Table 176-1) should be distinguished from infectious diseases that have a tendency to relapse. Biphasic fever indicates a single illness with 2 distinct periods (camel-back fever pattern); polyomyelitis is the classic example. A biphasic course is also characteristic of other enteroviral infections, leptocephosis, dengue fever, yellow fever, Colorado tick fever, siphillary rat bite fever (*Spirillum minus*), and the African hemorrhagic fevers (Marburg, Ebola, and Lassa fevers). The term *periodic fever* is used narrowly to describe fever syndromes with a regular periodicity (cyclic neutropenia and periodic fever, apthous stomatitis, pharyngitis, and adenopathy) or more broadly to include disorders characterized by recurrent episodes of fever that do not follow a strictly periodic pattern (familial Mediterranean fever, tumor necrosis factor receptor–associated periodic syndrome [Hibernian fever], hyperimmunoglobulin D syndrome, the Muckle–Wells syndrome) (see Chapter 163). Factitious fever, or self-induced fever, may be caused by intentional manipulation of the thermometer or injection of pyrogenic material.

The double quotidien fever (or fever that peaks twice in 24 hr) is classically associated with inflammatory arthritis. In general, a single isolated fever spike is not associated with an infectious disease. Such a spike can be attributed to the infusion of blood products and some drugs, as well as to some procedures, or to manipulation of a catheter on a colonized or infected body surface. Similarly, temperatures in excess of 41°C (105.8°F) are most often associated with a noninfectious cause. Causes for very high temperatures (>41°C [105.8°F]) include central fever (resulting from central nervous system dysfunction involving the hypothalamus), malignant hyperthermia, malignant neurolentic syndrome, drug fever, or heatstroke. Temperatures that are lower than normal (<36°C [96.8°F]) can be associated with overwhelming sepsis but are more commonly related to cold exposure, hypothyroidism, or overuse of antipyretics.

**CLINICAL FEATURES**

The clinical features of fever can range from no symptoms at all to extreme malaise. Children might complain of feeling hot or cold, display facial flushing, and experience shivering. Fatigue and irritability may be evident. Parents often report that the child looks ill or pale and has a decreased appetite. The underlying etiology also produces accompanying symptoms. Although the underlying etiologies can manifest in varied ways clinically, there are some predictable features. For instance, fever with petechiae in an ill-appearing patient indicates the high possibility of life-threatening conditions such as meningococcemia, Rocky Mountain spotted fever, or acute bacterial endocarditis.

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**Table 176-1  Fevers Prone to Relapse**

<table>
<thead>
<tr>
<th>INFECTIOUS CAUSES</th>
<th>NONINFECTIOUS CAUSES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relapsing fever (<em>Borrelia recurrentis</em>)</td>
<td>Behçet disease</td>
</tr>
<tr>
<td>Trench fever (<em>Bartonella quintana</em>)</td>
<td>Crohn disease</td>
</tr>
<tr>
<td>Q fever (<em>Coxiella burnetti</em>)</td>
<td>Weber–Christian disease (panniculitis)</td>
</tr>
<tr>
<td>Typhoid fever (<em>Salmonella typhi</em>)</td>
<td>Leukoclastic angiitis syndromes</td>
</tr>
<tr>
<td>Syphilis (<em>Treponema pallidum</em>)</td>
<td>Sweet syndrome</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>Systemic lupus erythematosus and other autoimmune disorders</td>
</tr>
<tr>
<td>Oroya fever (<em>Bartonella bacilliformis</em>)</td>
<td>PERIODIC FEVER SYNDROMES (see Chapter 163)</td>
</tr>
<tr>
<td>Acute rheumatic fever</td>
<td>Familial Mediterranean fever</td>
</tr>
<tr>
<td>Rat bite fever (<em>Spirillum minus</em>)</td>
<td>Cyclic neutropenia</td>
</tr>
<tr>
<td>Visceral leishmaniasis</td>
<td>Periodic fever, apthous stomatitis, pharyngitis, adenopathy (PFAPA)</td>
</tr>
<tr>
<td>Lyme disease (<em>Borrelia burgdorferi</em>)</td>
<td>Hyperimmunoglobulin D syndrome</td>
</tr>
<tr>
<td>Malaria</td>
<td>Hibernian fever (tumor necrosis factor superfamily immunoglobulin A–associated syndrome [TRAPS])</td>
</tr>
<tr>
<td>Babesiosis</td>
<td>Muckle-Wells syndrome</td>
</tr>
<tr>
<td>Noninfluenza respiratory viral infection</td>
<td>Others</td>
</tr>
<tr>
<td>Epstein–Barr virus infection</td>
<td></td>
</tr>
</tbody>
</table>
Changes in heart rate, most commonly tachycardia, accompany fever. Normally heart rate rises by 10 beats/min per 1°C (1.8°F) rise in temperature for children >2 mo of age. Relative tachycardia, when the pulse rate is elevated disproportionately to the temperature, is usually caused by noninfectious diseases or infectious diseases in which a toxin is responsible for the clinical manifestations. Relative bradycardia (temperature-pulse dissociation), when the pulse rate remains low in the presence of fever, can accompany typhoid fever, brucellosis, leptospirosis, or drug fever. Bradycardia in the presence of fever also may be a result of a conduction defect resulting from cardiac involvement with acute rheumatic fever, Lyme disease, viral myocarditis, or infective endocarditis.

**EVALUATION**

Most acute febrile episodes in a normal host can be diagnosed by a careful history and physical examination and require few, if any, laboratory tests. Because infection is the most likely etiology of the acute fever, the evaluation should initially be geared to discovering an underlying infectious cause (Table 176-2). The details of the history should include the onset and pattern of fever and any accompanying signs and symptoms. The patient often displays signs or symptoms that provide clues to the cause of the fever. Exposures to other ill persons at home, daycare, and school should be noted, along with any recent travel or medications. The past medical history should include information about underlying immune deficiencies or other major illnesses and receipt of childhood vaccines.

Physical examination should begin with a complete evaluation of vital signs, which should include pulse oximetry because hypoxia may indicate lower respiratory infection. In the acutely febrile child, the physical examination should focus on any localized complaints, but a complete head-to-toe examination is recommended, because clues to the underlying diagnosis may be found. For example, palsy and sole lesions may be discovered during a thorough skin examination and provide a clue for infection with coxsackievirus.

If a fever has an obvious cause, then laboratory evaluation may not be required, and management is tailored to the underlying cause with as-needed reevaluation. If the cause of the fever is not apparent, then further diagnostic evaluation should be considered on a case-by-case basis. The history of presentation and abnormal physical examination findings guide the evaluation. The child with respiratory symptoms and hypoxia may require a chest radiograph or rapid antigen testing for respiratory syncytial virus or influenza. The child with pharyngitis can benefit from rapid antigen detection testing for group A Streptococcus and a throat culture. Dysuria, back pain, or a history of vesicoureteral reflux should prompt a urinalysis and urine culture, and bloody diarrhea should prompt a stool culture. A complete blood count and blood culture should be considered in the ill-appearing child, along with cerebrospinal fluid studies if the child has neck stiffness or if the possibility of meningitis is considered. Well-defined high-risk groups require a more-extensive evaluation on the basis of age, associated disease, or immunodeficiency status, and might warrant prompt antimicrobial therapy before a pathogen is identified. The evaluations of infants <3 mo of age and children with recurrent fevers are discussed in Chapter 177.

**MANAGEMENT**

Although fear of fever is a common parental worry, evidence is lacking to support the belief that high fever can result in brain damage or other bodily harm, except in rare instances of febrile status epilepticus and heatstroke. Treating fever in self-limiting illnesses for the sole reason of bringing the body temperature back to normal is not necessary in the otherwise healthy child. Most evidence suggests that fever is an adaptive response and should be treated only in selected circumstances. In humans, increased temperatures are associated with decreased microbial replication and an increased inflammatory response. Although fever can have beneficial effects, it also increases oxygen consumption, carbon dioxide production, and cardiac output, and can exacerbate cardiac insufficiency in patients with heart disease or chronic anemia (e.g., sickle cell disease), pulmonary insufficiency in patients with chronic lung disease, and metabolic instability in patients with diabetes mellitus or inborn errors of metabolism. Children between the ages of 6 mo and 5 yr are at increased risk for simple febrile seizures. The focus of the evaluation and treatment of febrile seizures is aimed at determining the underlying cause of the fever. Children with idiopathic epilepsy also often have an increased frequency of seizures associated with a fever. High fever during pregnancy may be teratogenic.

Fever with temperatures <39°C (102.2°F) in healthy children generally does not require treatment. However, as temperatures become higher, patients tend to become more uncomfortable, and treatment of fever is then reasonable. If a child is included in 1 of the high-risk groups or if the child’s caregiver is concerned that the fever is adversely affecting the child’s behavior and causing discomfort, treatment may be given to hasten the resolution of the fever. Other than providing symptomatic relief, antipyretic therapy does not change the course of infectious diseases. Encouraging good hydration is the first step to replace fluids that are lost related to the increased metabolic demands of fever. Antipyretic therapy is beneficial in high-risk patients who have chronic cardiopulmonary diseases, metabolic disorders, or neurologic diseases and in those who are at risk for febrile seizures. Hyperpyrexia (>41°C [105.8°F]) indicates high probability of hypothalamic disorders or central nervous system hemorrhage and should be treated with antipyretics. Some studies show that hyperpyrexia may be associated with a significantly increased risk of serious bacterial infection, but other studies have not substantiated this relationship. Acetaminophen at a dose of 10-15 mg/kg/dose every 4 hr and ibuprofen in children >6 mo at a dose of 5-10 mg/kg/dose every 8 hr are the most commonly employed antipyretics. Antipyretics reduce fever by reducing production of prostaglandins. If used appropriately, antipyretics are safe; potential adverse effects include liver damage (acetaminophen) and gastrointestinal or kidney disturbances (ibuprofen). To reduce fever most safely, the caregiver should choose 1 type of medication and clearly record the dose and time of administration, so overdosage does not occur, especially if multiple caregivers are involved in the management. Physical measures such as tepid baths and cooling blankets are not considered effective to reduce fever. Evidence is also scarce for the use of complementary and alternative medicine interventions.

Fever caused by specific underlying etiologies resolves when the condition is properly treated. Examples include administration of intravenous immunoglobulin to treat Kawasaki disease or the administration of antibiotics to treat bacterial infections.

**Table 176-2** Evaluation of Acute Fever

<table>
<thead>
<tr>
<th>Table 176-2</th>
<th>Evaluation of Acute Fever</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thorough history: onset, other symptoms, exposures (daycare, school, family, pets, playmates), travel, medications, other underlying disorders, immunizations</td>
<td></td>
</tr>
<tr>
<td>Physical examination: complete, with focus on localizing symptoms</td>
<td></td>
</tr>
<tr>
<td>Laboratory studies on a case-by-case basis:</td>
<td></td>
</tr>
<tr>
<td>- Rapid antigen testing</td>
<td></td>
</tr>
<tr>
<td>- Nasopharyngeal: respiratory viruses by polymerase chain reaction</td>
<td></td>
</tr>
<tr>
<td>- Throat: group A Streptococcus</td>
<td></td>
</tr>
<tr>
<td>- Stool: rotavirus</td>
<td></td>
</tr>
<tr>
<td>- Blood: complete blood count, blood culture, C-reactive protein, sedimentation rate, procalcitonin</td>
<td></td>
</tr>
<tr>
<td>- Urine: urinalysis, culture</td>
<td></td>
</tr>
<tr>
<td>- Stool: Hemoccult, culture</td>
<td></td>
</tr>
<tr>
<td>- Cerebrospinal fluid: cell count, glucose, protein, Gram stain, culture</td>
<td></td>
</tr>
<tr>
<td>- Chest radiograph or other imaging studies on a case-by-case basis</td>
<td></td>
</tr>
</tbody>
</table>

Bibliography is available at Expert Consult.
Bibliography

Fever without a focus refers to a rectal temperature of 38°C (100.4°F) or higher as the sole presenting feature. The terms “fever without localizing signs” and “fever of unknown origin” (FUO) are subcategories of fever without a focus.

FEVER WITHOUT LOCALIZING SIGNS
Fever of acute onset, with duration of <1 wk and without localizing signs, is a common diagnostic dilemma in children <36 mo of age. The etiology and evaluation of fever without localizing signs depends on the age of the child. Traditionally, 3 age groups are considered: neonates or infants to 1 mo of age, infants >1 mo to 3 mo of age, and children >3 mo to 3 yr of age. In 1993, practice guidelines were published to aid the clinician in evaluating the otherwise healthy 0-36 mo old child with fever without a source. However, with the advent and extensive use of the conjugate Haemophilus influenzae type b (Hib) and Streptococcus pneumoniae vaccines, the rates of infections with these 2 pathogens have decreased substantially. As a consequence, modifications to the 1993 guidelines have been advocated as described in the section “3-36 Months of Age.” Children in high-risk groups (Table 177-1) require a more aggressive diagnostic approach and consideration of a broader differential diagnosis.

Neonates
Neonates who experience fever without focus are a challenge to evaluate because they display limited signs of infection, making it difficult to clinically distinguish between a serious bacterial or viral (herpes simplex virus [HSV]) infection and self-limited viral illness. Immature immune responses in the 1st few mo of life also increase the significance of fever in the young infant. In general, neonates who have a fever and do not appear ill have a 7% risk of having a serious bacterial infection. Serious bacterial infections include bacteremia, meningitis, pneumonia, osteomyelitis, septic arthritis, enteritis, and urinary tract infections. Although neonates with serious infection can acquire community pathogens, they are mainly at risk for late-onset neonatal bacterial diseases (group B streptococci, E. coli, and Listeria monocytogenes) and perinatally acquired herpes simplex virus (HSV) infection.

Practice guidelines recommend that if a neonate has had a fever recorded at home by a reliable parent, the patient should be treated as a febrile neonate. If excessive clothing and blankets encasing the infant are suspected of falsely elevating the body temperature, then the excessive coverings should be removed and the temperature retaken in 15-30 min. If body temperature is normal after the covers are removed, then the infant is considered afibrile.

Owing to the unreliability of physical findings and the presence of an immature immune system, all febrile neonates should be hospitalized; blood, urine, and cerebrospinal fluid (CSF) should be cultured, and the child should receive empirical intravenous antibiotics. CSF studies should include cell counts, glucose and protein levels, Gram stain, and culture; HSV and enterovirus polymerase chain reaction should be considered. Stool culture and chest radiograph may also be part of the evaluation. Combination antibiotics, such as ampicillin and cefotaxime or ampicillin and gentamicin, are recommended. Acyclovir should be included if HSV infection is suspected because of seizures, hypotension, transaminase elevation, CSF pleocytosis, or known maternal history of genital HSV, especially at the time of delivery.

1 to 3 Months of Age
The large majority of children with fever without localizing signs in the 1-3 mo age group likely have a viral syndrome. In contrast to bacterial infections, most viral diseases have a distinct seasonal pattern: respira-

<table>
<thead>
<tr>
<th>Table 177-1</th>
<th>Febrile Patients at Increased Risk for Serious Bacterial and Viral Infections</th>
</tr>
</thead>
<tbody>
<tr>
<td>RISK GROUP</td>
<td>DIAGNOSTIC CONSIDERATIONS</td>
</tr>
<tr>
<td>IMMUNOCOMPETENT PATIENTS</td>
<td></td>
</tr>
<tr>
<td>Neonates (&lt;28 days)</td>
<td>Sepsis and meningitis caused by group B Streptococcus, Escherichia coli, Listeria monocytogenes; neonatal herpes simplex virus infection, enteroviruses, parechovirus</td>
</tr>
<tr>
<td>Infants 1-3 mo</td>
<td>Serious bacterial disease in 5-15%, including bacteremia in 5%; urinary tract infection most common serious bacterial infection; E. coli most common pathogen; enterovirus, parechovirus, influenza</td>
</tr>
<tr>
<td>Infants and children 3-36 mo</td>
<td>Occult bacteremia in &lt;0.5% of children immunized with both Haemophilus influenzae type b and pneumococcal conjugate vaccines; urinary tract infections</td>
</tr>
<tr>
<td>Hyperpyrexia (&gt;40°C [104°F])</td>
<td>Meningitis, bacteremia, pneumonia, heatstroke, hemorrhagic shock-encephalopathy syndrome</td>
</tr>
<tr>
<td>Fever with petechiae</td>
<td>Bacteremia and meningitis caused by Neisseria meningitidis, H. influenzae type b, and Streptococcus pneumoniae Rickettsial disease Viral exanthem</td>
</tr>
<tr>
<td>IMMUNOCOMPROMISED PATIENTS</td>
<td></td>
</tr>
<tr>
<td>Sickle cell disease</td>
<td>Sepsis, pneumonia, and meningitis caused by S. pneumoniae, osteomyelitis caused by Salmonella and Staphylococcus aureus</td>
</tr>
<tr>
<td>Asplenia</td>
<td>Bacteremia and meningitis caused by N. meningitidis, H. influenzae type b, S. pneumoniae, and Capnocytophaga sp. Sepsis caused by N. meningitidis</td>
</tr>
<tr>
<td>Complement or properdin deficiency</td>
<td></td>
</tr>
<tr>
<td>Agammaglobulinemia</td>
<td>Bacteremia, sinusopulmonary infections S. pneumoniae, H. influenzae type b, and Salmonella infections</td>
</tr>
<tr>
<td>AIDS</td>
<td>Bacteremia, sinopulmonary infections S. pneumoniae, H. influenzae type b, and Salmonella infections</td>
</tr>
<tr>
<td>Congenital heart disease</td>
<td>Infective endocarditis, brain abscess with right-to-left shunting</td>
</tr>
<tr>
<td>Central venous line</td>
<td>S. aureus, coagulase-negative staphylococci, Candida</td>
</tr>
<tr>
<td>Malignancy</td>
<td>Bacteremia with gram-negative enteric bacteria, S. aureus, and coagulase-negative staphylococci, fungemia with Candida and Aspergillus</td>
</tr>
</tbody>
</table>
or cefotaxime is an effective initial antimicrobial regimen for ill-
appearing infants without focal findings. This regimen is effective
against the usual bacterial pathogens causing sepsis, urinary tract
infection, and enteritis in young infants. However, if meningitis is
suspected because of CSF abnormalities, vancomycin should be
included to treat possible penicillin-resistant *S. pneumoniae* until the
results of culture and susceptibility tests are known.

Many academic institutions have investigated the optimal manage-
ment of low-risk patients in this age group with fever without a focus
(Table 177-2). The use of viral diagnostic studies (enteroviruses, par-
echovirus, respiratory viruses, rotavirus, and herpesviruses) in combina-
tion with the Rochester Criteria or similar criteria can enhance the
ability to determine which infants are at high risk for serious bacterial
infections (Table 177-2). Febrile infants in whom a virus has been
detected are at low or no risk of a serious bacterial infection. Well-
appearing infants 1-3 mo of age can be managed safely using low-risk
laboratory and clinical criteria as indicated in Table 177-2 if reliable
parents are involved and close follow-up is assured.

Infants 1-3 mo of age with fever who appear generally well; who
have been previously healthy; who have no evidence of skin, soft tissue,
bone, joint, or ear infection; and who have a peripheral white blood
cell (WBC) count of 5,000-15,000 µ/L, an absolute band count of
<1,500 cells/µL, and normal urinalysis and negative culture (blood and
urine) results are unlikely to have a serious bacterial infection. The
negative predictive value with 95% confidence of these criteria for any
serious bacterial infection is >98% and for bacteremia is >99%. Among
serious bacterial infections, pyelonephritis is the most common and
may be seen in well-appearing infants who have fever without a focus
or in those who appear ill. Urinalysis may be negative in infants <2 mo
of age with pyelonephritis. Bacteremia is present in <30% of infants
with pyelonephritis. Procalcitonin, erythrocyte sedimentation rate
(ESR), and C-reactive protein are biologic markers that may be con-
sidered in the evaluation of a child with fever. Host-based microarray
gene expression profiles determined on the patient's leukocytes may be
able to detect RNA transcriptional patterns (biosignatures) that distin-
guish viral from bacterial infection (Fig. 177-1).

The decision to obtain CSF studies in the well-appearing 1-3 mo old
infant depends on the decision to administer empirical antibiotics. If
close observation without antibiotics is planned, a lumbar puncture
may be deferred. If the child deteriorates clinically, a full sepsis eval-
uation should be performed, and intravenous antibiotics should be
administered. If empirical antibiotics are initiated, CSF studies should
be obtained, preferably before administering antibiotics.

### 3 to 36 Months of Age

Approximately 30% of febrile children in the 3-36 mo age group have
no localizing signs of infection. Viral infections are the cause of the
vast majority of fevers in this population, but serious bacterial infec-
tions do occur and are caused by the same pathogens listed for patients
1-3 mo of age, except for the perinatally acquired infections. *S. pneu-
moniae*, *N. meningitidis*, and *Salmonella* account for most cases of
occult bacteremia. *H. influenzae* type b was an important cause of
occult bacteremia in young children before universal immunization
with conjugate Hib vaccines and remains common in underdeveloped
countries that have not implemented these vaccines in their immuniza-
tion schedule.

Risk factors indicating increased probability of occult bacteremia
include temperature ≥39°C (102.2°F), WBC count ≥15,000/µL, and

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**Table 177-2** Low-Risk Criteria in a Child 1-3 Months Old with Fever

| BOSTON CRITERIA | Infants are at low risk if they appear well, have a normal physical examination, and have a caretaker reachable by telephone and if laboratory tests are as follows: |
| CBC: >20,000 WBC/µL |
| Urine: negative leukocyte esterase |
| CSF: leukocyte count less than 10 x 10^3/L |

| PHILADELPHIA PROTOCOL | Infants are at low risk if they appear well and have a normal physical examination and if laboratory tests are as follows: |
| CBC: <15,000 WBC/µL; band: total neutrophil ratio <0.2 |
| Urine: <10 WBC/HFP; no bacteria on Gram stain |
| CSF: <8 WBC/µL; no bacteria on Gram stain |
| Chest radiograph: no infiltrate |
| Stool: no RBC; few to no WBC |

| PITTSBURGH GUIDELINES | Infants are at low risk if they appear well and have a normal physical examination and if laboratory tests are as follows: |
| CBC: 5,000-15,000 WBC/µL; peripheral absolute band count <1,500/µL |
| Urine (enhanced urinalysis): 9 WBC/µL and no bacteria on Gram stain |
| CSF: 5 WBC/µL and negative Gram stain; if bloody tap, then WBC/RBC ≤1:500 |
| Chest radiograph: no infiltrate |
| Stool: 5 WBC/HFP with diarrhea |

| ROCHESTER CRITERIA | Infants are at low risk if they appear well and have a normal physical examination and if laboratory findings are as follows: |
| CBC: 5,000-15,000 WBC/µL; absolute band count ≤1,500/µL |
| Urine: <10 WBC/HFP at 40x |
| Stool: <5 WBC/HFP if diarrhea |

CBC, complete blood count; CSF, cerebrospinal fluid; HPF, high-powered field; RBC, red blood cell; WBC, white blood cell.

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**Figure 177-1** Gene expression patterns may discriminate viral vs bacterial infections. **A**, Set of 35 genes that discriminates patients with viral infections (influenza A; green) and bacterial infections (*Escherichia coli* and *Streptococcus pneumoniae*; red). The discriminative pattern is shown by the gene expression patterns in the heat map (red indicates overexpressed genes; blue indicates underexpressed genes). **B**, The diagnostic signature was tested in an independent set of patients that confirmed its accuracy. K-NN indicates nearest neighbor algorithm. (Modified from Ramilo O, Allman W, Chung W, et al: Gene expression patterns in blood leukocytes discriminate patients with acute infections, Blood 109:2066-2077, 2007, Fig 1.)
elevated absolute neutrophil count, band count, erythrocyte sedimentation rate (ESR), or C-reactive protein. The probability of bacteremia and/or pneumonia or pyelonephritis among infants 3-36 mo of age increases as the temperature (especially >30°C (86°F)) and WBC count (especially >25,000/µL) increase. However, no combination of laboratory tests or clinical assessment is sensitive enough to predict the presence of occult bacteremia. Socioeconomic status, race, gender, and age (within the range of 3-36 mo) do not appear to affect the risk for occult bacteremia.

The pattern of sequelae of occult bacteremia may be related to host factors and the offending organism. In some children, the occult bacteremic illness can represent the early signs of serious localized infection rather than a transient disease state. Without therapy, occult bacteremia caused by pneumococcus can resolve spontaneously without sequelae, can persist, or can lead to localized infections such as meningitis, pneumonia, cellulitis, pericarditis, osteomyelitis, or supplicative arthritis. Among patients with pneumococcal bacteremia (occult or focal), spontaneous resolution occurs in 30-40%, with a higher rate of spontaneous resolution among well-appearing children.

Hib bacteremia is characterized with a higher risk for localized serious infection than is bacteremia caused by S. pneumoniae. Hospitalized children with Hib bacteremia often develop focal infections, such as meningitis, epiglottitis, cellulitis, pericarditis, or osteoarticular infection, and spontaneous resolution of bacteremia is rare. Important bacterial infections among children 3-36 mo of age with localizing signs include otitis media, sinusitis, pneumonia (not always evident without a chest radiograph), enteritis, urinary tract infection, osteomyelitis, and meningitis.

Management of toxic-appearing febrile children 3-36 mo of age who do not have focal signs of infection includes hospitalization and prompt institution of antimicrobial therapy after specimens of blood, urine, and CSF are obtained for culture. Consensus practice guidelines published in 1993 recommended that children 3-36 mo of age who have a temperature of <39°C (102.2°F) and do not appear toxic be observed as outpatients without performing diagnostic tests or administering antimicrobial agents. For nontoxic-appearing infants with a rectal temperature of ≥39°C (102.2°F), options include obtaining a blood culture and administering empirical antibiotic therapy (ceftriaxone, a single dose of 50 mg/kg, not to exceed 1 g); if the WBC count is >15,000/µL, obtaining a blood culture and beginning empirical ceftriaxone; or obtaining a blood culture and observing as outpatients without empirical antibiotic therapy, with return for reevaluation within 24 hr. Guidelines for managing febrile children 3-36 mo of age who have received both Hib and S. pneumoniae conjugate vaccines have not been established, but careful observation without empirical administration of antibiotic therapy is generally prudent. Because fully vaccinated young children are at a much lower risk of occult bacteremia and meningitis as the cause of acute fever without localizing signs, some advocate that the only laboratory tests needed in this age group when temperature is >39°C (102.2°F) are a urinalysis and urine culture for circumcised boys <6 mo of age and uncircumcised boys and all girls <24 mo of age. Regardless of the management option (Table 177-3), the family should be instructed to return immediately if the child’s condition deteriorates or new symptoms develop.

Empirical antibiotic therapy for well-appearing children <36 mo of age who have not received Hib and S. pneumoniae conjugate vaccines and who have a rectal temperature of >39°C (102.2°F) and a WBC count of >15,000/µL is strongly recommended. If blood cultures are obtained and S. pneumoniae is isolated from the blood, the child should return to the physician as soon as possible after the culture results are known. If the child appears well, is afebrile, and has a normal physical exam, a second blood culture should be obtained and the child should be treated with 7-10 days of oral antimicrobial therapy. If the child appears ill and continues to have fever with no identifiable focus of infection at the time of follow-up, or if H. influenzae or N. meningitidis is present in the initial blood culture, the child

<table>
<thead>
<tr>
<th>Table 177-3</th>
<th>Management of Fever Without Localizing Signs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>GROUP</strong></td>
<td><strong>MANAGEMENT</strong></td>
</tr>
<tr>
<td>Any toxic-appearing child 0-36 mo and temperature ≥38°C (100.4°F)</td>
<td>Hospitalize, broad cultures plus other tests,* parenteral antibiotics</td>
</tr>
<tr>
<td>Child &lt;1 mo and temperature ≥38°C (100.4°F)</td>
<td>Hospitalize, broad cultures plus other tests,* parenteral antibiotics</td>
</tr>
</tbody>
</table>
| Child 1-3 mo and temperature ≥38°C (100.4°F) | Two-step process  
1. Determine risk based on history, physical examination, and laboratory studies. 
   Low risk:  
   - Uncomplicated medical history  
   - Normal physical examination  
   - Normal laboratory studies  
   - Urine: negative leukocyte esterase, nitrite and <10 WBC/HPF  
   - Peripheral blood: 5,000-15,000 WBC/mm³; <1,500 bands or band: total neutrophil ratio <0.2  
   - Stool studies if diarrhea (no RBC and <5 WBC/HPF)  
   - CSF cell count (<8 WBC/µL) and negative Gram stain  
   - Chest radiograph without infiltrate  
2. If child fulfills all low-risk criteria, administer no antibiotics, ensure follow-up in 24 hr and access to emergency care if child deteriorates. Daily follow-up should occur until blood, urine, and CSF cultures are final. If any cultures are positive, child returns for further evaluation and treatment. If child does not fulfill all low-risk criteria, hospitalize and administer parenteral antibiotics until all cultures are final and definitive diagnosis determined and treated |
| Child 3-36 mo and temperature 38-39°C (100.4-102.2°F) | Reassurance that diagnosis is likely self-limiting viral infection, but advise return with persistence of fever, temperatures >39°C (102.2°F), and new signs and symptoms |
| Child 3-36 mo and temperature >39°C (102.2°F) | Two-step process:  
1. Determine immunization status  
2. If received conjugate pneumococcal and Haemophilus influenzae type b vaccines, obtain urine studies (urine WBC, leukocyte esterase, nitrite, and culture) for all girls, all boys <6 mo old, all uncircumcised boys <2 yr, all children with recurrent urinary tract infections  

*Other tests may include chest radiograph, stool studies, herpes simplex polymerase chain reaction. 
CSF, cerebrospinal fluid; HPF, high-powered field; RBC, red blood cell; WBC, white blood cell.
FEVER OF UNKNOWN ORIGIN

The classification of fever of unknown origin (FUO) is best reserved for children with fever documented by a healthcare provider and for which the cause could not be identified after 3 wk of evaluation as an outpatient or after 1 wk of evaluation in the hospital (Table 177-4).

Etiology

The many causes of FUO in children are infections, rheumatologic (connective tissue or autoimmune) diseases, or autoinflammatory diseases (see Chapter 163) (Table 177-5). Neoplastic disorders should also be seriously considered, although most children with malignancies do not have fever alone. The possibility of drug fever should be considered if the patient is receiving any drug. Drug fever is usually sustained and not associated with other symptoms. Discontinuation of the drug is not associated with resolution of the fever, generally within 72 hr, although certain drugs, such as iodiums, are excreted for a prolonged period with fever that can persist for as long as 1 mo after drug withdrawal.

Most fevers of unknown or unrecognized origin result from atypical presentations of common diseases. In some cases, the presentation as an FUO is characteristic of the disease, such as juvenile idiopathic arthritis, but the definitive diagnosis can be established only after prolonged observation because initially there are no associated or specific findings on physical examination and all laboratory results are negative or normal.

In the United States, the systemic infectious diseases most commonly implicated in children with FUO are salmonellosis, tuberculosis, rickettsial diseases, syphilis, Lyme disease, cat-scratch disease, atypical prolonged presentations of common viral diseases, Epstein-Barr virus infection, cytomegalovirus (CMV) infection, viral hepatitis, coccidioidomycosis, histoplasmosis, malaria, and toxoplasmosis. Less-common infectious causes of FUO include tularemia, brucellosis, leptospirosis, and rat bite fever. AIDS alone is not usually responsible for FUO, although febrile illnesses often occur in patients with AIDS as a result of opportunistic infections (see Table 177-4).

Juvenile idiopathic arthritis (JIA) and systemic lupus erythematosus are the connective tissue diseases associated most commonly with FUO. Inflammatory bowel disease and Kawasaki disease are also commonly reported as causes of FUO. If factitious fever (inoculation of pyogenic material or manipulation of the thermometer by the patient or parent) is suspected, the presence and pattern of fever should be documented in the hospital. Prolonged and continuous observation, which can include electronic or video surveillance, of patients is imperative. FUO lasting longer than 6 mo is uncommon in children and suggests granulomatous, autoimmune, or autoimmune disease.

### Table 177-4 Summary of Definitions and Major Features of the 4 Subtypes of Fever of Unknown Origin

<table>
<thead>
<tr>
<th>FEATURE</th>
<th>CLASSIC FUO</th>
<th>HEALTHCARE-ASSOCIATED FUO</th>
<th>IMMUNE-DEFICIENT FUO</th>
<th>HIV-RELATED FUO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definition</td>
<td>&gt;38°C (100.4°F), &gt;3 wk, &gt;2 visits or 1 wk in hospital</td>
<td>≥38°C (100.4°F), &gt;1 wk, not present or incubating on admission</td>
<td>≥38°C (100.4°F), &gt;1 wk, negative cultures after 48 hr</td>
<td>≥38°C (100.4°F), &gt;3 wk for outpatients, &gt;1 wk for inpatients, HIV infection confirmed</td>
</tr>
<tr>
<td>Patient location</td>
<td>Community, clinic, or hospital</td>
<td>Acute care hospital</td>
<td>Hospital or clinic</td>
<td>Community, clinic, or hospital</td>
</tr>
<tr>
<td>Leading causes</td>
<td>Cancer, infections, inflammatory conditions, undiagnosed, habitual hyperthermia</td>
<td>Healthcare-associated infections, postoperative complications, drug fever</td>
<td>Majority caused by infections, but cause documented in only 40-60%</td>
<td>HIV (primary infection), typical and atypical mycobacteria, CMV, lymphomas, toxoplasmosis, cryptococcosis, immune reconstitution inflammatory syndrome (IRIS)</td>
</tr>
<tr>
<td>History emphasis</td>
<td>Travel, contacts, animal and insect exposure, medications, immunizations, family history, cardiac valve disorder</td>
<td>Operations and procedures, devices, anatomic considerations, drug treatment</td>
<td>Stage of chemotherapy, drugs administered, underlying immunosuppressive disorder</td>
<td>Drugs, exposures, risk factors, travel, contacts, stage of HIV infection</td>
</tr>
<tr>
<td>Examination emphasis</td>
<td>Fundi, oropharynx, temporal artery, abdomen, lymph nodes, spleen, joints, skin, nails, genitalia, rectum or prostate, lower-limb deep veins</td>
<td>Wounds, drains, devices, sinuses, urine</td>
<td>Skin folds, IV sites, lungs, perianal area</td>
<td>Mouth, sinuses, skin, lymph nodes, eyes, lungs, perianal area</td>
</tr>
<tr>
<td>Investigation emphasis</td>
<td>Imaging, biopsies, sedimentation rate, skin tests</td>
<td>Imaging, bacterial cultures</td>
<td>CXR, bacterial cultures</td>
<td>Blood and lymphocyte count; serologic tests; CXR; stool examination; biopsies of lung, bone marrow, and liver for cultures and cytologic tests; brain imaging</td>
</tr>
<tr>
<td>Management</td>
<td>Observation, outpatient temperature chart, investigations, avoidance of empirical drug treatments</td>
<td>Depends on situation</td>
<td>Antimicrobial treatment protocols</td>
<td>Antiviral and antimicrobial protocols, vaccines, revision of treatment regimens, good nutrition</td>
</tr>
<tr>
<td>Time course of disease</td>
<td>Months</td>
<td>Weeks</td>
<td>Days</td>
<td>Weeks to months</td>
</tr>
<tr>
<td>Tempo of investigation</td>
<td>Weeks</td>
<td>Days</td>
<td>Hours</td>
<td>Days to weeks</td>
</tr>
</tbody>
</table>

CMV, cytomegalovirus; CXR, chest radiograph; FUO, fever of unknown origin.

<table>
<thead>
<tr>
<th><strong>Table 177-5</strong></th>
<th>Diagnostic Considerations of Fever of Unknown Origin in Children</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ABSCESSSES</strong></td>
<td>Abdominal, Brain, Dental, Hepatic, Pelvic, Perinephric, Rectal, Subphrenic, Psoas</td>
</tr>
<tr>
<td><strong>BACTERIAL DISEASES</strong></td>
<td>Actinomycosis, Bartonella henselae (cat-scratch disease), Brucellosis, Campylobacter, Francisella tularensis (tularemia), Listeria monocytogenes (listeriosis), Meningococcemia (chronic), Mycoplasma pneumoniae, Rat bite fever (<em>Streptobacillus moniliformis</em>; streptobacillary form of rat bite fever), Salmonella, Tuberculosis, Whipple disease, Yersiniosis</td>
</tr>
<tr>
<td><strong>LOCALIZED INFECTIONS</strong></td>
<td>Cholangitis, Infective endocarditis, Mastoiditis, Osteomyelitis, Pneumonia, Pyelonephritis, Sinusitis</td>
</tr>
<tr>
<td><strong>SPIROCHETES</strong></td>
<td><em>Borrelia burgdorferi</em> (Lyme disease), Relapsing fever (<em>Borrelia recurrentis</em>), Leptospirosis, Rat bite fever (<em>Spirillum minus</em>; spirillary form of rat bite fever), Syphilis</td>
</tr>
<tr>
<td><strong>FUNGAL DISEASES</strong></td>
<td>Blastomycosis (extrapulmonary), Coccidioidomycosis (disseminated), Histoplasmosis (disseminated), <em>Chlamydia</em>, Lymphogranuloma venereum, Psittacosis</td>
</tr>
<tr>
<td><strong>RICKETTSIA</strong></td>
<td><em>Ehrlichia canis</em>, Q fever, Rocky Mountain spotted fever, Tick-borne typhus</td>
</tr>
<tr>
<td><strong>VIRUSES</strong></td>
<td>Cytomegalovirus, Hepatitis viruses, HIV, Epstein-Barr virus</td>
</tr>
<tr>
<td><strong>PARASITIC DISEASES</strong></td>
<td>Amebiasis, Babesiosis, Giardiasis, Malaria, Toxoplasmosis, Trichinosis, Trypanosomiasis, Visceral larva migrans (Toxocara)</td>
</tr>
<tr>
<td><strong>RHEUMATOLOGIC DISEASES</strong></td>
<td>Behçet disease, Juvenile dermatomyositis, Juvenile idiopathic arthritis, Rheumatic fever, Systemic lupus erythematosus</td>
</tr>
<tr>
<td><strong>HYPERSENSITIVITY DISEASES</strong></td>
<td>Drug fever, Hypersensitivity pneumonitis, Serum sickness, Weber-Christian disease</td>
</tr>
<tr>
<td><strong>NEOPLASMS</strong></td>
<td>Atrial myxoma, Cholesterol granuloma, Hodgkin disease, Inflammatory pseudotumor, Leukemia, Lymphoma, Pheochromocytoma, Neuroblastoma, Wilms tumor</td>
</tr>
<tr>
<td><strong>GRANULOMATOUS DISEASES</strong></td>
<td>Crohn disease, Granulomatous hepatitis, sarcoidosis, Angitis</td>
</tr>
<tr>
<td><strong>FAMILIAL AND HEREDITARY DISEASES</strong></td>
<td>Anhidrotic ectodermal dysplasia, Autonomic neuropathies, Fabry disease, Familial dysautonomia, Familial Hibernian fever, Familial Mediterranean fever and the many other autoinflammatory diseases (see Chapter 163), Hypertriglyceridemia, Ichthyosis, Sickle cell crisis, Spinal cord/brain injury</td>
</tr>
<tr>
<td><strong>MISCELLANEOUS</strong></td>
<td>Addison disease, Castleman disease, Chronic active hepatitis, Cyclic neutropenia, Diabetes insipidus (nonnephrogenic and nephrogenic), Factitious fever, Hemophagocytic syndromes, Hypothalamic-central fever, Infantile cortical hyperostosis, Inflammatory bowel disease, Kawasaki disease, Kikuchi-Fujimoto disease, Metal fume fever, Pancreatitis, Periodic fever syndromes, Poisoning, Pulmonary embolism, Thrombophlebitis, Thyrotoxicosis, thyroiditis</td>
</tr>
</tbody>
</table>
Repeat interval evaluation, including history, physical examination, laboratory evaluation, and imaging studies, is required.

**Diagnosis**

The evaluation of FUO requires a thorough history and physical examination supplemented by a few screening laboratory tests and additional laboratory and imaging evaluation as indicated by the history or abnormalities on examination or initial screening tests (see Table 177-5).

**History**

A detailed fever history including onset, frequency, duration of fever, response or nonresponse to therapy, recurrence, and associated symptoms should be obtained. Repetitive chills and temperature spikes are common in children with septicemia (regardless of cause), particularly when associated with kidney disease, liver or biliary disease, infective endocarditis, malaria, brucellosis, rat bite fever, or a loculated collection of pus.

The age of the patient is helpful in evaluating FUO. Children >6 yr of age often have a respiratory or genitourinary tract infection, localized infection (abscess, osteomyelitis), JIA, or, rarely, leukemia. Adolescent patients are more likely to have inflammatory bowel disease, autoimmune processes, lymphoma, or tuberculosis, in addition to the causes of FUO found in younger children.

A history of exposure to wild or domestic animals should be solicited. The incidence of zoonotic infections in the United States is increasing, and these infections are often acquired from pets that are not overtly ill. Immunization of dogs against specific disorders such as leptospirosis can prevent canine disease but does not always prevent the animal from carrying and shedding leptospires, which may be transmitted to household contacts. A history of ingestion of rabbit or squirrel meat might provide a clue to the diagnosis of oropharyngeal, glandular, or typhoidal tularemia. A history of tick bite or travel to tick- or parasite-infested areas should be obtained.

Any history of pica should be elicited. Ingestion of dirt is a particularly important clue to infection with *Toxocara canis* (visceral larva migrans) or *Toxoplasma gondii* (toxoplasmosis).

A history of unusual dietary habits or travel as early as the birth of the child should be sought. Malaria, histoplasmosis, and coccidioidomycosis can reemerge years after visiting or living in an endemic area. It is important to identify prophylactic immunizations and precautions taken by the patient against ingestion of contaminated water or food during foreign travel. Rocks, dirt, and artifacts from geographically distant regions that have been collected and brought into the home as souvenirs can serve as vectors of disease.

A medication history should be pursued rigorously. This history should elicit information about nonprescription preparations and topical agents, including eyedrops, that may be associated with atropine-induced fever.

The genetic background of a patient also is important. Descendants of the Ulster Scots may have FUO because they are afflicted with nephrogenic diabetes insipidus. Familial dysautonomia (Riley-Day syndrome), a disorder in which hyperthermia is recurrent, is more common among Jews than among other population groups. Ancestry from the Mediterranean region should suggest the possibility of familial Mediterranean fever. Both familial Mediterranean fever and hyperimmunoglobulin D syndrome are inherited as autosomal recessive disorders. Tumor necrosis factor receptor–associated periodic syndrome and Muckle-Wells syndrome are inherited as autosomal dominant traits.

**Physical Examination**

A complete physical examination is essential to search for any clues to the underlying diagnosis (Table 177-6). The child’s general appearance, including sweating during fever, should be noted. The continuing absence of sweat in the presence of an elevated or changing body temperature suggests dehydration due to vomiting, diarrhea, or central or nephrogenic diabetes insipidus. It also should suggest anhidrotic ectodermal dysplasia, familial dysautonomia, or exposure to atropine. The general activity of the patient and the presence or absence of rashes should also be noted.

A careful ophthalmic examination is important. Red, weeping eyes may be a sign of connective tissue disease, particularly polyarteritis nodosa. Palpebral conjunctivitis in a febrile patient may be a clue to measles, coxsackievirus infection, tuberculosis, infectious mononucleosis, lymphogranuloma venereum, or cat-scratch disease. In contrast, bulbar conjunctivitis in a child with FUO suggests Kawasaki disease or leptospirosis. Petechial conjunctival hemorrhages suggest infective

### Table 177-6 Examples of Subtle Physical Findings Having Special Significance in Patients with Fever of Unknown Origin

<table>
<thead>
<tr>
<th>BODY SITE</th>
<th>PHYSICAL FINDING</th>
<th>DIAGNOSIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Head</td>
<td>Sinus tenderness</td>
<td>Sinusitis</td>
</tr>
<tr>
<td>Temporal artery</td>
<td>Nodules, reduced pulsations</td>
<td>Temporal arteritis</td>
</tr>
<tr>
<td>Oropharynx</td>
<td>Ulceration</td>
<td>Disseminated histoplasmosis, SLE, IBD, Behcet syndrome, periodic fever syndromes Periapical abscess</td>
</tr>
<tr>
<td></td>
<td>Tender tooth</td>
<td></td>
</tr>
<tr>
<td>Fundi or conjunctivae</td>
<td>Choroid tubercle Petechiae, Roth spot</td>
<td>Disseminated granulomatosis* Endocarditis</td>
</tr>
<tr>
<td>Thyroid</td>
<td>Enlargement, tenderness</td>
<td>Thyroiditis</td>
</tr>
<tr>
<td>Heart</td>
<td>Murmur</td>
<td>Infective or marantic endocarditis</td>
</tr>
<tr>
<td>Abdomen</td>
<td>Enlarged iliac crest lymph nodes, splenomegaly</td>
<td>Lymphoma, endocarditis, disseminated granulomatosis*</td>
</tr>
<tr>
<td>Rectum</td>
<td>Perirectal fluctuance, tenderness Prostatic tenderness, fluctuance</td>
<td>Abscess Abscess</td>
</tr>
<tr>
<td>Genitalia</td>
<td>Testicular nodule Epididymal nodule</td>
<td>Periarteritis nodosa, cancer Disseminated granulomatosis</td>
</tr>
<tr>
<td>Lower extremities</td>
<td>Deep venous tenderness</td>
<td>Thrombosis or thrombophlebitis</td>
</tr>
<tr>
<td>Skin and nails</td>
<td>Petechiae, splinter hemorrhages, subcutaneous nodules, clubbing</td>
<td>Vasculitis, endocarditis</td>
</tr>
</tbody>
</table>

*Includes tuberculosis, histoplasmosis, coccidioidomycosis, sarcoidosis, granulomatosis with polyangiitis, and syphilis.

endocarditis. Uveitis suggests sarcoidosis, JIA, systemic lupus erythematosus, Kawasaki disease, Behçet disease, and vasculitis. Chorioretinitis suggests CMV, toxoplasmosis, and syphilis. Propotosis suggests an orbital tumor, thyrotoxicosis, metastasis (neuroblastoma), orbital infection, Wegener granulomatosis, or pseudotumor. The ophthalmoscope should also be used to examine nailfold capillary abnormalities that are associated with connective tissue diseases such as juvenile dermatomyositis and systemic sclerosis. Immersion oil or lubricating jelly is placed on the skin adjacent to the nail bed, and the capillary pattern is observed with the ophthalmoscope set on +40.

FUO is sometimes caused by hypothalamic dysfunction. A clue to this disorder is failure of pupillary constriction because of absence of the sphincter constrictor muscle of the eye. This muscle develops embryologically when hypothalamic structure and function also are undergoing differentiation.

Fever resulting from familial dysautonomia may be suggested by lack of tears, an absent corneal reflex, or a smooth tongue with absence of fungiform papillae. Tenderness to tapping over the sinuses or the upper teeth suggests sinusitis. Recurrent oral candidiasis may be a clue to various disorders of the immune system especially involving the T lymphocytes. Hyperactive deep tendon reflexes can suggest thyrotoxicosis as the cause of FUO.

Fever blisters are common findings in patients with pneumococcal, streptococcal, malarial, and rickettsial infection as well as periodic fever syndromes. These lesions also are common in children with meningococcal meningitis (which usually does not manifest as FUO) but rarely are seen in children with meningococcemia. Fever blisters also are occasionally seen with Salmonella or staphylococcal infections.

Hyperemia of the pharynx, with or without exudate, suggests streptococcal infection, Epstein-Barr virus infection, CMV infection, toxoplasmosis, salmonellosis, tularemia, Kawasaki disease, or leptospirosis. The muscles and bones should be palpated carefully. Point tenderness over a bone can suggest occult osteomyelitis or bone marrow invasion from neoplastic disease. Tenderness over the trapezius muscle may be a clue to subdiphragmatic abscess. Generalized muscle tenderness suggests dermatomyositis, trichinosis, polyarteritis, Kawasaki disease, or mycoplasmal or arboviral infection. Rectal examination can reveal perirectal lymphadenopathy or tenderness, which suggests a deep pelvic abscess, iliac adenitis, or pelvic osteomyelitis. A guaiac test should be obtained; occult blood loss can suggest granulomatous colitis or ulcerative colitis as the cause of FUO.

**Laboratory Evaluation**

The laboratory evaluation of the child with FUO and whether the evaluation will occur in the inpatient or outpatient realm are determined on a case-by-case basis. Hospitalization may be required for laboratory or imaging studies that are unavailable or impractical in an ambulatory setting, for more-careful observation, or for temporary relief of parents’ anxiety. The tempo of diagnostic evaluation should be adjusted to the tempo of the illness; haste may be imperative in a critically ill patient, but if the illness is more chronic, the evaluation can proceed in systematic fashion and can be carried out in an outpatient setting. If there are no clues in the patient’s history or on physical examination that suggest a specific infection or area of suspicion, it is unlikely that diagnostic studies will be helpful. In that common scenario, continued surveillance and repeated reevaluations of the child should be employed to detect any new clinical findings.

Although ordering a large number of diagnostic tests in every child with FUO according to a predetermined list is discouraged, certain studies should be considered in the evaluation. A complete blood cell count with a differential WBC count and a urinalysis should be part of the initial laboratory evaluation. An absolute neutrophil count of ˂5,000/µL is evidence against indolent bacterial infection other than typhoid fever. Conversely, in patients with a polymorphonuclear leukocyte count of ˃10,000/µL or a nonsegmented polymorphonuclear leukocyte count of ˃500/µL a severe bacterial infection is highly likely.

Direct examination of the blood smear with Giemsa or Wright stain can reveal organisms of malaria, trypanosomiasis, babesiosis, or relapsing fever.

An ESR of ˃30 mm/hr indicates inflammation and the need for further evaluation for infectious, autoimmune, autoinflammatory, or malignant diseases, tuberculosis, Kawasaki disease, or autoimmune disease. A low ESR does not eliminate the possibility of infection or JIA. C-reactive protein is another acute-phase reactant that becomes elevated and returns to normal more rapidly than the ESR. Experts recommend checking 1 of the 2 because there is no evidence that measuring both the ESR and C-reactive protein in the same patient with FUO is clinically useful.

Blood cultures should be obtained aerobically. Anaerobic blood cultures have an extremely low yield and should be obtained only if there are specific reasons to suspect anaerobic infection. Multiple or repeated blood cultures may be required to detect bacteremia associated with infective endocarditis, osteomyelitis, or deep-seated abscesses. Polymicrobial bacteremia suggests factitious self-induced infection or gastrointestinal (GI) pathology. The isolation of leptospires, Francisella, or Yersinia requires selective media or specific conditions not routinely used. Therefore, it is important to inform the laboratory what organisms you are suspecting in a particular case. Urine culture should be obtained in all cases.

Tuberculin skin testing should be performed with intradermal placement of 5 units of purified protein derivative that has been kept appropriately refrigerated.

Imaging studies of the chest, sinuses, mastoids, or GI tract may be indicated by specific historical or physical findings. Radiographic evaluation of the GI tract for inflammatory bowel disease may be helpful in evaluating selected children with FUO and no other localizing signs or symptoms.

Examination of the bone marrow can reveal leukemia; metastatic neoplasm; mycobacterial, fungal, or parasitic infections; histiocytesis; hemophagocytosis; or storage diseases. If a bone marrow aspirate is performed, cultures for bacteria, mycobacteria, and fungi should be obtained.

Serologic tests can aid in the diagnosis of Epstein-Barr virus infection, CMV infection, toxoplasmosis, salmonellosis, tularemia, brucellosis, leptospirosis, cat-scratch disease, Lyme disease, rickettsial disease, and, on some occasions, JIA. The clinician should be aware that the reliability and sensitivity and specificity of these tests vary; for instance, serologic tests for Lyme disease outside of reference laboratories have been generally unreliuable.

Radionuclide scans may be helpful in detecting abdominal abscesses as well as osteomyelitis, especially if the focus cannot be localized to a specific limb or multifocal disease is suspected. Gallium citrate localizes inflammatory tissues (leukocytes) associated with tumors or abscesses. Technetium-99m phosphate is useful for detecting osteomyelitis before plain roentgenograms demonstrate bone lesions. Granulocytes tagged with indium or iodinated immunoglobulin G may be useful in detecting localized pyogenic processes. 18F-fluorodeoxyglucose positron emission tomography is a helpful imaging modality in adults with an FUO and can contribute to an ultimate diagnosis in 30-60% of patients. Echocardiograms can demonstrate the presence of a vegetation on the leaflets of heart valves, suggesting infective endocarditis. Ultrasonography can identify intraabdominal abscesses of the liver, subphrenic space, pelvis, or spleen.

Total-body CT or MRI (both with contrast) is usually the first imaging study of choice; both permit detection of neoplasms and collections of purulent material without the use of surgical exploration or radioisotopes. CT and MRI are helpful in identifying lesions of the head, neck, chest, retroperitoneal spaces, liver, spleen, intraabdominal and intrathoracic lymph nodes, kidneys, pelvis, and mediastinum. CT or ultrasound-guided aspiration or biopsy of suspicious lesions has reduced the need for exploratory laparotomy or thoracotomy. MRI is particularly useful for detecting osteomyelitis or myositis if there is concern about a specific limb. Diagnostic imaging can be very helpful in confirming or evaluating a suspected diagnosis; in the case of CT scans, the child is exposed to large amounts of radiation.
Biopsy is occasionally helpful in establishing a diagnosis of FUO. Bronchoscopy, laparoscopy, mediastinoscopy, and GI endoscopy can provide direct visualization and biopsy material when organ-specific manifestations are present. When employing any of the more-invasive testing procedures, the risk:benefit ratio for the patient must always be taken into consideration before proceeding further.

**Management**
The ultimate treatment of FUO is tailored to the underlying diagnosis. Fever and infection in children are not synonymous; antimicrobial agents should not be used as antipyretics, and empirical trials of medication should generally be avoided. An exception may be the use of antituberculous treatment in critically ill children with suspected disseminated tuberculosis. Empirical trials of other antimicrobial agents may be dangerous and can obscure the diagnosis of infective endocarditis, meningitis, parameningeal infection, or osteomyelitis. After a complete evaluation, antipyretics may be indicated to control fever associated with adverse symptoms.

**Prognosis**
Children with FUO have a better prognosis than do adults. The outcome in a child depends on the primary disease process, which is usually an atypical presentation of a common childhood illness. In many cases, no diagnosis can be established and fever abates spontaneously. In as many as 25% of children in whom fever persists, the cause of the fever remains unclear, even after thorough evaluation.

*Bibliography is available at Expert Consult.*
Bibliography


Infection and disease develop when the host immune system fails to adequately protect against potential pathogens. In individuals with an intact immune system, infection occurs in the setting of naïveté to the microbe and absence or inadequate preexisting microbe-specific immunity or when protective barriers of the body such as the skin have been breached. Healthy children are able to meet the challenge of most infectious agents with an immunologic armamentarium capable of preventing significant disease. Once an infection begins to develop, an array of immune responses is set into action to control the disease and prevent it from reappearing. In contrast, immunocompromised children might not have this same capability. Depending on the level and type of immune defect, the affected child might not be able to contain the pathogen or to develop an appropriate immune response to prevent recurrence (see Chapter 122).

General practitioners are likely to see children with abnormal immune systems in their practices because increasing numbers of children survive with primary immunodeficiencies or receive immunosuppressive therapy for treatment of malignancy, autoimmune disorders, or transplantation.

Primary immunodeficiencies are compromised states that result from genetic defects affecting 1 or more arms of the immune system (Table 178-1). Acquired, or secondary, immunodeficiencies may result from infection (e.g., infection with HIV), from malignancy, or as an adverse effect of immunomodulating or immunosuppressing medications. Such immunosuppressing medications include medications that affect T cells (steroids, calcineurin inhibitors, tumor necrosis factor inhibitors, and chemotherapy), neutrophils (myelosuppressive agents, idiosyncratic or immune-mediated neutropenia), specific immune regulatory cells (tumor necrosis factor blockers, interleukin-2 inhibitors), or all immune cells (chemotherapy). Perturbations of the mucosal and skin barriers or normal microbial flora can also be characterized as secondary immunodeficiencies, predisposing the host open to infections, if only for a temporary period.

The major pathogens causing infections among immunocompetent hosts are also the main pathogens responsible for infections among children with immunodeficiencies. In addition, less-virulent organisms, including normal skin flora, commensal bacteria of the oral pharynx or gastrointestinal tract, environmental fungi, and common community viruses of low-level pathogenicity, can cause severe, life-threatening illnesses in immunocompromised patients (Table 178-2). For this reason, close communication with the diagnostic laboratory is critical so that the laboratory does not disregard normal flora and organisms normally considered to be contaminants as being unimportant.
Most Common Causes of Infections in Immunocompromised Children

<table>
<thead>
<tr>
<th>Table 178-2</th>
<th>Most Common Causes of Infections in Immunocompromised Children</th>
</tr>
</thead>
</table>
| **BACTERIA, AEROBIC** | Acinetobacter  
Burkholderia cepacia  
Citrobacter  
Escherichia coli  
Klebsiella spp.  
Listeria monocytogenes  
Mycobacterium spp.  
Neisseria meningitidis  
Nocardia  
Pseudomonas aeruginosa  
Staphylococcus aureus  
Streptococcus pneumoniae  
Streptococcus pyogenes  |
| **BACTERIA, ANAEROBIC** | Bacillus  
Clostridium  
Fusobacterium  
Peptostreptococcus  
Peptococcus  |
| **FUNGI** | Aspergillus  
Candida albicans  
Other Candida spp.  
Cryptococcus neoformans  
Fusarium spp.  
Pneumocystis jiroveci  |
| **VIRUSES** | Adenoviruses  
CMV  
Epstein-Barr virus  
Herpes simplex virus  
Human herpesvirus 6  
Polyomavirus (BK)  
Respiratory and enteric community-acquired viruses  
Varicella-zoster virus  |
| **PROTOZOA** | Cryptosporidium parvum  
Giardia lamblia  
Toxoplasma gondii  |

*Listed alphabetically.

178.1 Infections Occurring with Primary Immunodeficiencies

Marian G. Michaels and Michael Green

More than 120 genes have been identified, accounting for >150 different primary immunodeficiencies.

ABNORMALITIES OF THE PHAGOCYTIC SYSTEM

Children with abnormalities of the phagocytic and neutrophil system have problems with bacteria as well as environmental fungi. Disease manifests as recurrent infections of the skin, mucous membranes, lungs, liver, and bones. Dysfunction of this arm of the immune system can be a result of inadequate numbers, abnormal movement properties, or aberrant function of neutrophils (see Chapter 130).

Neutropenia is defined as an absolute neutrophil count of <1,000 cells/mm³ and can be associated with significant risk for developing severe bacterial and fungal disease, particularly when the absolute count is <500 cells/mm³ (see Chapter 127). Although acquired neutropenia secondary to bone marrow suppression from a virus or medication is common, genetic causes of neutropenia also exist. Primary congenital neutropenia most often manifests during the 1st yr of life with cellulitis, perirectal abscesses, or stomatitis from Staphylococcus aureus or Pseudomonas aeruginosa. Episodes of severe disease, including bacteremia or meningitis, are also possible. Bone marrow evaluation shows a failure of maturation of myeloid precursors. Most forms of congenital neutropenia are autosomal dominant, but some, such as Kostmann syndrome (see Chapter 127) and Shwachman-Diamond syndrome (see Chapter 469), are caused by autosomal recessive mutations. Cyclic neutropenia can be associated with autosomal dominant inheritance or de novo sporadic mutations and manifests as fixed cycles of severe neutropenia between periods of normal granulocyte numbers. Often the neutrophil count has normalized by the time the patient presents with symptoms, thus hampering the diagnosis. The cycles classically occur every 21 days (range: 14-36 days), with neutropenia lasting 3-6 days. Most often the disease is characterized by recurrent aphthous ulcers and stomatitis during the periods of neutropenia. However, life-threatening necrotizing myositis or cellulitis and systemic disease can occur, especially with Clostridium septicum or Clostridium perfringens. Many of the neutropenic syndromes respond to colony-stimulating factor.

Leukocyte adhesion defects are caused by defects in the β chain of integrin (CD18), which is required for the normal process of neutrophil aggregation and attachment to endothelial surfaces (see Chapter 130). In the most-severe form there is a total absence of CD18. Children with this defect can have a history of delayed cord separation and recurrent infections of the skin, oral mucosa, and genital tract beginning early in life. Ecthyma gangrenosum also occurs. Because the defect involves leukocyte migration and adherence, the neutrophil count in the peripheral blood is usually extremely elevated but pus is not found at the site of infection. Survival is usually <10 yr in the absence of hematopoietic stem cell transplantation (HSCT).

Chronic granulomatous disease is an inherited neutrophil dysfunction syndrome, which can be either X-linked or autosomal recessive (see Chapter 130). In addition, chronic granulomatous disease can develop in response to spontaneous mutations in the genes associated with heritable chronic granulomatous disease. Neutrophils and other myeloid cells have defects in their nicotinamide-adenine dinucleotide phosphate oxidase function, rendering them incapable of generating superoxide and thereby impairing intracellular killing. According to microbes that destroy their own hydrogen peroxide (S. aureus, Serratia marcescens, B. cepacia, Nocardia spp., Aspergillus) cause recurrent infections in these children. Infections have a predilection to involve the lungs, liver, and bone. In addition, these children can present with recurrent abscesses affecting the skin or perirectal region or lymph nodes. Prophylaxis with trimethoprim-sulfamethoxazole, recombinant human interferon-γ, and oral antifungal agents that have activity against Aspergillus spp., such as itraconazole or newer azoles, substantially reduce the incidence of severe infections. Patients with life-threatening infections are also reported to benefit from aggressive treatment with white cell transfusions in addition to antimicrobial agents directed against the specific pathogen. In addition, HSCT can be curative but because of associated risks is not routinely performed.

DEFECTIVE SPLENIC FUNCTION, OPSONIZATION, OR COMPLEMENT ACTIVITY

Children who have congenital asplenia or splenic dysfunction associated with polycythaemia or hemoglobinopathies, such as sickle cell disease, as well as those who have undergone splenectomy, are at risk for serious infections from encapsulated bacteria and blood-borne protozoa such as Plasmodium and Babesia. Prophylaxis against bacterial
infection with penicillin should be considered for these patients, particularly children <5 yr of age. The most common causative organisms include *S. pneumoniae*, *H. influenzae* type b, and *Salmonella*, which can cause sepsis, pneumonia, meningitis, and osteomyelitis. Defects in the early complement components, particularly C2 and C3, can also be associated with severe infection from these bacteria. **Terminal complement defects** (C5, C6, C7, C8, and C9) are associated with recurrent infections with *Neisseria*. Patients with complement deficiency also have an increased incidence of autoimmune disorders. Vaccines for *S. pneumoniae*, *H. influenzae* type b, and *N. meningitidis* should be administered to all children with abnormalities in opsonization or complement pathways (see Chapter 134).

**B-CELL DEFECTS (HUMORAL IMMUNODEFICIENCIES)**

Antibody deficiencies account for the majority of primary immunodeficiencies among humans (see Chapter 124). Patients with defects in the B-cell arm of the immune system fail to develop appropriate antibody responses, with abnormalities that range from complete agammaglobulinemia to isolated failure to produce antibody against a specific antigen or organism. Antibody deficiencies found in children with diseases such as X-linked agammaglobulinemia or common variable immunodeficiency predispose to infections with encapsulated organisms such as *S. pneumoniae* and *H. influenzae* type b. Other bacteria can also be problematic in these children (see Table 178-2). Even though most other classes of microbes do not cause problems for these patients, some notable exceptions exist. Rotavirus can lead to chronic diarrhea, and enteroviruses can disseminate and cause a chronic meningonecephalitis syndrome in these patients. Paralytic polio has developed after immunization with live polio vaccine. Protopzoan infections such as giardiasis can be severe and persistent. Children with B-cell defects can develop bronchiectasis over time following chronic or recurrent pulmonary infections.

Children with antibody deficiencies are usually asymptomatic until 5-6 mo of age, when maternally derived antibody levels begin to wane. These children begin to develop recurrent episodes of otitis media, bronchitis, pneumonia, bacteremia, and meningitis. Many of these infections respond quickly to antibiotics, which can delay the recognition of antibody deficiency. Children who require myringotomy tube placement before 2 yr of age because of recurrent episodes of otitis media (≥3 episodes within 6 mo, or ≥4 episodes within 12 mo) should be considered for screening measurement of immunoglobulin levels.

The significance and impact of specific immunoglobulin (Ig) G subclass deficiencies is less-well understood and remains controversial. Deficiencies of specific IgG subclasses were first noted in healthy adult blood donors in whom no increased susceptibility to infections was documented. However, others have identified specific IgG deficiencies to be associated with a predisposition to recurrent bacterial sinopulmonary infection, bacteremia, meningitis, osteomyelitis, and pyoderma. Deficiency of subclass IgG3 is associated with poor antibody production after exposure to polysaccharide antigens, either after vaccination or after infection with a polysaccharide-encapsulated organism such as *S. pneumoniae* or *H. influenzae* type b.

**Selective IgA deficiency** leads to a lack of production of secretory antibody at the mucosal membranes (see Chapter 124). Even though most patients have no increased risk for infections, some have mild to moderate disease at sites of mucosal barriers. Accordingly, recurrent sinopulmonary infection and gastrointestinal disease are the major clinical manifestations. These patients also have an increased incidence of allergies and autoimmune disorders compared with the normal population.

**Hyper-IgM syndrome** is caused by a defect in the CD40 ligand on the T cell and is associated with a deficiency in the production of IgG and IgA antibody (see Chapter 124). In addition, recurrent neutropenia, hemolytic anemia, or aplastic anemia can be present. Similar to patients with agammaglobulinemia, these patients are at risk for bacterial sinopulmonary infections, *Pneumocystis jiroveci* pneumonia (PCP), and *Cryptosporidium* intestinal infection.

Replacement of antibody with immunoglobulin, administered intravenously every 3-4 wk or weekly, using a subcutaneous formulation, has been the mainstay of treatment for most of the primary IgG antibody deficiencies. Immunoglobulin replacement is not advocated for IgA deficiency, because it does not correct the defect. Prophylaxis with specific antibiotic regimens is controversial and should be individualized for patients who do not respond to immunoglobulin replacement.

**T-CELL DEFECTS (CELL-MEDIATED IMMUNODEFICIENCIES)**

Children with primary cell-mediated immunodeficiencies, either isolated or more commonly in combination with B-cell defects, present early in life and are susceptible to viral, fungal, and protozoan infections. Clinical manifestations include chronic diarrhea, mucocutaneous candidiasis, and recurrent pneumonia, rhinitis, and otitis media. In thymic hypoplasia (DiGeorge syndrome), hypoplasia or aplasia of the thymus and parathyroid glands occurs during fetal development in association with the presence of other congenital abnormalities. Hypocalcemia and cardiac anomalies are usually the presenting features of DiGeorge syndrome, which should prompt evaluation of the T-cell system. **Chronic mucocutaneous candidiasis** is a rare immunodeficiency associated primarily with T-cell dysfunction (see Chapter 125). These patients might not demonstrate delayed hypersensitivity to skin tests for *Candida* antigen despite having chronic superficial infection with yeast, but they do not appear to be at increased risk for systemic yeast infections. Endocrinopathies are commonly associated with chronic mucocutaneous candidiasis.

**COMBINED B-CELL AND T-CELL DEFECTS**

Patients with defects in both the T-cell and B-cell components of the immune system have variable manifestations depending on the extent of the defect (see Chapter 126). Complete or almost complete immunodeficiency is found with severe combined immunodeficiency disorder, whereas partial defects can be present in such states as ataxia-telangiectasia, Wiskott-Aldrich syndrome, hyper-IgE syndrome, and X-linked lymphoproliferative disorder. Rather than 1 disorder, it is now recognized that severe combined immunodeficiency disorder represents a heterogeneous group of genetic defects that leave the infant globally immune deficient and present in the 1st 6 mo of life with recurrent and typically severe infections caused by a variety of bacteria, fungi, and viruses. Failure to thrive, chronic diarrhea, mucocutaneous or systemic candidiasis, PCP, or cytomegalovirus (CMV) infections are common early in life. Passive maternal antibody is relatively protective against the bacterial pathogens during the 1st few mo of life, but thereafter patients are susceptible to both Gram-positive and Gram-negative organisms. Exposure to live virus vaccines can also lead to disseminated disease; accordingly, the use of live vaccines (including rotavirus vaccine) is contraindicated in patients with suspected or proven severe combined immunodeficiency disorder. Without stem cell transplantation or gene therapy, most affected children succumb to opportunistic infections within the 1st yr of life.

Children with ataxia-telangiectasia develop late onset of recurrent sinopulmonary infections from both bacteria and respiratory viruses. In addition, these children experience an increased incidence of malignancies. Wiskott-Aldrich syndrome is an X-linked recessive disease associated with eczema, thrombocytopenia, a reduced number of CD3 lymphocytes, moderately suppressed mitogen responses, and impaired antibody response to polysaccharide antigens. Accordingly, infections with *S. pneumoniae* or *H. influenzae* type b and PCP are common. Children with hyper-IgE syndrome have markedly elevated levels of IgE and present with recurrent episodes of *S. aureus* abscesses of the skin, lungs, and musculoskeletal system. Although the antibody abnormality is notable, these patients also have marked eosinophilia and poor cell-mediated responses to neoantigens and are also at increased risk for fungal infections.

Bibliography is available at Expert Consult.
Bibliography
178.2 Infections Occurring with Acquired Immunodeficiencies

Marian G. Michaels and Michael Green

Immunodeficiencies can be secondarily acquired as a result of infections or as a consequence of other underlying disorders such as malignancy, cystic fibrosis, diabetes mellitus, sickle cell disease, or malnutrition. Immunosuppressive medications used to prevent rejection after organ transplantation, to prevent graft-versus-host disease after stem cell transplantation (see Chapter 137), or to treat malignancies can also leave the host vulnerable to infections. Similarly, medications used to control rheumatologic or other autoimmune diseases may be associated with an increased risk for developing infection. Any process that disrupts the normal mucosal and skin barriers (e.g., burns, surgery, indwelling catheters) can lead to an increased risk for infection.

ACQUIRED IMMUNODEFICIENCY FROM INFECTIOUS AGENTS

Infection with HIV, the causative agent of AIDS, is the most important infectious cause of acquired immunodeficiency (see Chapter 276). Left untreated, HIV infection has profound effects on many parts of the immune system but in particular T-cell–mediated immunity that leads to susceptibility to the same types of infections as with primary T-cell immunodeficiencies.

Other organisms can also lead to temporary alterations of the immune system. Very rarely transient neutropenia associated with community-acquired viruses can lead to significant disease with bacterial infections. Secondary infections can occur because of impaired immunity or disruption of normal mucosal immunity, as exemplified by the increased risk for pneumonia from S. pneumoniae or S. aureus following influenza infection and group A streptococcus cellulitis and fasciitis following varicella.

MALIGNANCIES

The immune systems of children with malignancies are compromised by the therapies used to treat the cancer and, at times, by direct effects of the cancer itself. The type, duration, and intensity of anticancer therapy remain the major risk factors for infections in these children and often affect multiple arms of the immune system. The presence of mucous membrane abnormalities, indwelling catheters, malnutrition, prolonged exposure to antibiotics, and frequent hospitalizations adds to the risk for infection in these children.

Even though several arms of the immune system can be affected, the major abnormality predisposing to infection in children with cancer is neutropenia. The depth and duration of neutropenia are the primary predictors of the risk of infection in children being treated for cancer. Patients are at particular risk for bacterial and fungal infections if the

**Figure 178-1** Guide to the initial management of the febrile neutropenic patient. Monotherapy can be considered with cefepime, imipenem/cilastatin, meropenem, piperacillin-tazobactam, or ticarcillin-clavulanic acid. *Aminoglycoside* antibiotics should be avoided if the patient is also receiving nephrotoxic, ototoxic, or neuromuscular blocking agents; has renal or severe electrolyte dysfunction; or is suspected of having meningitis (because of poor blood-brain perfusion). (Adapted from Freifeld AG, Bow EJ, Sepkowitz KA, et al. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the Infectious Diseases Society of America. Clin Infect Dis 52:e56–e92, 2011.)
children in association with central venous catheters, these infections are typically indolent, and a short delay in treatment usually does not lead to a detrimental outcome. Other Gram-positive bacteria, such as *S. aureus* and *S. pneumoniae*, can cause more-fulminant disease and require prompt institution of therapy. Viridans streptococci are important potential pathogens in patients with the oral mucositis that is often associated with use of cytarabine and in patients who experience selective pressure from treatment with certain antibiotics such as quinolones. Infection caused by this organism can present as acute septic shock syndrome. Patients with prolonged neutropenia are at increased risk for opportunistic fungal infections, with *Candida* spp. and *Aspergillus* spp. being the most commonly identified fungi. Other fungi that can cause serious disease in these children include *Mucor* spp., *Fusarium* spp., and dematiaceous molds.

**FEVER AND NEUTOPENIA**

The use of empiric antimicrobial treatment as part of the management of fever and neutropenia decreases the risk of progression to sepsis, septic shock, acute respiratory distress syndrome, organ dysfunction, and death. In 2010, the Infectious Diseases Society of America updated a comprehensive guideline for the use of antimicrobial agents in neutropenic children and adults with cancer (see Fig. 178-1).

First-line antimicrobial therapy should take into consideration the types of microbes anticipated and the local resistance patterns encountered at each institution as well as the level of risk for severe infection associated with a given patient. In addition, antibiotic choices may be limited by specific circumstances, such as the presence of drug allergy and renal or hepatic dysfunction. The empirical use of oral antibiotics has been shown to be safe in some low-risk adults who have no evidence of bacterial focus or signs of significant illness (rigors, hypotension, mental status changes) and for whom a quick recovery of the bone marrow is anticipated. Guidelines for the management of fever and neutropenia in children with cancer and/or undergoing HSCT, which were published on 2012, conclude that the use of oral antimicrobial therapy as either initial or stepdown therapy can be considered in low-risk children who can tolerate oral antibiotics and in whom careful monitoring can be ensured. However, the authors of this guideline point out that oral medication use may present major challenges in children, including availability of liquid formulations of appropriate antibiotics, cooperation of young children, and presence of mucositis potentially interfering with absorption. Accordingly, decisions to implement this approach should be reserved for a very select subset of these children presenting with fever and neutropenia.

The decision to initially use intravenous monotherapy vs an expanded regimen of antibiotics depends on the severity of illness of the patient, history of previous colonization with resistant organisms, and obvious presence of catheter-related infection. Vancomycin should be added to the empiric initial regimen if the patient has hypotension or other evidence of septic shock, an obvious catheter-related infection, or a history of colonization with methicillin-resistant *S. aureus*, or if the patient is at high risk for viridans streptococci (severe mucositis, acute myelogenous leukemia, or prior use of quinolone prophylaxis). Monotherapy can be considered with cefepime, imipenem/cilastatin, meropenem, piperacillin-tazobactam, or ticarcillin-clavulanic acid. Cefazidime should not be used as monotherapy if concern exists for Gram-positive organisms or resistant Gram-negative bacteria. The addition of a 2nd Gram-negative bacterial agent for empiric therapy can be considered in patients who are clinically unstable when resistant organisms are suspected.

Regardless of the regimen chosen initially, it is critical to carefully and continually evaluate the patient for response to therapy, development of secondary infections, and adverse effects. Management recommendations for these children are evolving. Based upon the 2012 published guidelines, patients who have negative blood cultures at 48 hr, who have been afebrile for at least 24 hr, and who have evidence of bone marrow recovery (absolute neutrophil counts of >100 cells/mm³) can have antibiotics discontinued. However, if symptoms persist or evolve, intravenous antibiotics should be continued. Continuation of antibiotics in children whose fever has abated and who are clinically well but continue to have depression of neutrophils is more controversial. The 2012 pediatric guidelines advocate pediatric guidelines advocate discontinuing antibiotics in low-risk patients at 72 hr for patients who have negative blood cultures and who have been afebrile for at least 24 hr regardless of bone marrow recovery, as long as careful follow-up is ensured. In contrast, others continue to advocate for continuing antibiotics in this circumstance to prevent recurrence of fever.

Patients without an identified etiology but with persistent fever should be reevaluated after 3-5 days. Those remaining clinically well may continue on the same regimen, although consideration should be given to discontinuing vancomycin or double Gram-negative bacterial coverage if they were included initially. Patients who remain febrile with clinical progression warrant the addition of vancomycin or double Gram-negative bacterial coverage and adverse effects. Management recommendations for these children are evolving. Based upon the 2012 published guidelines, patients who have negative blood cultures at 48 hr, who have been afebrile for at least 24 hr, and who have evidence of bone marrow recovery (absolute neutrophil counts of >100 cells/mm³) can have antibiotics discontinued. However, if symptoms persist or evolve, intravenous antibiotics should be continued. Continuation of antibiotics in children whose fever has abated and who are clinically well but continue to have depression of neutrophils is more controversial. The 2012 pediatric guidelines advocate pediatric guidelines advocate discontinuing antibiotics in low-risk patients at 72 hr for patients who have negative blood cultures and who have been afebrile for at least 24 hr regardless of bone marrow recovery, as long as careful follow-up is ensured. In contrast, others continue to advocate for continuing antibiotics in this circumstance to prevent recurrence of fever.

### Table 178-3 Possible Causes of Fever in Neutropenic Patients Not Responding to Broad-Spectrum Antibiotics

<table>
<thead>
<tr>
<th>CAUSES</th>
<th>APPROXIMATE FREQUENCY IN HIGH-RISK PATIENTS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fungal infections susceptible to empirical therapy</td>
<td>40</td>
</tr>
<tr>
<td>Fungal infections resistant to empirical antifungal therapy</td>
<td>5</td>
</tr>
<tr>
<td>Bacterial infections (with cryptic foci, biofilms, and resistant organisms)</td>
<td>10</td>
</tr>
<tr>
<td><em>Toxoplasma gondii, mycobacteria, or fastidious pathogens (Legionella, Mycoplasma, Chlamydo phila pneumoniae, Bartonella)</em></td>
<td>5</td>
</tr>
<tr>
<td>Viral infections (herpesviruses, cytomegalovirus, Epstein-Barr virus, human herpesvirus 6, varicella-zoster virus, herpes simplex virus, parainfluenza virus, respiratory syncytial virus, influenzaviruses)</td>
<td>5</td>
</tr>
<tr>
<td>Graft-versus-host disease after hematopoietic stem cell transplantation</td>
<td>10</td>
</tr>
<tr>
<td>Undefined (e.g., drug fever, toxic effects of chemotherapy, antitumor responses, undefined pathogens)</td>
<td>25</td>
</tr>
</tbody>
</table>

for bacteria and fungi. CMV is a rare cause of fever in children with cancer and neutropenia. If CMV infection is suspected, assays to evaluate viral load in the blood and organ-specific infection should be obtained. Ganciclovir, foscarinet, or cidofovir may be considered while evaluation is pending, although ganciclovir can cause bone marrow suppression and foscarinet and cidofovir can be nephrotoxic (see Chapter 255). If influenza is identified, specific treatment with antiviral agents should be administered. Choice of treatment (oseltamivir, zanamivir) should be based on the anticipated susceptibility of the circulating influenza (see Chapter 258).

The use of hematopoietic growth factors shortens the duration of neutropenia but has not been proved to reduce morbidity or mortality. Accordingly, the 2010 recommendations from the Infectious Diseases Society of America do not endorse the routine use of hematopoietic growth factors in patients with established fever and neutropenia, although the recommendations do note that hematopoietic growth factors can be considered as prophylaxis in those with neutropenia who have a high risk for fever. Infections occur in children with cancer even without neutropenia. Most often these infections are viral in etiology. However, *P. jiroveci* can cause pneumonia regardless of the neutrophil count. Prophylaxis with trimethoprim-sulfamethoxazole against PCP is an effective preventive strategy and should be provided to all children undergoing active treatment for malignancy (see Chapter 244). Environmental fungi such as *Cryptococcus, Histoplasma*, and *Coccidioides* can also cause disease. *Toxoplasma gondii* is an uncommon but occasional pathogen in children with cancer. Infections encountered in healthy children (*S. pneumoniae*, group A *Streptococcus*) can cause disease in children with cancer regardless of the granulocyte count.

**Table 178-4** Host Defense Defects and Common Pathogens by Time After Bone Marrow Transplantation/Hematopoietic Stem Cell Transplantation

<table>
<thead>
<tr>
<th>TIME PERIOD</th>
<th>HOST DEFENSE DEFECTS</th>
<th>CAUSES</th>
<th>COMMON PATHOGENS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pretransplant</td>
<td>Neutropenia Abnormal anatomic barriers</td>
<td>Underlying disease Prior chemotherapy</td>
<td>Aerobic Gram-negative bacilli</td>
</tr>
<tr>
<td>Preengraftment</td>
<td>Neutropenia Abnormal anatomic barriers</td>
<td>Chemotherapy Radiation Indwelling catheters</td>
<td>Aerobic Gram-positive cocci Aerobic Gram-negative bacilli Candida Aspergillus</td>
</tr>
<tr>
<td>Postengraftment</td>
<td>Abnormal cell-mediated immunity Abnormal anatomic barriers</td>
<td>Chemotherapy Immunosuppressive medications Radiation Indwelling catheters Unrelated cord blood donor</td>
<td>Gram-positive cocci Aerobic Gram-negative bacilli Cytomegalovirus Adenoviruses Community-acquired viral pathogens Pneumocystis jiroveci</td>
</tr>
<tr>
<td>Late posttransplant</td>
<td>Delayed recovery of immune function (cell-mediated, humoral, and abnormal anatomic barriers)</td>
<td>Time required to develop donor-related immune function Graft-versus-host disease</td>
<td>Varicella-zoster virus Streptococcus pneumoniae</td>
</tr>
</tbody>
</table>

**Transplantation Period**

Children come to HSCT with a heterogeneous history of underlying diseases, chemotherapy exposure, degree of immunosuppression, and previous infections. Approximately 12% of all infections among adult HSCT recipients occur during the pretransplantation period. These infections are often caused by aerobic Gram-negative bacilli and manifest as localized infections of the skin, soft tissue, and urinary tract. Importantly, the development of infection during this period does not delay or adversely affect the success of engraftment.

**Pretransplantation Period**

**Bacterial infections** predominate in the pretransplantation period (0-30 days). Bacteremia is the most common documented infection and occurs in as many as 50% of all HSCT recipients during the 1st 30 days following transplantation. Bacteremia is typically associated with the presence of either mucositis or an indwelling catheter, but may also be seen with pneumonia. Similarly, more than 40% of children undergoing HSCT experienced 1 or more infections in the preengraftment period. Gram-positive cocci, Gram-negative bacilli, yeast, and, less commonly, other fungi cause infection during this period. *Aspergillus* has been identified in 4-20% of HSCT recipients, most often after 3 wk of neutropenia. Infections caused by the emerging fungal pathogens *Fusarium* and *Pseudallescheria boydii* are associated with the prolonged neutropenia during the postengraftment period.

**Viral infections** also occur during the preengraftment period. Among adults, reactivation of herpes simplex virus is the most common viral disease observed, but this is less common among children, which is likely related to absence of the virus in the recipient before HSCT. A history of herpes simplex infection or seropositivity indicates the need for prophylaxis. Nosocomial exposure to community-acquired viral pathogens, including respiratory syncytial virus (RSV), influenza virus, adenovirus, and rotavirus, represents another important source of infection during this period. There is growing evidence that community-acquired viruses cause increased morbidity and mortality for HSCT recipients.

**Preengraftment Period**

**Bacterial infections** predominate in the preengraftment period (30-100 days), or **late post-transplantation period** (>100 days). Specific defects in host defenses predisposing to infection vary within each of these periods (Table 178-4). Neutropenia and abnormalities in cell-mediated and humoral immune function occur predictably during specific periods of time following transplantation. In contrast, breaches of anatomic barriers caused by indwelling catheters and mucositis secondary to radiation or chemotherapy create defects in host defenses that may be present any time following transplantation.

**Stem Cell Transplantation**

Infections following HSCT can be classified as occurring during the pretransplantation period, preengraftment period (0-30 days after transplantation), postengraftment period (30-100 days), or late post-transplantation period (>100 days). Specific defects in host defenses predisposing to infection vary within each of these periods (Table 178-4). Neutropenia and abnormalities in cell-mediated and humoral immune function occur predictably during specific periods of time following transplantation. In contrast, breaches of anatomic barriers caused by indwelling catheters and mucositis secondary to radiation or chemotherapy create defects in host defenses that may be present any time following transplantation.
recipients during this period. Adenovirus is a particularly important viral pathogen that can occur early, although it typically presents after engraftment.

**Postengraftment Period**
The predominant defect in host defenses in the postengraftment period is altered cell-mediated immunity. Accordingly, organisms historically categorized as opportunistic pathogens predominate during this period. The risk is especially accentuated 50–100 days after transplantation when host immunity is lost and donor immunity is not yet established. *P. jiroveci* presents during this period if patients are not maintained on appropriate prophylaxis. Reactivation of *T. gondii*, a rare cause of disease among HSCT recipients, can also occur after engraftment. Hepatosplenic candidiasis often presents during the postengraftment period, although seeding likely occurred during the neutropenic phase.

CMV is an important cause of morbidity and mortality among HSCT recipients. Unlike patients undergoing solid-organ transplantation where primary infection from the donor causes the greatest harm, CMV reactivation in an HSCT recipient whose donor is naïve to the virus can cause severe disease. Disease risk from CMV after HSCT is also increased in recipients of matched unrelated T cell–depleted transplants and those who suffer from graft-versus-host disease. Adenovirus is another important viral pathogen; it has been recovered from up to 5% of adult and pediatric HSCT recipients and causes invasive disease in approximately 20% of cases. Children receiving matched unrelated donor organs or unrelated cord blood cell transplants have an incidence of adenovirus infection as high as 14% during this early postengraftment period. Polyomaviruses such as BK virus have been increasingly recognized as a cause of renal dysfunction and hemorrhagic cystitis after bone marrow transplantation. Infections with other herpesviruses (Epstein-Barr virus [EBV] and human herpesvirus 6), as well as community-acquired pathogens, are associated with excess morbidity and mortality during this period, similar to the preengraftment period.

**Late Posttransplantation Period**
Infection is unusual after 100 days in the absence of chronic graft-versus-host disease. However, the presence of chronic graft–versus-host disease significantly affects anatomic barriers and is associated with defects in humoral, splenic, and cell-mediated immune function (see Chapter 137). Viral infections, including primary infection with or reactivation of varicella-zoster virus, are responsible for more than 40% of infections during this period. Bacterial infections, particularly of the upper and lower respiratory tract, account for approximately 30% of infections. These may be associated with deficiencies in immunoglobulin production, especially IgG. Fungal infections account for <20% of confirmed infections during the late posttransplantation period.

**Solid-Organ Transplantation**
Factors predisposing to infection after organ transplantation include those that either existed before transplantation or are secondary to intraoperative events or posttransplantation therapies (Table 178-5). Some of these additional risks cannot be prevented, and some risks acquired during or after the operation depend on decisions or actions of members of the transplant team. Similar to other children who have undergone surgical procedures, surgical site infections are a frequent cause of infection early after transplantation. Beyond this, the need for immunosuppressive agents to prevent rejection is the major factor predisposing to infection following transplantation. Despite efforts to optimize immunosuppressive regimens to prevent or treat rejection with minimal impairment of immunity, all current regimens interfere with the ability of the immune system to prevent infection. The primary target of the majority of these immunosuppressive agents is the cell-mediated immune system, but regimens can and do impair many other aspects of the transplant recipient's immune system as well.

**Timing**
The timing of specific types of infections is generally predictable, regardless of which organ is transplanted (Table 178-6). Infectious complications typically develop in 1 of 3 time intervals: early (0–30 days after transplantation), intermediate (30–180 days), and late (>180 days); most infections present in the 1st 180 days after transplantation. Table 178-6 should be used as a general guideline to the types of infections encountered but may be modified with the introduction of newer immunosuppressive therapies and by the use of prophylaxis. Early infections are usually the result of a complication of the transplant surgery itself, the unexpected acquisition of a bacterial or fungal pathogen from the donor, or the presence of an indwelling catheter. In contrast, infections during the intermediate period typically result from a complication of the immunosuppression, which tends to be at its greatest intensity during the 1st 6 mo following transplantation. This is the period of greatest risk for infections caused by opportunistic pathogens such as CMV, EBV, and *P. jiroveci*. Anatomic abnormalities, such as bronchial stenosis and biliary stenosis, that develop as a consequence of the transplant surgery can also predispose to recurrent infection in this period.

Infections developing late after transplantation typically result as a consequence of uncorrected anatomic abnormalities, chronic rejection, or exposure to community-acquired pathogens. Acquisition of infection from community-acquired pathogens such as RSV can result in severe infection secondary to the immunocompromised state of the transplant recipient during the early and intermediate periods. Compared with the earlier periods, community-acquired infections in the late period are usually benign, because immunosuppression is typically maintained at significantly lower levels. However, certain pathogens such as varicella-zoster virus and EBV may be associated with severe disease even at this late period.

**Bacterial and Fungal Infections**
Although there are important graft-specific considerations for bacterial and fungal infections following transplantation, some principles are generally applicable to all transplant recipients. Bacterial and fungal infections following organ transplantation are usually a direct consequence of the surgery, a breach in an anatomic barrier, the presence of a foreign body, or an abnormal anatomic narrowing or obstruction. With the exception of infections related to the use of indwelling catheters, sites of bacterial infection tend to occur at or near the transplanted organ. Infections following abdominal transplantation (liver, intestine, or renal) usually occur in the abdomen or at the surgical wound. The pathogens are typically enteric Gram-negative bacteria, *Enterococcus*, and occasionally *Candida*. Infections following thoracic transplantation (heart, lung) usually occur in the lower respiratory tract or at the surgical wound. Pathogens associated with these infections include *S. aureus* and Gram-negative bacteria.
Patients undergoing lung transplantation for cystic fibrosis experience a particularly high rate of infectious complications, because they are often colonized with *P. aeruginosa* or *Aspergillus* before transplantation. Even though the infected lungs are removed, the sinuses and upper airways remain colonized with these pathogens, and subsequent reinfection of the transplanted lungs can occur. Children receiving organ transplants are often hospitalized for long periods and receive many antibiotics; thus, recovery of bacteria with multiple antibiotic resistance patterns is common after all types of organ transplantation. Infections caused by *Aspergillus* are less common but occur after all types of organ transplantation and are associated with high rates of morbidity and mortality.

**Viral Infections**

Viral pathogens, especially herpesviruses, are a major source of morbidity and mortality following solid organ transplantation. In addition, BK virus is a major cause of renal disease following kidney transplantation. The patterns of disease associated with individual viral pathogens are generally similar among all organ transplant recipients. However, the incidence, mode of presentation, and severity differ according to type of organ transplanted and, for many viral pathogens, pretransplant serologic status of the recipient.

Viral pathogens can generally be categorized as latent pathogens, which cause infection through reactivation in the host or via acquisition from the donor (e.g., CMV and EBV), or as community-acquired viruses (e.g., RSV). For CMV and EBV, primary infection occurring after transplantation is associated with the greatest degree of morbidity and mortality. The highest risk is seen in a naive host who receives an organ from a donor who previously was infected with 1 of these viruses. This “mismatched” state is frequently associated with severe disease. However, even if the donor is negative for CMV and EBV, primary infection can be acquired from a close contact or via blood products. Secondary infections (reactivation of a latent strain within the host or superinfection with a new strain) tend to result in milder illness unless the patient is highly immunosuppressed, which can occur in the setting of treatment of significant rejection.

CMV is one of the most commonly recognized transplant viral pathogens. Disease from CMV has decreased significantly with the use of preventive strategies including antiviral prophylaxis as well as viral load monitoring to inform preemptive antiviral therapy. Clinical manifestations of CMV disease can range from a syndrome of fatigue and fever to disseminated disease that most often affects the liver, lungs, and gastrointestinal tract.

Infection caused by EBV is another important complication of solid-organ transplantation. Clinical symptoms range from a mild mononucleosis syndrome to disseminated posttransplant lymphoproliferative disorder. Posttransplant lymphoproliferative disorder is more common among children than adults because primary EBV infection in the immunosuppressed host is more likely to lead to uncontrolled proliferative disorders, including posttransplant lymphoma.

Other viruses, such as adenovirus, have the capacity to be donor associated, but appear to be less common. The unexpected development of donor-associated viral pathogens, including hepatitis B virus, hepatitis C virus, and HIV, is rare today owing to intensive donor screening.

Community-acquired viruses, including those associated with respiratory tract infection (RSV, influenza virus, adenovirus, and parainfluenza) and gastrointestinal infection (enteroviruses, rotavirus), can cause important disease in children following organ transplantation. In general, risk factors for more-severe infection include young age, acquisition of infection early after transplantation, and augmented immune suppression. Infection in the absence of these risk factors typically results in a clinical illness that is comparable with that seen in immunocompetent children. However, some community-acquired viruses, such as adenovirus, can be associated with graft dysfunction even when acquired late after transplantation.

**Opportunistic Pathogens**

Children undergoing solid-organ transplantation are also at risk for symptomatic infections from pathogens that do not usually cause clinical disease in immunocompetent hosts. Although these most commonly present in the intermediate period, these infections can also occur late in patients requiring prolonged and high levels of immunosuppression. *P. jiroveci* is a well-recognized cause of pneumonia following solid-organ transplantation, although routine prophylaxis has essentially eliminated this problem. *T. gondii* can complicate cardiac transplantations because of tropism of the organism for cardiac muscle and risk for donor transmission; less commonly it complicates other types of organ transplantation.

**Bibliography is available at Expert Consult.**
Bibliography
Infections cannot be completely prevented in children who have defects in one or more arms of their immune system, although some measures can decrease the risks for infection. Replacement immunoglobulin is a benefit to children with primary B-cell deficiencies. Interferon-γ, trimethoprim-sulfamethoxazole, and oral antifungal agents reduce the number of infections occurring in children with chronic granulomatous disease. Children who have depressed cellular immunity resulting from primary diseases, advanced HIV infection, or immunosuppressive medications benefit from prophylaxis against *P. jiroveci*. Immunizations prevent many infections and are particularly important for children with compromised immune systems. When possible, immunizations should be administered before any treatment that would compromise the child's immune system.

Although immunodeficient children are a heterogeneous group, some principles of prevention are generally applicable. The use of inactivated vaccines does not lead to an increased risk for adverse effects, although their efficacy may be reduced due to an impaired immune response. In most cases, children with immunodeficiencies should receive all of the recommended inactivated vaccines. Live-attenuated virus vaccinations can cause disease in some children with immunologic defects, and therefore alternative immunizations should be used whenever possible, such as inactivated influenza vaccine rather than live virus attenuated influenza vaccine. In general, live virus vaccines should not be used in children with primary T-cell abnormalities; efforts should be made to ensure that close contacts are all immunized to decrease the risk of exposure. In some instances in which wild-type viral infection can be severe, immunizations, even with live virus vaccine, are warranted in the immunosuppressed child. For example, children with HIV infection and a CD4 percentage of >15% should receive vaccinations against measles and varicella. Some vaccines should be given to children with immunodeficiencies in addition to routine vaccinations. As an example, children with asplenia or splenic dysfunction should receive meningococcal vaccine and both the polysaccharide pneumococcal vaccine and the conjugate pneumococcal vaccine. Influenza vaccination is recommended for immunocompromised children as well as all household contacts to minimize risk for transmission to the immunocompromised child.

*Bibliography is available at Expert Consult.*
Bibliography
Use of implanted synthetic and prosthetic devices has revolutionized pediatric practice by providing long-term venous access, limb-salvage surgery, and successful treatment of hydrocephalus, urinary retention, and renal failure. However, infectious complications of these devices remain a major concern. These infections are related to the development of biofilms, organized communities of microorganisms protected from the immune system and antimicrobial therapy, on the device surface. A number of factors are important to the development of infection, including the host susceptibility, device composition, duration of implantation, and exposure to colonizing organisms.

**INTRAVASCULAR ACCESS DEVICES**

Intravascular access devices range from short, stainless steel needles or plastic cannulae inserted for brief periods to multilumen implantable synthetic plastic catheters that are expected to remain in use for years. Infectious complications include local skin and soft tissue infections such as exit site, tunnel, and device-pocket infections, and catheter-related bloodstream infections (CRBSIs). The use of central venous devices has improved the quality of life of high-risk patients but has also increased the risk of infection.

**Catheter Types**

Short-term peripheral cannulae are most commonly used in pediatric patients, and infectious complications occur infrequently. The rate of peripheral CRBSIs in children is <0.15%. Patient age <1 yr, duration of use for longer than 144 hr, and some infusates are associated with increased risk for catheter-related infection. Catheter-associated phlebitis is more common (1-6%) but is rarely infective and can be treated conservatively.

Central venous catheters (CVCs), which terminate in a central vein such as the superior vena cava or inferior vena cava, are widely used in both adults and pediatric patients and are responsible for the majority of catheter-related infections. These catheters are commonly used in critically ill patients, including neonates, who have many other risk factors for nosocomial infection. Patients in an intensive care unit with a CVC in place have a 5-fold greater risk for developing a nosocomial bloodstream infection than those without.

The use of peripherally inserted central catheters, which are inserted into a peripheral vein and terminate in a central vein, has increased in pediatric patients. Infection rates seem to be similar to long-term tunneled CVCs (~2/1,000 days), but other complications such as fracture, dislodgement, and occlusion are more common.

When prolonged intravenous access is required, a cuffed silicone rubber (Silastic) or polyurethane catheter may be inserted into the superior vena cava through the subclavian, cephalic, or jugular vein. The extravascular segment of the catheter passes through a subcutaneous tunnel before exiting the skin, usually on the superior aspect of the chest (Broviac or Hickman catheter). A cuff around the catheter near the exit site induces a fibrotic reaction to seal the tunnel. Totally implanted devices also include a subcutaneous reservoir or port with a self-sealing silicone septum immediately under the skin that permits repeated percutaneous needle access.

The incidence of local (exit site, tunnel, and pocket) infection with long-term catheters is 0.2-2.8/1,000 catheter-days. The incidence of Broviac or Hickman CRBSI is 0.5-11.0/1,000 catheter-days, whereas that for implantable devices is 0.3-1.8/1,000 catheter-days. The risk for CRBSI is increased among premature infants, young children, and patients receiving total parenteral nutrition.

**Catheter-Associated Skin and Soft Tissue Infection**

A number of local infections can occur in the presence of a CVC. The clinical manifestations of local infection include erythema, tenderness, and purulent discharge at the exit site or along the subcutaneous tunnel tract of the catheter. Exit-site infection denotes infection localized to the exit site, without significant tracking along the tunnel, often with purulent discharge. Tunnel-track infection indicates infection in the subcutaneous tissues tracking along a tunneled catheter, which may also include serous or serosanguineous discharge from a draining sinus along the path. Pocket infection indicates supplicative infection of a subcutaneous pocket containing a totally implanted device. Bloodstream infection may coexist with local infection.

The diagnosis of local infection is established clinically, but a gram-stained smear and culture of any exit-site drainage should be performed to identify the microbiologic cause. The source is usually contamination by skin or gastrointestinal flora, and the most common organisms are *S. aureus*, coagulase-negative staphylococci,
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P. aeruginosa, Candida spp., and mycobacteria. Green discharge is strongly suggestive of mycobacterial infection and appropriate stains and culture should be performed.

Treatment of local infection related to a short-term peripheral cannula or CVC should include device removal. Exit-site infection may resolve with device removal alone, but systemic symptoms should be managed with antimicrobial therapy as recommended below for treatment of CRBSI. In the case of long-term CVCs, exit-site infections usually respond to local care with topical or systemic antibiotics alone. However, tunnel or pocket infections require removal of the catheter and systemic antibiotic therapy in most cases. When a CVC is removed as a result of tunnel infection, the cuff should also be removed and sent for culture if possible. In cases of mycobacterial infection, wide surgical debridement of the tissues is usually required for cure.

**Catheter-Related Bloodstream Infection**

CRBSI occurs when microorganisms attached to the CVC are shed into the bloodstream leading to bacteremia. On the device, the organisms are embedded in biofilms as organism communities. Colonization may be present even in the absence of symptoms or positive cultures. Organisms may contaminate the external surface of the CVC during insertion, or the intraluminal surface through handling of the catheter hub or contaminated infusate. Most cases of CRBSI appear to be caused by intraluminal colonization, but external colonization may play a greater role in infections related to recently inserted (<30 days) catheters. Gram-positive cocci predominate, with around half of infections caused by coagulase-negative staphylococci. Gram-negative enteric bacteria are isolated in approximately 20-30% of episodes, and fungi account for 5-10% of episodes.

Fever without an identifiable focus is the most common clinical presentation of CRBSI; local soft tissue symptoms and signs are usually absent. Onset of fever or rigors during or soon after flushing of a catheter is highly suggestive of CRBSI. Symptoms and signs of complicated infection, such as septic thrombophlebitis, endocarditis, or ecthyma gangrenosum, may also be present.

Blood cultures collected prior to the beginning of antibiotic therapy are generally positive from both the CVC and peripheral blood. It is important not to collect cultures unless infection is suspected, as blood-culture contamination may occur and can lead to inappropriate therapy. Blood culture should be collected from at least 2 sites, preferably including all lumens of a CVC and the peripheral blood, before initiation of antibiotic therapy to help interpret positive cultures with common skin contaminants.

Tests to differentiate CRBSI from other sources of bacteremia in the presence of a CVC include culture of the catheter tip, quantitative blood cultures, or differential time to positivity of blood cultures drawn from different sites. Definitive diagnosis of CRBSI can be important to identify those patients who might benefit from catheter removal or adjunctive therapy. Although CVC tip culture can identify CRBSI, it precludes salvage of the catheter. The most readily available technique to confirm CRBSI without catheter removal is calculation of differential time to positivity between blood cultures drawn through a catheter and from a peripheral vein or separate lumen. During CRBSI, blood obtained through the responsible lumen will usually indicate growth at least 2-3 hr before peripheral blood or uncolonized lumens because of a higher intraluminal microorganism burden. Identical volumes of blood must be collected simultaneously from each site and a continuously monitored blood culture system is required. Specificity of this test is good (94-100%), and sensitivity is good when a peripheral blood culture is available (~90%) but poorer when comparing 2 lumens of a CVC (64%). Where available, quantitative blood culture showing at least a 3-fold higher number of organisms from central compared with peripheral blood is similarly diagnostic.

Treatment of CRBSI related to long-term vascular access devices (Hickman, Broviac, totally implantable devices) with systemic antibiotics is successful for many bacterial infections without removal of the device. Antibiotic therapy should be directed to the isolated pathogen and given for a total of 10-14 days from the date of blood culture clearance. Until identification and susceptibility testing are available, empiric therapy, based on local antimicrobial susceptibility data and usually including vancomycin plus an antipseudomonal aminoglycoside (e.g., gentamicin), penicillin (e.g., piperacillin-tazobactam), or cephalosporin (e.g., ceftazidime or cefepime) is indicated. An echinocandin should be initiated if fungemia is suspected. Antibiotic lock or dwell therapy, with administration of solutions of high concentrations of antibiotics or ethanol that remain in the catheter for up to 24 hr, might improve outcome when used as an adjuvant to systemic therapy and appear safe, but insufficient data are available to strongly recommend their use. If blood cultures remain positive after 72 hr of appropriate therapy, or if a patient deteriorates clinically, the device should be removed. Failure of CRBSI salvage therapy is very common in infections caused by S. aureus (~50%), Candida spp. (>70%), and Mycobacterium spp. (>70%), although some case reports of cure with antimicrobial lock therapy are promising. Other indications for removing a long-term catheter include severe sepsis, supplicative thrombophlebitis, and endocarditis. Prolonged therapy (4-6 wk) is indicated for persistent bacteremia or fungemia despite catheter removal. The decision to attempt catheter salvage should weigh the risk and clinical impact of persistent or relapsed infection against the risk of surgical intervention.

CRBSI may be complicated by other intravascular infections such as septic thrombophlebitis or endocarditis. Presence of these conditions may be suggested by preexisting risk factors (such as congenital heart disease), signs and symptoms, or persistent bacteremia or fungemia 72 hr after device removal and appropriate therapy. Screening for these complications in otherwise low-risk children, even those with S. aureus infection, is not recommended, as the overall frequency is low and the tests can be difficult to interpret and may lead to inappropriate therapy.

**Prevention of Infection**

Catheters should routinely be removed as soon as they are no longer needed. Although prevalence of infection increases with prolonged duration of catheter use, routine replacement of a required CVC, either at a new site or over a guidewire, results in significant morbidity and is not recommended. Optimal prevention of infections related to long-term vascular access devices includes “bundles” of interventions, including meticulous aseptic surgical insertion technique in an operating room–like environment, avoidance of bathing or swimming (except with totally implantable devices), and careful catheter care. Use of antibiotic or ethanol lock solutions, heparin with preservatives, and alcohol-impregnated caps and use of antimicrobial-impregnated or coated catheters may also be appropriate to reduce the risk for catheter-associated bloodstream infections in high-risk populations. Although the Centers for Disease Control and Prevention recommends that short-term peripheral catheters be replaced every 72-96 hr to prevent phlebitis, pediatric data do not support this practice.

**CEREBROSPINAL FLUID SHUNTS**

Cerebrospinal fluid (CSF) shunting is required for the treatment of many children with hydrocephalus. The usual procedure uses a silicone rubber device with a proximal portion inserted into the ventricle, a unidirectional valve, and a distant segment that diverts the CSF from the ventricles to either the peritoneal cavity (ventriculoperitoneal [VP] shunt) or right atrium (ventriculoatrial [VA] shunt). The incidence of shunt infection ranges from 1-20%, with an average of 10%. The highest rates are reported in young infants, prior shunt infections, and certain etiologies of hydrocephalus. Most infections are a result of intraoperative contamination of the surgical wound by skin flora. Accordingly, coagulase-negative staphylococci are isolated in more than half of the cases. S. aureus is isolated in approximately 20% and Gram-negative bacilli in 15% of cases.

Four distinct clinical syndromes have been described: colonization of the shunt, infection associated with wound infection, distal infection with peritonitis, and infection associated with meningitis. The most common type of infection is colonization of the shunt with symptoms that reflect shunt malfunction as opposed to frank infection. Symptoms associated with colonized VP shunts include lethargy, headache, vomiting, a full fontanel, and abdominal pain. Fever is common but may be <39°C (102.2°F). Symptoms usually occur within months of the surgical procedure. Colonization of a VA shunt results
in more severe systemic symptoms and specific symptoms of shunt malfunction are often absent. Septic pulmonary emboli, pulmonary hypertension, and infective endocarditis are frequently reported complications of VA shunt colonization. Chronic VA shunt colonization may cause hypocomplementemric glomerulonephritis as a consequence of antigen–antibody complex deposition in the glomeruli, commonly called shunt nephritis; clinical findings include hypertension, microscopic hematuria, elevated blood urea nitrogen and serum creatinine levels, and anemia.

Diagnosis is by Gram stain, microscopy, biochemistry, and culture of CSF. CSF should be obtained by direct aspiration of the shunt, as CSF obtained from either lumbar or venipuncture is often sterile. It is unusual to observe signs of ventriculitis, and CSF findings can be only minimally abnormal. Blood culture results are usually positive in VA shunt colonization but negative in cases of VP colonization.

Wound infection presents with obvious erythema, swelling, discharge, or dehiscence along the shunt tract and most often occurs within days to weeks of the surgical procedure. S. aureus is the most common isolate. In addition to the physical findings, fever is common, and signs of shunt malfunction eventually ensue in most cases.

Distal infection of VP shunts with peritonitis presents with abdominal symptoms, usually without evidence of shunt malfunction. The pathogenesis is likely related to perforation of bowel at the time of VP shunt placement or translocation of bacteria across the bowel wall. Thus, Gram-negative isolates predominate and mixed infection is common. The infecting organisms are often isolated from only the distal portion of the shunt.

Common pathogens responsible for community-acquired meningitis, including S. pneumoniae, N. meningitidis, and H. influenzae type b, can also cause bacterial meningitis in patients with shunts. The clinical presentation is similar to that for acute bacterial meningitis in other children (see Chapter 602.1).

**Treatment** of shunt colonization includes removal of the shunt and systemic antibiotic therapy directed against the isolated organisms. After collection of appropriate samples for culture, empiric therapy is usually with vancomycin plus an antipseudomonal agent with relatively good CSF penetration such as cefadizime or meropenem. Definitive therapy should be directed toward the isolate and account for poor penetration of most antibiotics into the CSF across noninflamed meninges. Accordingly, intraventricular antibiotics may be indicated but are usually reserved unless there is evidence of treatment failure. If the isolate is susceptible, a parenteral antistaphylococcal penicillin with or without intraventricular vancomycin is the treatment of choice. If the organism is resistant to penicillins, systemic vancomycin and possibly intraventricular vancomycin are recommended. In cases of Gram-negative infections, a combination of a third-generation cephalosporin with or without intraventricular aminoglycoside is optimal. When using intraventricular antibiotics, monitoring of CSF levels is necessary to avoid toxicity.

Removal of the colonized device is required for cure, and final replacement should be delayed until clearance of CSF cultures is documented. Many neurosurgeons immediately remove the shunt and place an external ventricular drain to relieve intracranial pressure, with a 2nd-stage shunt replacement once CSF sterilization has been confirmed. Others opt to initially exteriorize the distal end of the shunt, and replace the shunt in a single-stage procedure once CSF cultures remain sterile for 48-72 hr. Daily CSF cultures should be collected until clearance has been documented on 2-3 consecutive specimens, and antibiotics should be continued for at least 10 days after documented sterilization of the CSF. Gram-negative organisms may require a longer duration of therapy (up to 21 days). The CSF white cell count generally increases for the 1st 3-5 days of appropriate therapy and should not prompt concern for treatment failure. Distal shunt infection with peritonitis and wound infection are managed in a similar fashion.

**Prevention of Infection**

Prevention of shunt infection includes meticulous cutaneous preparation and surgical technique. Systemic and intraventricular antibiotics, antibiotic-impregnated shunts, and soaking the shunt tubing in antibiotics are used to reduce the incidence of infection, with varying success. Systemic prophylactic antibiotics given prior to shunt insertion reduce the risk for infection and should be used routinely. Antibiotic-impregnated catheters also appear to reduce the risk of infection, although limited evidence is available, and may be used in high-risk patients where the devices are available.

**URETHRAL CATHETERS**

Urinary catheters are a frequent cause of nosocomial infection, with about 14 infections per 1,000 admissions. Like other devices, microorganisms adhere to the catheter surface and establish a biofilm that allows proliferation. The physical presence of the catheter reduces the normal host defenses by preventing complete emptying of the bladder, thus providing a medium for growth, distending the urethra, and blocking periurethral glands. Almost all patients catheterized for longer than 30 days develop bacteruria. The organism burden in catheter-associated urinary tract infection is typically ≥10,000 colony-forming units/mL. Lower thresholds may be used where there is a high index of suspicion, but these episodes may represent colonization rather than infection. Urine culture should only be performed in catheterized patients when infection is suspected, as asymptomatic colonization is ubiquitous and may lead to overtreatment and subsequent development of bacterial resistance. Gram-negative bacilli and *Enterococcus* spp. are the predominant organisms isolated in catheter-related urinary tract infection; coagulase-negative staphylococci are implicated in approximately 15% of cases. Symptomatic urinary tract infections should be treated with antibiotics and catheter removal. Catheter colonization with *Candida* spp. is common but rarely leads to invasive infection, and treatment does not have a long-term impact on colonization. Treatment for asymptomatic candiduria is therefore not recommended except in neonates, immunocompromised patients, and those with urinary tract obstruction.

**Prevention of Infection**

All urinary catheters introduce a risk for infection, and their casual use should be avoided. When they are in place, their duration of use should be minimized. Technologic advances have led to development of silver- or antibiotic-impregnated urinary catheters that are associated with lower rates of infection. Prophylactic antibiotics do not significantly reduce the infection rates for long-term catheters but clearly increase the risk for infection with antibiotic resistant organisms.

**PERITONEAL DIALYSIS CATHETERS**

During the 1st yr of peritoneal dialysis for end-stage renal disease, 65% of children will have 1 or more episodes of peritonitis. Bacterial entry comes from luminal or periluminal contamination of the catheter or by translocation across the intestinal wall. Hematogenous infection is rare. Infections can be localized at the exit site or associated with peritonitis, or both. Organisms responsible for peritonitis include coagulase-negative staphylococci (30-40%), *S. aureus* (10-20%), streptococci (10-15%), *E. coli* (5-10%), *Pseudomonas* spp. (5-10%), other Gram-negative bacteria (5-15%), *Enterococcus* spp. (3-6%), and fungi (2-10%). *S. aureus* is more common in localized exit-site or tunnel-tract infections (42%). Most infectious episodes are caused by a patient's own flora, and carriers of *S. aureus* have increased rates of infection as compared with noncarriers.

**The clinical manifestations** of peritonitis may be subtle and include low-grade fever with mild abdominal pain or tenderness. Cloudy peritoneal dialysis fluid may be the first and predominant sign. With peritonitis, the peritoneal fluid cell count is usually >100 white blood cells/µL. When peritonitis is suspected, the effluent dialysate should be submitted for a cell count, Gram stain, and culture. The Gram stain is positive in up to 40% of cases of peritonitis.

Patients with cloudy fluid and clinical symptoms should receive empiric therapy, preferably guided by results of a Gram stain. If no organisms are visualized, vancomycin and either an aminoglycoside or
third or fourth generation cephalosporin with antipseudomonal activity should be given via the intraperitoneal route. Blood levels should be measured for glycopeptides and aminoglycosides. Patients without cloudy fluid and with minimal symptoms may have therapy withheld pending culture results. Once the cause is identified by culture, changes in the therapeutic regimen may be needed. Oral rifampin may be added for *S. aureus* infections. Fungal peritonitis should be treated with a combination of oral flucytosine and intraperitoneal or oral fluconazole. The duration of therapy is a minimum of 14 days, with longer treatment of 21–28 days for episodes of *S. aureus*, *Pseudomonas* spp., and resistant Gram-negative bacteria and of 28–42 days for fungi. Repeat episodes of peritonitis within 4 wk of previous therapy represent “apparently relapsing” peritonitis. If the patient responds to reinstitution of antimicrobial therapy, a course of up to 6 wk should be continued. In all cases, if the infection fails to clear following appropriate therapy or if a patient’s condition is deteriorating, the catheter should be removed. Exit-site and tunnel infections may occur independently of peritonitis or may precede it. Appropriate antibiotics should be administered on the basis of Gram stain and culture findings and are typically given systemically only unless peritonitis is also present. Some experts recommend that the peritoneal catheter be removed if *Pseudomonas* or fungal organisms are isolated.

### Prevention of Infection

In addition to usual hygienic practices, regular application of mupirocin or gentamicin cream to the catheter exit site reduces exit-site infections and peritonitis. Some practitioners recommend against the use of gentamicin cream because of the risk of infection with gentamicin-resistant bacteria. Systemic antibiotic prophylaxis should be considered at the time of catheter insertion, if there is accidental contamination, and at the time of dental procedures. Antifungal prophylaxis can be considered during antibiotic therapy to prevent fungal infection.

### ORTHOPEDIC PROSTHESSES

Orthopedic prostheses are used infrequently in children. Infection most often follows introduction of microorganisms at surgery through airborne contamination or direct inoculation; via hematogenous spread; or via contiguous spread from an adjacent infection. Early postoperative infection occurs within 2–4 wk of surgery with typical manifestations that include fever, pain, and local symptoms of wound infection. Rapid assessment, including isolation of the infecting organism by joint aspiration or intraoperative culture, operative debridement, and antimicrobial treatment may allow salvage of the implant if the duration of symptoms is less than 1 mo, the prosthesis is stable, and the pathogen is susceptible to antibiotics. Chronic infection presents >1 mo after surgery and is often caused by organisms of low virulence that contaminated the implant at the time of surgery. Typical manifestations include pain and deterioration in function. Local symptoms such as erythema, swelling, or drainage may also occur. These infections respond poorly to antibiotic treatment and usually require removal of the implant using either a 1- or 2-stage procedure. Surgical debridement of the site with long-term suppressive antibiotic therapy may be considered, but eradication of infection is uncommon. Acute hematogenous infections are most often observed 2 yr or more after surgery. Retention of the prosthesis is sometimes attempted, but there are inadequate long-term data to determine the success rate. If salvage therapy is attempted, prompt debridement and appropriate antibiotic therapy are recommended. As with other long-term implanted devices, the most common organisms are about equally divided between coagulase-negative staphylococci and *S. aureus*. With prior antibiotic therapy, the prosthesis culture may be negative; in these situations, determining 16S ribosomal RNA typing may help identify the organism.

The use of systemic antibiotic prophylaxis, antibiotic-containing bone cement, and operating rooms fitted with laminar airflow all have been proposed as beneficial in reducing infection. To date, results from clinical studies are conflicting.

*Bibliography is available at Expert Consult.*
Bibliography


Antibacterial therapy in infants and children presents many challenges. A daunting problem is the paucity of pediatric data regarding pharmacokinetics and optimal dosages; as a consequence, pediatric recommendations are commonly extrapolated from studies in adults. A second challenge is the need for the clinician to consider important differences among various age groups with respect to the pathogenic species responsible for pediatric bacterial infections. Age-appropriate antibiotic dosing and toxicities must be considered, taking into account the developmental status and physiology of infants and children. Finally, the style of usage of antibiotics has some important differences compared with usage in adult patients. Specific antibiotic therapy is optimally driven by a microbiologic diagnosis, predicated on isolation of the pathogenic organism from a sterile body site, and supported by antimicrobial susceptibility testing. Given the inherent difficulties that can arise in collecting specimens from pediatric patients, and given the high risk of mortality and disability associated with serious bacterial infections in very young infants, much of pediatric infectious diseases practice is based on a clinical diagnosis with empirical use of antibacterial agents, administered before or even without eventual identification of the specific pathogen.

Several key considerations influence decisions about the appropriate empirical use of antibacterial agents in infants and children. It is important to know the age-appropriate differential diagnosis with respect to likely pathogens. This information affects the choice of antimicrobial agent and also the dose, dosing interval, and route of administration (oral vs parenteral). A complete history and physical examination, combined with appropriate laboratory and radiographic studies, are necessary to identify specific diagnoses, in turn affecting the choice, dosing, and degree of urgency of administration of antimicrobial agents. The vaccination history may reflect reduced risk for some invasive infections, but not necessarily elimination of risk. The risk of serious bacterial infection in pediatric practice is also affected by the child’s immunologic status, which may be compromised by immaturity (neonates), underlying disease, and associated treatments (see Chapter 178). Infections in immunocompromised children may result from bacteria that are not considered pathogenic in immunocompetent children. The presence of foreign bodies also increases the risk of bacterial infections (see Chapter 179). The likelihood of central nervous system (CNS) involvement must be considered in all pediatric patients with serious bacterial infections, because many of the more common bacteremic infections in childhood, including disease caused by Haemophilus influenzae type b, pneumococcus, Salmonella, and meningococcus, carry a significant risk for hematogenous spread to the CNS.

The patterns of antimicrobial resistance in the community and for the potential causative pathogen being empirically treated must also be considered. Resistance to penicillin and cephalosporins is commonplace among strains of Streptococcus pneumoniae, often necessitating the use of other classes of antibiotics. Similarly, the striking emergence of community-acquired methicillin-resistant Staphylococcus aureus (MRSA) infections has complicated antibiotic choices for
this pathogen. Furthermore, carbapenem-resistant Enterobacteriaceae are an increasing problem among hospitalized patients.

Antimicrobial resistance occurs through many modifications of the bacterial genome (Tables 180-1 and 180-2). Mechanisms include enzyme inactivation of the antibiotic, decreased cell membrane permeability to intracellularly active antibiotics, efflux of antibiotics out of the bacteria, protection or alteration of the antibiotic target site, excessive production of the target site, and bypassing the antimicrobial site of action.

Antimicrobial resistance has reached crisis proportions, driven by the emergence of new resistance mechanisms (such as carbapenemases) and by overuse of antibiotics, both in healthcare and in other venues, such as agriculture. This increase in antibiotic resistance has rendered some bacterial infections encountered in clinical practice virtually untreatable. Accordingly, there is an urgent need to develop new antimicrobials. In addition, it is important for practitioners to use antibiotics only as necessary, with the narrowest feasible antimicrobial spectrum, to help thwart emergence of resistance. Advocacy for vaccines, particularly conjugate pneumococcal vaccine, can also decrease the selective pressure that excessive antimicrobial use exerts on resistance.

Effective antibiotic action requires achieving therapeutic levels of the drug at the site of infection. Although measuring the level of antibiotic at the site of infection is not always possible, one may measure the serum level and use this level as a surrogate marker for achievement of the desired effect at the tissue level. Various target serum levels are appropriate for different antibiotic agents and are assessed by the peak and trough serum levels, and the area under the therapeutic drug level curve (Fig. 180-1). These levels are, in turn, a reflection of the route of administration, drug absorption (IM, PO), volume of distribution, and drug elimination half-life, as well as of drug-drug interactions that might enhance or impede enzymatic inactivation of an antibiotic or result in antimicrobial synergism or antagonism (Fig. 180-2).

### Table 180-1: Mechanisms of Resistance to β-Lactam Antibiotics

<table>
<thead>
<tr>
<th>Category</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. Alter target site (PBP)</td>
<td>A. Decrease affinity of PBP for β-lactam antibiotic</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>II. Destroy β-lactam antibiotic</td>
<td>A. Increase production of β-lactamases, carbapenemases</td>
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</tbody>
</table>

PBP, penicillin-binding protein.

### Table 180-2: Aminoglycoside-Modifying Enzymes

<table>
<thead>
<tr>
<th>ENZYMES</th>
<th>USUAL ANTIBIOTICS MODIFIED</th>
<th>COMMON GENERA</th>
</tr>
</thead>
<tbody>
<tr>
<td>PHOSPHORYLATION</td>
<td>APH(2′)</td>
<td>K, T, G</td>
</tr>
<tr>
<td></td>
<td>APH(3′)-I</td>
<td>K</td>
</tr>
<tr>
<td></td>
<td>APH(3′)-III</td>
<td>K ± A</td>
</tr>
<tr>
<td>ACETYLATION</td>
<td>AAC(2′)</td>
<td>G</td>
</tr>
<tr>
<td></td>
<td>AAC(3′)</td>
<td>±T, G</td>
</tr>
<tr>
<td></td>
<td>AAC(3′)-III, -IV, OR-V</td>
<td>K, T, G</td>
</tr>
<tr>
<td></td>
<td>AAC(6′)</td>
<td>K, T, A</td>
</tr>
<tr>
<td>ADENYLATION</td>
<td>ANT(2′)</td>
<td>K, T, G</td>
</tr>
<tr>
<td></td>
<td>ANT(4′)</td>
<td>K, T, A</td>
</tr>
</tbody>
</table>

A, amikacin; AAC, aminoglycoside acetyltransferase; ANT, aminoglycoside nucleotidyltransferase; APH, aminoglycoside phosphotransferase; E, Enterobacteriaceae; G, gentamicin; K, kanamycin; PR, Providencia-Proteus; PS, pseudomonads; SA, staphylococci; SR, streptococci; T, tobramycin.

### AGE-AND RISK-SPECIFIC USE OF ANTIBIOTICS IN CHILDREN

#### Neonates

The causative pathogens of neonatal infections are typically acquired around the time of delivery. Thus, empirical antibiotic selection must take into account the importance of these pathogens in neonates (see Chapter 109). Among the causes of neonatal sepsis in infants, group B streptococcus is the most common, although intrapartum antibiotic prophylaxis administered to women at increased risk for transmission of this pathogen to the infant has greatly decreased the incidence of this infection in neonates (see Chapter 184). Gram-negative enteric organisms acquired from the maternal birth canal, in particular Escherichia coli, are other common causes of neonatal sepsis. Although rare, Listeria monocytogenes is also an important pathogen, insofar as it is intrinsically resistant to cephalosporin antibiotics, which are often used as empirical therapy for serious bacterial infections in young children. Salmonella species are also being increasingly recognized as important pathogens in infancy. All of these organisms can be associated with meningitis in the neonate; therefore, lumbar puncture should always be considered in the setting of bacteremic infections in this age group, and, if meningitis cannot be excluded, antibiotic management should include agents capable of crossing the blood–brain barrier.

#### Older Children

Antibiotic choices in toddlers and young children were once driven by the high risk of this age group to invasive disease caused by H. influenzae type b (see Chapter 194). With the advent of conjugate vaccines against H. influenzae type b, invasive disease has declined dramatically. However, outbreaks of invasive disease still occur, particularly in the setting of parental refusal of vaccines. It is, therefore, still important to utilize antimicrobials that are active against this pathogen in many clinical settings, particularly if meningitis is a consideration. Other particularly important pathogens to be considered in this age group include E. coli, S. pneumoniae, Neisseria meningitidis, and S. aureus. Antimicrobial resistance is commonly exhibited by S. pneumoniae and S. aureus. Strains of S. pneumoniae that are resistant to penicillin and cephalosporin antibiotics are frequently encountered in clinical practice. Similarly, MRSA is highly prevalent in many regions. Resistance of S. pneumoniae, as well as MRSA, is a result of mutations that confer alterations in penicillin-binding proteins, the molecular targets of penicillin and cephalosporin activity (see Table 180-1).

Depending on the specific clinical diagnosis, other pathogens that are commonly encountered among older children include Moraxella catarrhalis, nontypable strains of H. influenzae, and Mycoplasma pneumoniae, which cause upper respiratory tract infections and pneumonia; group A streptococcus, which causes pharyngitis, skin and soft-tissue infections, osteomyelitis, septic arthritis, and, rarely, bactereemia with toxic shock syndrome; Kingella kingae, which causes bone and joint infections; viridans streptococci and Enterococcus, which cause endocarditis; and Salmonella, which causes enteritis, bacteremia, osteomyelitis, and septic arthritis. This complexity underscores the
Infectious etiologies and commonly caused by Gram-negative enteric organisms. In nosocomial infections, often associated with indwelling lines and catheters, fungal, or parasitic infections. Prolonged hospitalization can lead to serious viral infections, particularly with influenza, can also predispose to invasive infections, especially with Streptococcus pneumoniae. Immunocompromised and hospitalized patients are predisposed to develop a wide range of bacterial, viral, fungal, or parasitic infections. Prolonged hospitalization (intensive care, trauma, burns) can lead to serious viral infections, especially with influenza, can also predispose to invasive infections, especially with Streptococcus pneumoniae. Immunocompromised and hospitalized patients are predisposed to develop a wide range of bacterial, viral, fungal, or parasitic infections. Prolonged hospitalization can lead to nosocomial infections, often associated with indwelling lines and catheters and commonly caused by Gram-negative enteric organisms. In addition to the usual bacterial pathogens, Pseudomonas aeruginosa and enteric organisms, including E. coli, Klebsiella pneumoniae, Enterobacter, and Serratia, are important considerations as opportunistic pathogens in these settings. Selection of appropriate antimicrobials is challenging because of the diverse causes and scope of antimicrobial resistance exhibited by these organisms. Many strains of enteric organisms have resistance because of extended spectrum β-lactamase, which is different from other multidrug-resistant microorganisms in that they are susceptible to few (if any) antibacterial agents. P. aeruginosa encodes proteins that function as efflux pumps to eliminate multiple classes of antimicrobials from the cytoplasm or periplasmic space. In addition to these Gram-negative pathogens, infections caused by Enterococcus faecalis and Enterococcus faecium are inherently difficult to treat. These organisms may cause urinary tract infection or infective endocarditis in immunocompetent children and may be responsible for a variety of syndromes in immunocompromised patients, especially in the setting of prolonged intensive care. The emergence of infections caused by vancomycin-resistant Enterococcus (VRE) has further complicated antimicrobial selection in high-risk patients and has necessitated the development of newer antimicrobials that target these highly resistant Gram-positive bacteria. Although experience with many of these newer agents in the management of complex hospitalized pediatric patients is limited, they are important agents to be aware of (described below).

**Immunocompromised and Hospitalized Patients**

It is important to consider the risks associated with immunocompromising conditions (malignancy, solid-organ, or hematopoietic stem cell transplantation) and the risks conferred by conditions leading to prolonged hospitalization (intensive care, trauma, burns). Serious viral infections, particularly with influenza, can also predispose to invasive bacterial infections, especially with Staphylococcus aureus. Immunocompromised children are predisposed to develop a wide range of bacterial, viral, fungal, or parasitic infections. Prolonged hospitalization can lead to nosocomial infections, often associated with indwelling lines and catheters and commonly caused by Gram-negative enteric organisms. In

**Figure 180-1** The area under the curve (shaded area) for different antibiotics. The area under the curve provides a measure of antibiotic exposure to bacterial pathogens. The greatest exposure comes with antibiotics that have a long serum half-life and are administered parenterally (upper left panel, antibiotic A). The lowest exposure occurs with oral administration (lower right panel, antibiotic C). Dosing of antibiotic B once a day (upper right panel) provides far less exposure than dosing the same antibiotic every 6 hr (lower left panel). MIC, minimal inhibitory concentration. (From Pong AL, Bradley JS: Guidelines for the selection of antibacterial therapy in children, Pediatr Clin North Am 52:869–894, 2005.)

**Figure 180-2** Antibacterial effects of antibiotic combinations. Left: Curve of A + B illustrates synergism (increased killing). Center: Curve of C + D illustrates antagonism (D is less effective when C is added). Right: Curve of E + F illustrates indifference, or additive effect (addition of E to F has no effect on F). (From Mandell GL, Bennett JE, Dolin R, editors: Principles and practice of infectious diseases, ed 6. Philadelphia, 2005, Elsevier, p. 247.)
Antibacterial Medications (Antibiotics)*

Principles

Penicillins, these agents remain valuable and are commonly used for management of many pediatric infectious diseases.

Table 180-3 lists commonly used antibiotics.

Penicillins

Although there has been ever-increasing emergence of resistance to penicillins, these agents remain valuable and are commonly used for management of many pediatric infectious diseases.

- **Penicillin**
  - **Amoxicillin**
    - **Aminoglycoside antibiotic active against Gram-negative bacilli, especially Escherichia coli, Klebsiella, Proteus, Enterobacter, Serratia, and Pseudomonas**
    - Neonates: Postnatal age ≤7 days: weight ≤2,000 g: 7.5 mg/kg q 12-18 hr IV or IM; weight >2,000 g: 10 mg/kg q 12 hr IV or IM; postnatal age >7 days: weight 1,000-2,000 g IV or IM: 7.5 mg/kg q 8-12 hr IV or IM; weight >2,000 g: 10 mg/kg q 8 hr IV or IM
    - Children: 15-25 mg/kg/24 hr divided q 8-12 hr IV or IM
    - Adults: 15 mg/kg/24 hr divided q 8-12 hr IV or IM

- **Ampicillin**
  - **Penicillinase-susceptible β-lactam: Gram-positive pathogens except Staphylococcus; Salmonella, Shigella, Neisseria, E. coli, and Proteus mirabilis**
  - Children: 20-50 mg/kg/24 hr divided q 8-12 hr PO.
  - Higher dose of 80-90 mg/kg/24 hr PO for otitis media
  - Adults: 250-500 mg q 8-12 hr PO

- **Amoxicillin-clavulanate**
  - **β-Lactam (amoxicillin) combined with β-lactamase inhibitor (clavulanate) enhances amoxicillin activity against penicillinase-producing bacteria. S. aureus (not methicillin-resistant organism), Streptococcus, Haemophilus influenzae, Moraxella catarrhalis, E. coli, Klebsiella, Bacteroides fragilis**
  - Neonates: 30 mg/kg/24 hr divided q 12 hr PO
  - Children: 40-55 mg/kg/24 hr divided q 8-12 hr PO.
  - Higher dose 80-90 mg/kg/24 hr PO for otitis media

- **Amoxicillin**
  - **β-Lactam (amoxicillin) and β-lactamase inhibitor (sulbactam) enhances amoxicillin activity against penicillinase-producing bacteria: S. aureus, H. influenzae, M. catarrhalis, E. coli, Klebsiella, B. fragilis**
  - Children: 100-200 mg/kg/24 hr divided q 4-6 hr IV or IM
  - Adults: 250-500 mg q 4-8 hr IV or IM

Penicillins remain the drugs of choice for pediatric infections caused by group A and group B Streptococcus, Treponema pallidum (syphilis), L. monocytogenes, and N. meningitidis. The semisynthetic penicillins (nafcillin, cloxacillin, dicloxacillin) are useful for management of susceptible staphylococcal infections, although the increasing incidence of MRSA has limited the usefulness of these drugs. The aminopenicillins (amoxicillin, amoxicillin) were developed to provide broad-spectrum activity against Gram-negative organisms, including E. coli and H. influenzae, but the emergence of resistance has limited their utility in many clinical settings. The carboxypenicillins (carbenicillin, ticarcillin) and ureidopenicillins (piperacillin, mezlocillin, azlocillin) also have bactericidal activity against most strains of P. aeruginosa.

Text continued on p. 1311

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*In the Drug column, the generic drug name is in **bold**. In the Indications column, **bold** indicates major organisms targeted and mechanisms of action. Continued*
<table>
<thead>
<tr>
<th>DRUG (TRADE NAMES, FORMULATIONS)</th>
<th>INDICATIONS (MECHANISM OF ACTION) AND DOSING</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azithromycin Zithromax Tablet: 250 mg Suspension: 100 mg/5 mL, 200 mg/5 mL</td>
<td>Azalide antibiotic with activity against <em>S. aureus</em>, <em>Streptococcus</em>, <em>H. influenzae</em>, <em>Mycoplasma</em>, <em>Legionella</em>, <em>Chlamydia trachomatis</em> Children: 10 mg/kg PO on day 1 (max dose: 500 mg) followed by 5 mg/kg PO q 24 hr for 4 days Group A streptococcus pharyngitis: 12 mg/kg/24 hr PO (max dose: 500 mg) for 5 days Adults: 500 mg PO day 1 followed by 250 mg for 4 days Uncomplicated <em>C. trachomatis</em> infection: single 1 g dose PO</td>
<td>Note: Very long half-life permitting once-daily dosing. No metabolic-based drug interactions (unlike erythromycin and clarithromycin), limited gastrointestinal distress. Shorter-course regimens (e.g., 1-3 days) under investigation. 3 day therapy (10 mg/kg/24 hr x 3 days) and single-dose therapy (30 mg/kg) use with increasing frequency (not for streptococcus pharyngitis)</td>
</tr>
<tr>
<td>Aztreonam Azactam Injection</td>
<td>β-Lactam (monobactam) antibiotic with activity against Gram-negative aerobic bacteria, <em>Enterobacteriaceae</em>, and <em>Pseudomonas aeruginosa</em> Neonates: Postnatal age ≤7 days weight ≤2,000 g: 60 mg/kg/24 hr divided q 12 hr IV or IM; weight &gt;2,000 g: 90 mg/kg/24 hr divided q 8 hr IV or IM; postnatal age &gt;7 days weight &lt;1,200 g: 60 mg/kg/24 hr divided q 12 hr IV or IM; weight 1,200-2,000 g: 50 mg/kg/24 hr divided q 8 hr IV or IM; weight &gt;2,000 g: 120 mg/kg/24 hr divided q 8 hr IV or IM Children: 90-120 mg/kg/24 hr divided q 6-8 hr IV or IM. For cystic fibrosis up to 200 mg/kg/24 hr IV Adults: 1-2 g IV or IM q 8-12 hr (max dose: 8 g/24 hr)</td>
<td>Cautions: Rash, thrombophlebitis, eosinophilia. Renally eliminated Drug interaction: Probencid</td>
</tr>
<tr>
<td>Carbenicillin Geopen Injection Geoceillin oral tablet</td>
<td>Extended-spectrum penicillin (remains susceptible to penicillinase destruction) active against <em>Enterobacter</em>, indole-positive <em>Proteus</em>, and <em>Pseudomonas</em> Neonates: Postnatal age ≤7 days weight ≤2,000 g: 225 mg/kg/24 hr divided q 8 hr IV or IM; weight &gt;2,000 g: 300 mg/kg/24 hr divided q 6 hr IV or IM; &gt;7 days: 300-400 mg/kg/24 hr divided q 6 hr IV or IM Children: 400-600 mg/kg/24 hr divided q 4-6 hr IV or IM</td>
<td>Cautions: Painful given intramuscularly; rash; each gram contains 5.3 mEq sodium. Interferes with platelet aggregation at high doses, increases in liver transaminase levels. Renally eliminated. Oral tablet for treatment of urinary tract infection only Drug interaction: Probencid</td>
</tr>
<tr>
<td>Cefaclor Cefclor Capsule: 250, 500 mg Suspension: 125 mg/5 mL, 187 mg/5 mL, 250 mg/5 mL, 375 mg/5 mL</td>
<td>Second-generation cephalosporin active against <em>S. aureus</em>, <em>Streptococcus</em>, and <em>Enterobacteriaceae</em>, including <em>S. pneumoniae</em>, <em>H. influenzae</em>, <em>E. coli</em>, <em>Klebsiella</em>, and <em>Proteus</em> Children: 20-40 mg/kg/24 hr divided q 8-12 hr PO (max dose: 2 g) Adults: 250-500 mg q 6-8 hr PO</td>
<td>Cautions: β-Lactam safety profile (rash, eosinophilia) with high incidence of serum sickness reaction. Renally eliminated Drug interaction: Probencid</td>
</tr>
<tr>
<td>Cefadroxil Duricef, Ultracef Capsule: 500 mg Tablet: 1,000 mg Suspension: 125 mg/5 mL, 250 mg/5 mL, 500 mg/5 mL</td>
<td>First-generation cephalosporin active against <em>S. aureus</em>, <em>Streptococcus</em>, <em>E. coli</em>, <em>Klebsiella</em>, and <em>Proteus</em> Children: 30 mg/kg/24 hr divided q 12 hr PO (max dose: 2 g) Adults: 250-500 mg q 8-12 hr PO</td>
<td>Cautions: β-Lactam safety profile (rash, eosinophilia). Renally eliminated. Long half-life permits q 12-24 hr dosing Drug interaction: Probencid</td>
</tr>
<tr>
<td>Cefazolin Ancef, Kefzol Injection</td>
<td>First-generation cephalosporin active against <em>S. aureus</em>, <em>Streptococcus</em>, <em>E. coli</em>, <em>Klebsiella</em>, and <em>Proteus</em> Neonates: Postnatal age ≤7 days 40 mg/kg/24 hr divided q 12 hr IV or IM; &gt;7 days 40-60 mg/kg/24 hr divided q 8 hr IV or IM Children: 50-100 mg/kg/24 hr divided q 8 hr IV or IM Adults: 0.5-2 g q 8 hr IV or IM (max dose: 12 g/24 hr)</td>
<td>Caution: β-Lactam safety profile (rash, eosinophilia). Renally eliminated. Does not adequately penetrate CNS Drug interaction: Probencid</td>
</tr>
<tr>
<td>Cefdinir Omnicef Capsule: 300 mg Oral suspension: 125 mg/5 mL</td>
<td>Extended-spectrum, semisynthetic cephalosporin Children 6 mo-12 yr: 14 mg/kg/24 hr in 1 or 2 doses PO (max dose: 600 mg/24 hr) Adults: 600 mg q 24 hr PO</td>
<td>Cautions: Reduce dosage in renal insufficiency (creatinine clearance &lt;60 mL/min). Avoid taking concurrently with iron-containing products and antacids because absorption is markedly decreased; take at least 2 hr apart Drug interaction: Probencid</td>
</tr>
<tr>
<td>Cefepime Maxipime Injection</td>
<td>Extended-spectrum, fourth-generation cephalosporin active against many Gram-positive and Gram-negative pathogens, including <em>P. aeruginosa</em> many multidrug-resistant pathogens Children: 100-150 mg/kg/24 hr q 8-12 hr IV or IM Adults: 2-4 g/24 hr q 12 hr IV or IM</td>
<td>Adverse events: Diarrhea, nausea, vaginal candidiasis Cautions: β-Lactam safety profile (rash, eosinophilia). Renally eliminated Drug interaction: Probencid</td>
</tr>
</tbody>
</table>

*In the Drug column, the generic drug name is in **bold**. In the Indications column, **bold** indicates major organisms targeted and mechanisms of action.
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<th>DRUG (TRADE NAMES, FORMULATIONS)</th>
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<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cefixime</strong>&lt;br&gt;Suprax&lt;br&gt;Tablet: 200, 400 mg&lt;br&gt;Suspension: 100 mg/5 mL</td>
<td>Third-generation cephalosporin active against Streptococci, <em>H. influenzae</em>, <em>M. catarrhalis</em>, <em>Neisseria gonorrhoeae</em>, <em>Serratia marcescens</em>, and <em>Proteus vulgaris</em>. No antistaphylococcal or antipseudomonal activity&lt;br&gt;Children: 8 mg/kg/24 hr divided q 12-24 hr PO&lt;br&gt;Adults: 400 mg/24 hr divided q 12-24 hr PO</td>
<td>Cautions: β-Lactam safety profile ( Rash, eosinophilia). Renally eliminated. Does not adequately penetrate CNS&lt;br&gt;Drug interaction: Probenecid</td>
</tr>
<tr>
<td><strong>Cefoperazone sodium</strong>&lt;br&gt;Cefobid&lt;br&gt;Injection</td>
<td>Third-generation cephalosporin active against many Gram-positive and Gram-negative pathogens&lt;br&gt;Neonates: 100 mg/kg/24 hr divided q 12-16 hr IV or IM&lt;br&gt;Children: 100-150 mg/kg/24 hr divided q 8-12 hr IV or IM&lt;br&gt;Adults: 1-2 g/24 hr divided q 8-12 hr IV or IM (max dose: 12 g/24 hr)</td>
<td>Cautions: Highly protein-bound cephalosporin with limited potency reflected by weak antipseudomonal activity. Variable Gram-positive activity. Primarily hepatically eliminated in bile&lt;br&gt;Drug interaction: Disulfiram-like reaction with alcohol</td>
</tr>
<tr>
<td><strong>Cefotaxime sodium</strong>&lt;br&gt;Clavoran&lt;br&gt;Injection</td>
<td>Third-generation cephalosporin active against Gram-positive and Gram-negative pathogens. No antipseudomonal activity&lt;br&gt;Neonates: ≤7 days: 100 mg/kg/24 hr divided q 12 hr IV or IM; &gt;7 days: weight &lt;1,200 g 100 mg/kg/24 hr divided q 12 hr IV or IM; weight &gt;1,200 g: 150 mg/kg/24 hr divided q 8 hr IV or IM&lt;br&gt;Children: 150 mg/kg/24 hr divided q 6-8 hr IV or IM (meningitis: 200 mg/kg/24 hr divided q 6-8 hr IV)&lt;br&gt;Adults: 1-2 g q 8-12 hr IV or IM (max dose: 12 g/24 hr)</td>
<td>Cautions: β-Lactam safety profile ( Rash, eosinophilia). Renally eliminated. Each gram of drug contains 2.2 mEq sodium. Active metabolite&lt;br&gt;Drug interaction: Probenecid</td>
</tr>
<tr>
<td><strong>Cefotetan disodium</strong>&lt;br&gt;Cefotan&lt;br&gt;Injection</td>
<td>Second-generation cephalosporin active against <em>S. aureus</em>, <em>Streptococcus</em>, <em>H. influenzae</em>, <em>E. coli</em>, <em>Klebsiella</em>, <em>Proteus</em>, and <em>Bacteroides</em>. Inactive against <em>Enterobacter</em>&lt;br&gt;Children: 40-80 mg/kg/24 hr divided IV or IM q 12 hr&lt;br&gt;Adults: 2-4 g/24 hr divided q 12 hr IV or IM (max dose: 6 g/24 hr)</td>
<td>Cautions: Highly protein-bound cephalosporin, poor CNS penetration; β-lactam safety profile ( Rash, eosinophilia), disulfiram-like reaction with alcohol. Renally eliminated (~20% in bile)</td>
</tr>
<tr>
<td><strong>Cefoxitin sodium</strong>&lt;br&gt;Mefoxin&lt;br&gt;Injection</td>
<td>Second-generation cephalosporin active against <em>S. aureus</em>, <em>Streptococcus</em>, <em>H. influenzae</em>, <em>E. coli</em>, <em>Klebsiella</em>, <em>Proteus</em>, and <em>Bacteroides</em>. Inactive against <em>Enterobacter</em>&lt;br&gt;Neonates: 70-100 mg/kg/24 hr divided q 8-12 hr IV or IM&lt;br&gt;Children: 80-160 mg/kg/24 hr divided q 6-8 hr IV or IM&lt;br&gt;Adults: 1-2 g q 6-8 hr IV or IM (max dose: 12 g/24 hr)</td>
<td>Cautions: Poor CNS penetration; β-lactam safety profile ( Rash, eosinophilia). Renally eliminated. Painful given intramuscularly&lt;br&gt;Drug interaction: Probenecid</td>
</tr>
<tr>
<td><strong>Cefpodoxime proxetil</strong>&lt;br&gt;Vantin&lt;br&gt;Tablet: 100 mg, 200 mg&lt;br&gt;Suspension: 50 mg/5 mL, 100 mg/5 mL</td>
<td>Third-generation cephalosporin active against <em>S. aureus</em>, <em>Streptococcus</em>, <em>H. influenzae</em>, <em>M. catarrhalis</em>, <em>N. gonorrhoeae</em>, <em>E. coli</em>, <em>Klebsiella</em> and <em>Proteus</em>. No antipseudomonal activity&lt;br&gt;Children: 10 mg/kg/24 hr divided q 12 hr PO&lt;br&gt;Adults: 200-800 mg/24 hr divided q 12 hr PO (max dose: 800 mg/24 hr)&lt;br&gt;Uncomplicated gonorrhea: 200 mg PO as single-dose therapy</td>
<td>Cautions: β-Lactam safety profile ( Rash, eosinophilia). Renally eliminated. Does not adequately penetrate CNS. Increased bioavailability when taken with food&lt;br&gt;Drug interaction: Probenecid; antacids and H-2 receptor antagonists may decrease absorption</td>
</tr>
<tr>
<td><strong>Ceftaroline fosamil</strong>&lt;br&gt;Teflaro&lt;br&gt;Injection</td>
<td>Fifth-generation cephalosporin active against <em>S. aureus</em> (including MRSA when used for skin and soft-tissue infection), <em>Streptococcus pyogenes</em>, <em>Streptococcus agalactiae</em>, <em>Escherichia coli</em>, <em>Klebsiella pneumoniae</em>, <em>H. influenzae</em>, and <em>Klebsiella oxytoca</em>&lt;br&gt;*Children: 24 mg/kg/24 hr divided q 8 hr IV (≤60 kg of age); 36 mg/kg/24 hr divided q 8 hr IV (weight &gt;60 kg); 400 mg q 8 hr IV (weight &gt;33 kg)&lt;br&gt;Adults: 600 mg q 12 hr IV&lt;br&gt;*Suggested dose; safety and effectiveness in pediatric patients have not yet been established</td>
<td>Caution: β-Lactam safety profile ( Rash, eosinophilia)&lt;br&gt;Drug interaction: Probenecid</td>
</tr>
<tr>
<td><strong>Cefprozil</strong>&lt;br&gt;Cefzil&lt;br&gt;Tablet: 250, 500 mg&lt;br&gt;Suspension: 125 mg/5 mL, 250 mg/5 mL</td>
<td>Second-generation cephalosporin active against <em>S. aureus</em>, <em>Streptococcus</em>, <em>H. influenzae</em>, <em>E. coli</em>, <em>M. catarrhalis</em>, <em>Klebsiella</em>, and <em>Proteus</em>&lt;br&gt;Children: 30 mg/kg/24 hr divided q 8-12 hr PO&lt;br&gt;Adults: 500-1,000 mg/24 hr divided q 12 hr PO (max dose: 1.5 g/24 hr)</td>
<td>Cautions: β-Lactam safety profile ( Rash, eosinophilia). Renally eliminated. Good bioavailability; food does not affect bioavailability&lt;br&gt;Drug interaction: Probenecid</td>
</tr>
</tbody>
</table>

*In the Drug column, the generic drug name is in **bold**. In the Indications column, **bold** indicates major organisms targeted and mechanisms of action.
### Table 180-3 Antibacterial Medications (Antibiotics)—cont’d

<table>
<thead>
<tr>
<th>DRUG (TRADE NAMES, FORMULATIONS)</th>
<th>INDICATIONS (MECHANISM OF ACTION) AND DOsing</th>
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<tbody>
<tr>
<td><strong>Ceftazidime</strong>&lt;br&gt;Fortaz, Ceptaz, Tazicef, Tazidime&lt;br&gt;Injection</td>
<td>Third-generation cephalosporin active against Gram-positive and Gram-negative pathogens, including &lt;i&gt;P. aeruginosa&lt;/i&gt;&lt;br&gt;Neonates: Postnatal age ≤7 days: 100 mg/kg/24 hr divided q 12 hr IV or IM; &gt;7 days weight ≤1,200 g: 100 mg/kg/24 hr divided q 12 hr IV or IM; weight &gt;1,200 g: 150 mg/kg/24 hr divided q 8 hr IV or IM&lt;br&gt;Children: 150 mg/kg/24 hr divided q 8 hr IV or IM (meningitis: 150 mg/kg/24 hr IV divided q 8 hr)&lt;br&gt;Adults: 1-2 g q 8-12 hr IV or IM (max dose: 8-12 g/24 hr)</td>
<td>Cautions: β-Lactam safety profile (rash, eosinophilia). Renally eliminated. Increasing pathogen resistance developing with long-term, widespread use&lt;br&gt;Drug interaction: Probencid</td>
</tr>
<tr>
<td><strong>Ceftriaxone sodium</strong>&lt;br&gt;Rocephin&lt;br&gt;Injection</td>
<td>Third-generation cephalosporin active against Gram-positive and Gram-negative pathogens. No antipseudomonal activity&lt;br&gt;Neonates: 50-75 mg/kg q 24 hr IV or IM&lt;br&gt;Children: 50-75 mg/kg q 24 hr IV or IM (meningitis: 75 mg/kg dose 1 then 80-100 mg/kg/24 hr divided q 12-24 hr IV or IM)&lt;br&gt;Adults: 1-2 g q 24 hr IV or IM (max dose: 4 g/24 hr)</td>
<td>Cautions: β-Lactam safety profile (rash, eosinophilia). Renally eliminated&lt;br&gt;Drug interaction: Probencid</td>
</tr>
<tr>
<td><strong>Cefuroxime</strong>&lt;br&gt;(cefuroxime axetil for oral administration)&lt;br&gt;Ceftin, Kefurox, Zinacef&lt;br&gt;Injection</td>
<td>Second-generation cephalosporin active against &lt;i&gt;S. aureus, Streptococcus, H. influenzae, E. coli, M. catarrhalis, Klebsiella, and Proteus&lt;/i&gt;&lt;br&gt;Neonates: 40-100 mg/kg/24 hr divided q 12 hr IV or IM&lt;br&gt;Children: 200-240 mg/kg/24 hr divided q 8 hr IV or IM; PO administration: 20-30 mg/kg/24 hr divided q 8 hr PO&lt;br&gt;Adults: 750-1,500 mg q 8 hr IV or IM (max dose: 6 g/24 hr)</td>
<td>Cautions: β-Lactam safety profile (rash, eosinophilia). Renally eliminated. Food increases PO bioavailability&lt;br&gt;Drug interaction: Probencid</td>
</tr>
<tr>
<td><strong>Cephalexin</strong>&lt;br&gt;Keflex, Keftab&lt;br&gt;Cap: 250, 500 mg&lt;br&gt;Tablet: 500 mg, 1 g&lt;br&gt;Susp: 125 mg/5 mL, 250 mg/5 mL, 100 mg/mL drops</td>
<td>First-generation cephalosporin active against &lt;i&gt;S. aureus, Streptococcus, E. coli, Klebsiella, and Proteus&lt;/i&gt;&lt;br&gt;Children: 25-100 mg/kg/24 hr divided q 6-8 hr PO&lt;br&gt;Adults: 250-500 mg q 6 hr PO (max dose: 4 g/24 hr)</td>
<td>Cautions: β-Lactam safety profile (rash, eosinophilia). Renally eliminated&lt;br&gt;Drug interaction: Probencid</td>
</tr>
<tr>
<td><strong>Cefradine</strong>&lt;br&gt;Velosef&lt;br&gt;Cap: 250, 500 mg&lt;br&gt;Susp: 125 mg/5 mL, 250 mg/5 mL</td>
<td>First-generation cephalosporin active against &lt;i&gt;S. aureus, Streptococcus, E. coli, Klebsiella, and Proteus&lt;/i&gt;&lt;br&gt;Children: 50-100 mg/kg/24 hr divided q 6-12 hr PO&lt;br&gt;Adults: 250-500 mg q 6-12 hr PO (max dose: 4 g/24 hr)</td>
<td>Cautions: β-Lactam safety profile (rash, eosinophilia). Renally eliminated&lt;br&gt;Drug interaction: Probencid</td>
</tr>
<tr>
<td><strong>Chloramphenicol</strong>&lt;br&gt;Chloromycetin&lt;br&gt;Injection&lt;br&gt;Cap: 250 mg&lt;br&gt;Opthalmic, otic solutions&lt;br&gt;Ointment</td>
<td>Broad-spectrum protein synthesis inhibitor active against many Gram-positive and Gram-negative bacteria, &lt;i&gt;Salmonella&lt;/i&gt;, vancomycin-resistant &lt;i&gt;Enterococcus faecium, Bacteroides&lt;/i&gt;, other anaerobes, &lt;i&gt;Mycoplasma, Chlamydia&lt;/i&gt;, and &lt;i&gt;Rickettsia&lt;/i&gt;; usually inactive against &lt;i&gt;Pseudomonas&lt;/i&gt;&lt;br&gt;Neonates: Initial loading dose 20 mg/kg followed 12 hr later by: postnatal age ≤7 days: 25 mg/kg/24 hr q 24 hr IV; &gt;7 days: weight ≤2,000 g: 25 mg/kg/24 hr q 24 hr IV; weight &gt;2,000 g: 50 mg/kg/24 hr divided q 12 hr IV&lt;br&gt;Children: 50-75 mg/kg/24 hr divided q 6-8 hr IV or PO (meningitis: 75-100 mg/kg/24 hr IV divided q 6 hr)&lt;br&gt;Adults: 50 mg/kg/24 hr divided q 6 hr IV or PO (max dose: 4 g/24 hr)</td>
<td>Cautions: Gray-baby syndrome (from too-high dose in neonate), bone marrow suppression aplastic anemia (monitor hematocrit, free serum iron)&lt;br&gt;Drug interactions: Phenytoin, phenobarbital, rifampin may decrease levels&lt;br&gt;Target serum concentrations: Peak 20-30 mg/L; trough 5-10 mg/L</td>
</tr>
</tbody>
</table>

*In the Drug column, the generic drug name is in **bold**. In the Indications column, **bold** indicates major organisms targeted and mechanisms of action.*
### Table 180-3  Antibacterial Medications (Antibiotics)—cont’d

<table>
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<th>DRUG (TRADE NAMES, FORMULATIONS)</th>
<th>INDICATIONS (MECHANISM OF ACTION) AND DOSING</th>
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</tr>
</thead>
<tbody>
<tr>
<td><strong>Ciprofloxacin</strong>  Cipro</td>
<td>Quinolone antibiotic active against <em>P. aeruginosa, Serratia, Enterobacter, Shigella, Salmonella, Campylobacter, N. gonorrhoae, H. influenzae, M. catarrhalis, some S. aureus, and some Streptococcus</em>*&lt;br&gt;Neonates: 10 mg/kg q 12 hr PO or IV  Children: 15-30 mg/kg/24 hr divided q 12 hr PO or IV; cystic fibrosis: 20-40 mg/kg/24 hr divided q 8-12 hr PO or IV  Adults: 250-750 mg q 12 hr; 200-400 mg IV q 12 hr PO (max dose: 1.5 g/24 hr)<strong>&lt;br&gt;Cautions: Concerns of joint destruction in juvenile animals not seen in humans; tendonitis, superinfection, dizziness, confusion, crystalluria, some photosensitivity</strong>&lt;br&gt;Drug interactions: Theophylline; magnesium-, aluminum-, or calcium-containing antacids; sucralfate; probenecid; warfarin; cyclosporine</td>
<td><strong>Continued</strong></td>
</tr>
<tr>
<td><strong>Clarithromycin</strong>  Biaxin</td>
<td>Macrolide antibiotic with activity against <em>S. aureus, Streptococcus, H. influenzae, Legionella, Mycoplasma, and C. trachomatis</em>*&lt;br&gt;Children: 15 mg/kg/24 hr divided q 12 hr PO  Adults: 250-500 mg q 12 hr PO (max dose: 1 g/24 hr)<strong>&lt;br&gt;Cautions: Adverse events less than erythromycin; gastrointestinal upset, dyspepsia, nausea, cramping</strong>&lt;br&gt;Drug interactions: Same as erythromycin: astemizole carbamazepine, terfenadine, cyclosporine, theophylline, digoxin, tacrolimus</td>
<td><strong>Continued</strong></td>
</tr>
<tr>
<td><strong>Clindamycin</strong>  Cleocin</td>
<td>Protein synthesis inhibitor active against most Gram-positive aerobic and anaerobic cocci except <em>Enterococcus</em>*&lt;br&gt;Neonates: Postnatal age ≤7 days weight &lt;2,000 g: 10 mg/kg/24 hr divided q 12 hr IV or IM; weight &gt;2,000 g: 15 mg/kg/24 hr divided q 8 hr IV or IM; &gt;7 days weight &lt;1,200 g: 10 mg/kg/24 hr IV or IM divided q 12 hr; weight 1,200-2,000 g: 15 mg/kg/24 hr divided q 8 hr IV or IM; weight &gt;2,000 g: 20 mg/kg/24 hr divided q 8 hr IV or IM  Children: 10-40 mg/kg/24 hr divided q 6-8 hr IV, IM, or PO  Adults: 150-600 mg q 6-8 hr IV, IM, or PO (max dose: 5 g/24 hr IV or IM or 2 g/24 hr PO)<strong>&lt;br&gt;Cautions: Diarrhea, nausea, Clostridium difficile–associated colitis, rash</strong>&lt;br&gt;Topically active as an acne treatment</td>
<td><strong>Continued</strong></td>
</tr>
<tr>
<td><strong>Cloxacillin sodium</strong>  Tegopen</td>
<td>Penicillinase-resistant penicillin active against <em>S. aureus and other Gram-positive cocci except Enterococcus and coagulase-negative staphylococci</em>*&lt;br&gt;Children: 50-100 mg/kg/24 hr divided q 6 hr PO  Adults: 250-500 mg q 6 hr PO (max dose: 4 g/24 hr)<strong>&lt;br&gt;Cautions: β-Lactam safety profile (rash, eosinophilia). Primarily hepatically eliminated; requires dose reduction in renal disease. Food decreases bioavailability</strong>&lt;br&gt;Drug interaction: Probenecid</td>
<td><strong>Continued</strong></td>
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<tr>
<td><strong>Colistin (Colistimethate sodium; polymyxin E)</strong>  Inhalation</td>
<td>Treatment of multidrug resistant Gram-negative organisms (Enterobacteriaceae including extended-spectrum betalactamase and carbapenemase-producing strains)<strong>&lt;br&gt;Children: 2.5-5 mg/kg/day divided in 2-4 divided doses IV  Adults: 300 mg/day in 2-4 divided doses IV</strong>&lt;br&gt;Cautions: Nephrotoxicity (~3% in young children; higher rates in adolescents and adults); adjust dose for renal insufficiency; neurotoxicity (headaches, paresthesia, ataxia)**&lt;br&gt;Drug interactions: Should not be administered concomitantly with polymyxins or aminoglycosides</td>
<td><strong>Continued</strong></td>
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<tr>
<td><strong>Co-trimoxazole (trimethoprim-sulfamethoxazole; TMP-SMZ)</strong>  Bactrim, Cotrim, Septra, Sulfa-trim</td>
<td>Antibiotic combination with sequential antagonism of bacterial folate synthesis with broad antibacterial activity: <em>Shigella, Legionella, Nocardia, Chlamydia, Pneumocystis jiroveci</em>. Dosage based on TMP component&lt;br&gt;Children: 6-20 mg TMP/kg/24 hr or IV divided q 12 hr PO  <em>Pneumocystis carinii</em> pneumonia: 15-20 mg TMP/kg/24 hr divided q 12 hr PO or IV  <em>P. carinii</em> prophylaxis: 5 mg TMP/kg/24 hr or 3 times/wk PO  Adults: 160 mg TMP q 12 hr PO**&lt;br&gt;Cautions: Drug dosed on TMP (trimethoprim) component. Sulfonylurea skin reactions: rash, erythema multiforme, Stevens-Johnson syndrome, nausea, leukopenia. Renal and hepatic elimination; reduce dose in renal failure**&lt;br&gt;Drug interactions: Protein displacement with warfarin, possibly phenytoin, cyclosporine</td>
<td><strong>Continued</strong></td>
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</table>

*In the Drug column, the generic drug name is in **bold**. In the Indications column, **bold** indicates major organisms targeted and mechanisms of action.*
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<td><strong>Daptomycin</strong> &lt;br&gt; Cubicin</td>
<td>Disrupts bacterial cell membrane function, causing depolarization leading to inhibition of protein, DNA and RNA synthesis, which results in bacterial cell death. Active against enterococci (including glycopeptide-resistant strains), staphylococci (including MRSA), streptococci, and corynebacteria. Approved for skin and soft-tissue infections. Acceptable for bacteremia and right-sided endocarditis with susceptible strains. Adults: In skin and soft-tissue infections, 4 mg/kg daptomycin is given intravenously once daily. For S. aureus bacteremia or right-sided endocarditis, the approved dose is 6 mg/kg given intravenously once daily. Children: Unknown. Doses of 5-9 mg/kg/day in once-daily dosing have been reported in pediatric clinical trials.</td>
<td>Cautions: Should not be used for pneumonia as drug inactivated by surfactants. Associated with rash, renal failure, anemia, headache. Is reported to cause myopathy, rhabdomyolysis, and eosinophilic pneumonia. Drug interactions: Should not be administered with statins.</td>
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<tr>
<td><strong>Demeclocycline</strong> &lt;br&gt; Declomycin &lt;br&gt; Tablet: 150, 300 mg &lt;br&gt; Capsule: 150 mg</td>
<td>Tetracycline active against most Gram-positive cocci except Enterococcus, many Gram-negative bacilli, anaerobes, <em>Borrelia burgdorferi</em> (Lyme disease), <em>Mycoplasma</em>, and <em>Chlamydia</em>. Children: 8-12 mg/kg/24 hr divided q 6-12 hr PO. Adults: 150 mg PO q 8-6 hr. Syndrome of inappropriate antidiuretic hormone secretion: 900-1,200 mg/24 hr or 13-15 mg/kg/24 hr divided q 6-8 hr PO with dose reduction based on response to 600-900 mg/24 hr.</td>
<td>Cautions: Teeth staining, possibly permanent (if administered &lt;8 yr of age) with prolonged use; photosensitivity, diabetes insipidus, nausea, vomiting, diarrhea, superinfections. Drug interactions: Aluminum-, calcium-, magnesium-, zinc- and iron-containing food, milk, dairy products may decrease absorption.</td>
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<tr>
<td><strong>Dicloxacillin</strong> &lt;br&gt; Dynapen, Pathocil &lt;br&gt; Capsule: 125, 250, 500 mg &lt;br&gt; Suspension: 62.5 mg/5 mL</td>
<td>Penicillinase-resistant penicillin active against <em>S. aureus</em> and other Gram-positive cocci except <em>Enterococcus</em> and coagulase-negative staphylococci. Children: 12.5-100 mg/kg/24 hr divided q 6 hr PO. Adults: 125-500 mg q 6 hr PO.</td>
<td>Cautions: β-Lactam safety profile (rash, eosinophilia). Primarily renal (65%) and biliary (30%) elimination. Food may decrease bioavailability. Drug interaction: Probenecid.</td>
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<tr>
<td><strong>Doripenem</strong> &lt;br&gt; Doribax &lt;br&gt; Injection</td>
<td>Carbapenem antibiotic with broad-spectrum activity against Gram-positive cocci and Gram-negative bacilli, including <em>P. aeruginosa</em> and anaerobes. Children: dose unknown. Adults: 500 mg q 8 hr IV.</td>
<td>Cautions: β-Lactam safety profile; does not undergo hepatic metabolism. Renal elimination (70-75%); dose adjustment for renal failure. Drug interactions: Valproic acid, probenecid.</td>
</tr>
<tr>
<td><strong>Doxycycline</strong> &lt;br&gt; Vibramycin, Doxy &lt;br&gt; Injection &lt;br&gt; Capsule: 50, 100 mg &lt;br&gt; Tablet: 50, 100 mg &lt;br&gt; Suspension: 25 mg/5 mL &lt;br&gt; Syrup: 50 mg/5 mL</td>
<td>Tetracycline antibiotic active against most Gram-positive cocci except <em>Enterococcus</em>, many Gram-negative bacilli, anaerobes, <em>B. burgdorferi</em> (Lyme disease), <em>Mycoplasma</em>, and <em>Chlamydia</em>. Children: 2-5 mg/kg/24 hr divided q 12-24 hr PO or IV (max dose: 200 mg/24 hr). Adults: 100-200 mg/24 hr divided q 12-24 hr PO or IV.</td>
<td>Cautions: Teeth staining, possibly permanent (&lt;8 yr of age) with prolonged use; photosensitivity, nausea, vomiting, diarrhea, superinfections. Drug interactions: Aluminum-, calcium-, magnesium-, zinc-, iron-, kaolin-, and pectin-containing foods, milk, dairy products may decrease absorption. Carbamazepine, rifampin, barbiturates may decrease half-life.</td>
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<tr>
<td><strong>Erythromycin</strong> &lt;br&gt; E-Mycin, Ery-Tab, Eryc, Ilosone</td>
<td>Bacteriostatic macrolide antibiotic most active against Gram-positive organisms, <em>Corynebacterium diphtheriae</em>, and <em>Mycoplasma pneumoniae</em>. Neonates: Postnatal age ≤7 days: 20 mg/kg/24 hr divided q 12 hr PO; &gt;7 days weight ≤1,200 g: 20 mg/kg/24 hr divided q 12 hr PO; weight &gt;1,200 g: 30 mg/kg/24 hr divided q 8 hr PO (give as 5 mg/kg/dose q 6 hr to improve feeding intolerance). Children: Usual max dose 2 g/24 hr. Base: 30-50 mg/kg/24 hr divided q 6-8 hr PO. Estolate: 30-50 mg/kg/24 hr divided q 6-8 hr PO. Stearate: 20-40 mg/kg/24 hr divided q 6 hr PO. Lactobionate: 20-40 mg/kg/24 hr divided q 6-8 hr PO. Gluceptate: 20-50 mg/kg/24 hr divided q 6 hr PO; usual max dose 4 g/24 hr IV. Adults: Base: 333 mg PO q 8 hr; estolate/stearate/base: 250-500 mg q 6 hr PO.</td>
<td>Cautions: Motilin agonist leading to marked abdominal cramping, nausea, vomiting, diarrhea. Associated with hypertrophic pyloric stenosis in young infants. Many different salts with questionable tempering of gastrointestinal adverse events. Rare cardiac toxicity with IV use. Dose of salts differ. Topical formulation for treatment of acne. Drug interactions: Antagonizes hepatic CYP 3A4 activity: astemizole, carbamazepine, terfenadine, cyclosporine, theophylline, digoxin, tacrolimus, carbamazepine.</td>
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<td>Gentamicin Garamycin Injection Ophthalmic solution, ointment, topical cream</td>
<td>Aminoglycoside antibiotic active against Gram-negative bacilli, especially <em>E. coli</em>, <em>Klebsiella</em>, <em>Proteus</em>, <em>Enterobacter</em>, <em>Serratia</em>, and <em>Pseudomonas</em> Neonates: Postnatal age ≤7 days weight 1,200-2,000 g: 2.5 mg/kg q 12-18 hr IV or IM; weight &lt;2,000 g: 2.5 mg/kg q 12 hr IV or IM; postnatal age &gt;7 days weight 1,200-2,000 g: 2.5 mg/kg q 8-12 hr IV or IM; weight &gt;2,000 g: 2.5 mg/kg q 8 hr IV or IM Children: 2.5 mg/kg/24 hr divided q 8-12 hr IV or IM. Alternatively may administer 5-7.5 mg/kg/24 hr IV once daily Intrathecal: Preservative-free preparation for intraventricular or intrathecal use: neonate: 1 mg/24 hr; children: 1-2 mg/24 hr intrathecal; adults: 4-8 mg/24 hr Adults: 3-6 mg/kg/24 hr divided q 8 hr IV or IM</td>
<td>Cautions: Anaerobes, <em>S. pneumoniae</em>, and other Streptococcus are resistant. May cause ototoxicity and nephrotoxicity. Monitor renal function. Drug eliminated renally. Administered IV over 30-60 min Drug interactions: May potentiate other ototoxic and nephrototoxic drugs Target serum concentrations: Peak 6-12 mg/L; trough &gt;2 mg/L with intermittent daily dose regimens only</td>
</tr>
<tr>
<td>Imipenem-cilastatin Primaxin Injection</td>
<td>Carbapenem antibiotic with broad-spectrum activity against Gram-positive cocci and Gram-negative bacilli, including <em>P. aeruginosa</em> and anaerobes. No activity against <em>Stenotrophomonas maltophilia</em> Neonates: Postnatal age ≤7 days weight &lt;1,200 g: 20 mg/kg q 18-24 hr IV or IM; weight &gt;1,200 g: 40 mg/kg divided q 12 hr IV or IM; postnatal age &gt;7 days weight 1,200-2,000 g: 40 mg/kg q 12 hr IV or IM; weight &gt;2,000 g: 60 mg/kg q 8 hr IV or IM Children: 60-100 mg/kg/24 hr divided q 6-8 hr IV or IM Adults: 2-4 g/24 hr divided q 6-8 hr IV or IM (max dose: 4 g/24 hr)</td>
<td>Cautions: ß-Lactam safety profile (rash, eosinophilia), nausea, seizures. Cilastatin possesses no antibacterial activity; reduces renal imipenem metabolism. Primarily renally eliminated Drug interaction: Possibly ganciclovir</td>
</tr>
<tr>
<td>Linezolid Zyvox Tablet: 400, 600 mg Oral suspension: 100 mg/5 mL Injection: 100 mg/5 mL</td>
<td>Oxazolidinone antibiotic active against Gram-positive cocci (especially drug-resistant organisms), including <em>Staphylococcus</em>, <em>Streptococcus</em>, <em>E. faecium</em>, and <em>Enterococcus faecalis</em>. Interferes with protein synthesis by binding to 50S ribosome subunit Children: 10 mg/kg q 12 hr IV or PO; Adults: Pneumonia: 600 mg q 12 hr IV or PO; skin infections: 400 mg q 12 hr IV or PO</td>
<td>Adverse events: Myelosuppression, pseudomembranous colitis, nausea, diarrhea, headache Drug interaction: Probenecid</td>
</tr>
<tr>
<td>Loracarbef Lorabid Capsule: 200 mg Suspension: 100 mg/5 mL, 200 mg/5 mL</td>
<td>Carbacephem very closely related to cefaclor (second-generation cephalosporin) active against <em>S. aureus</em>, <em>Streptococcus</em>, <em>H. influenzae</em>, <em>M. catarrhalis</em>, <em>E. coli</em>, <em>Klebsiella</em>, and <em>Proteus</em> Children: 30 mg/kg/24 hr divided q 12 hr PO (max dose: 2 g) Adults: 200-400 mg q 12 hr PO (max dose: 800 mg/24 hr)</td>
<td>Cautions: ß-Lactam safety profile (rash, eosinophilia). Renally eliminated Drug interaction: Probenecid</td>
</tr>
<tr>
<td>Meropenem Merrem Injection</td>
<td>Carbapenem antibiotic with broad-spectrum activity against Gram-positive cocci and Gram-negative bacilli, including <em>P. aeruginosa</em> and anaerobes. No activity against <em>S. maltophilia</em> Children: 60 mg/kg/24 hr divided q 8 hr IV meningitis: 120 mg/kg/24 hr (max dose: 6 g/24 hr) q 8 hr IV Adults: 1.5-3 g q 8 hr IV</td>
<td>Cautions: ß-Lactam safety profile; appears to possess less CNS excitation than imipenem. 80% renal elimination Drug interaction: Probenecid</td>
</tr>
<tr>
<td>Metronidazole Flagyl, Metro I.V., Topical gel, vaginal gel Injection Tablet: 250, 500 mg</td>
<td>Highly effective in the treatment of infections caused by anaerobes. Oral therapy of <em>C. difficile</em> colitis Neonates: weight &lt;1,200 g: 7.5 mg/kg 48 hr PO or IV; postnatal age ≤7 days weight 1,200-2,000 g: 7.5 mg/kg/24 hr q 24 hr PO or IV; weight 2,000 g: 15 mg/kg/24 hr divided q 12 hr PO or IV; postnatal age &lt;7 days weight 1,200-2,000 g: 15 mg/kg/24 hr divided q 12 hr PO or IV; weight &gt;2,000 g: 30 mg/kg/24 hr divided q 12 hr PO or IV Children: 30 mg/kg/24 hr divided q 6-8 hr PO or IV Adults: 30 mg/kg/24 hr divided q 6 hr PO or IV (max dose: 4 g/24 hr)</td>
<td>Cautions: Dizziness, seizures, metallic taste, nausea, disulfiram-like reaction with alcohol. Administer IV slow over 30-60 min. Adjust dose with hepatic impairment Drug interactions: Carbamazepine, rifampin, phenobarbital may enhance metabolism; may increase levels of warfarin, phenytoin, lithium</td>
</tr>
</tbody>
</table>

*In the Drug column, the generic drug name is in **bold**. In the Indications column, **bold** indicates major organisms targeted and mechanisms of action.*
<table>
<thead>
<tr>
<th>DRUG (TRADE NAMES, FORMULATIONS)</th>
<th>INDICATIONS (MECHANISM OF ACTION) AND DOSING</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mezlocillin sodium</strong></td>
<td>Extended-spectrum penicillin active against <em>E. coli</em>, <em>Enterobacter, Serratia, and Bacteroides</em>; limited antipseudomonal activity</td>
<td>Cautions: β-Lactam safety profile (rash, eosinophilia); painful given intramuscularly; each gram contains 1.8 mEq sodium. Interferes with platelet aggregation with high doses; increases noted in liver function test results. Renally eliminated. Inactivated by β-lactamase enzyme. Drug interaction: Probenecid.</td>
</tr>
</tbody>
</table>
| Mezin                        | **Neonates:** Postnatal age ≤7 days: 150 mg/kg/24 hr divided q 12 hr IV; >7 days: 225 mg/kg divided q 8 hr IV  
**Children:** 200-300 mg/kg/24 hr divided q 4-6 hr IV; cystic fibrosis 300-450 mg/kg/24 hr IV  
**Adults:** 2-4 g/dose q 4-6 hr IV (max dose: 12 g/24 hr) | Caution: Minimal systemic absorption as drug metabolized within the skin. |
| **Mupirocin**  | Topical antibiotic active against *Staphylococcus and Streptococcus*  
**Topical application:** Nasal (eliminate nasal carriage) and to the skin 2-4 times per day | |
| **Nafcil, Unipen**  | Penicillinase-resistant penicillin active against *S. aureus* and other Gram-positive cocci, except *Enterococcus and coagulase-negative staphylococci*  
**Neonates:** Postnatal age ≤7 days weight 1,200-2,000 g: 50 mg/kg/24 hr divided q 12 hr IV or IM; weight >2,000 g: 75 mg/kg/24 hr divided q 8 hr IV or IM; postnatal age >7 days weight 1,200-2,000 g: 75 mg/kg/q 8 hr weight >2,000 g: 100 mg/kg divided q 6-8 hr IV (meningitis: 200 mg/kg/24 hr divided q 6 hr IV)  
**Children:** 100-200 mg/kg/24 hr divided q 4-6 hr IV  
**Adults:** 4-12 g/24 hr divided q 4-6 hr IV (max dose: 12 g/24 hr) | Cautions: β-Lactam safety profile (rash, eosinophilia), phlebitis; painful given intramuscularly; oral absorption highly variable and erratic (not recommended)  
Adverse effect: Neutropenia. |
| **NegGram**  | First-generation quinolone effective for short-term treatment of lower urinary tract infections caused by *E. coli, Enterobacter, Klebsiella, and Proteus*  
**Children:** 50-55 mg/kg/24 hr divided q 6 hr PO; suppressive therapy 25-33 mg/kg/24 hr divided q 6-8 hr PO  
**Adults:** 1 g q 6 hr PO; suppressive therapy: 500 mg q 6 hr PO | Cautions: Vertigo, dizziness, rash. Not for use in systemic infections  
Drug interactions: Liquid antacids. |
| **NegGram**  | Aminoglycoside antibiotic used for topical application or orally before surgery to decrease gastrointestinal flora (nonabsorbable) and hyperammonemia  
**Infants:** 50 mg/kg/24 hr divided q 6 hr PO  
**Children:** 50-100 mg/kg/24 hr divided q 6-8 hr PO  
**Adults:** 500-2,000 mg/dose q 6-8 hr PO | Cautions: In patients with renal dysfunction because small amount absorbed may accumulate  
Adverse events: Primarily related to topical application, abdominal cramps, diarrhea, rash  
Aminoglycoside ototoxicity and nephrotoxicity if absorbed. |
| **Nitrofurantoin**  | Effective in the treatment of lower urinary tract infections caused by Gram-positive and Gram-negative pathogens  
**Children:** 5-7 mg/kg/24 hr divided q 6 hr PO  
**Children:** 5-7 mg/kg/24 hr divided q 6 hr PO (max dose: 400 mg/24 hr); suppressive therapy 1-2.5 mg/kg/24 hr divided q 12-24 hr PO (max dose: 100 mg/24 hr)  
**Adults:** 50-100 mg/24 hr divided q 6 hr PO | Cautions: Vertigo, dizziness, rash, jaundice, interstitial pneumonitis. Do not use with moderate to severe renal dysfunction  
Drug interactions: Liquid antacids. |
| **Ofloxacin**  | Quinolone antibiotic for treatment of conjunctivitis or corneal ulcers (ophthalmic solution) and otitis externa or chronic suppurative otitis media (otic solution) caused by susceptible Gram-positive, Gram-negative, anaerobic bacteria, or *C. trachomatis*  
**Child** >1-12 yr:  
Conjunctivitis: 1-2 drops in affected eye(s) q 2-4 hr for 2 days, then 1-2 drops qid for 5 days  
Corneal ulcers: 1-2 drops q 30 min while awake and at 4 hr intervals at night for 2 days, then 1-2 drops hourly for 5 days while awake, then 1-2 drops q 6 hr for 2 days  
Otitis externa (otic solution): 5 drops into affected ear bid for 10 days  
**Child** >12 yr and adults: Ophthalmic solution doses same as for younger children. Otitis externa (otic solution): Use 10 drops bid for 10 or 14 days as for younger children | Adverse events: Burning, stinging, eye redness (ophthalmic solution), dizziness with otic solution if not warmed. |

*In the Drug column, the generic drug name is in **bold**. In the Indications column, **bold** indicates major organisms targeted and mechanisms of action.*
### Table 180-3  Antibacterial Medications (Antibiotics)—cont’d

<table>
<thead>
<tr>
<th>DRUG (TRADE NAMES, FORMULATIONS)</th>
<th>INDICATIONS (MECHANISM OF ACTION) AND DOSING</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Oxacillin sodium</strong>&lt;br&gt;Prostaphlin Injection&lt;br&gt;Capsule: 250, 500 mg&lt;br&gt;Suspension: 250 mg/5 mL</td>
<td>Penicillinase-resistant penicillin active against S. aureus and other Gram-positive cocci, except Enterococcus and coagulase-negative staphylococci&lt;br&gt;Neonates: Postnatal age ≤7 days weight 1,200-2,000 g: 50 mg/kg/24 hr divided q 12 hr IV, weight &gt;2,000 g: 75 mg/kg/24 hr IV divided q 8 hr IV; postnatal age &gt;7 days weight ≤1,200 g: 50 mg/kg/24 hr IV divided q 12 hr IV, weight &gt;1,200 g: 75 mg/kg/24 hr divided q 8 hr IV, weight &gt;2,000 g: 100 mg/kg/24 hr IV divided q 6 hr IV&lt;br&gt;Infants: 100-200 mg/kg/24 hr divided q 4-6 hr IV&lt;br&gt;Children: PO 50-100 mg/kg/24 hr divided q 4-6 hr IV&lt;br&gt;Adults: 2-12 g/24 hr divided q 4-6 hr IV (max dose: 12 g/24 hr)</td>
<td>Cautions: β-Lactam safety profile (rash, eosinophilia). Moderate oral bioavailability (35-65%). Primarily renally eliminated. Drug interaction: Probenecid. Adverse effect: Neutropenia.</td>
</tr>
<tr>
<td><strong>Penicillin G</strong>&lt;br&gt;Injection Tablets</td>
<td>Penicillin active against most Gram-positive cocci; <em>S. pneumoniae</em> (resistance is increasing), group A Streptococcus, and some Gram-negative bacteria (e.g., <em>N. gonorrhoeae, N. meningitidis</em>)&lt;br&gt;Neonates: Postnatal age ≤7 days weight 1,200-2,000 g: 50,000 units/kg/24 hr divided q 12 hr IV or IM (meningitis: 100,000 units/kg/24 hr divided q 12 hr IV or IM); weight &gt;2,000 g: 75,000 units/kg/24 hr divided q 8 hr IV or IM (meningitis: 150,000 units/kg/24 hr divided q 8 hr IV or IM); postnatal age &gt;7 days weight ≤1,200 g: 50,000 units/kg/24 hr divided q 12 hr IV (meningitis: 100,000 units/kg/24 hr divided q 12 hr IV); weight 1,200-2,000 g: 75,000 units/kg/24 hr q 8 hr IV (meningitis: 225,000 units/kg/24 hr divided q 12 hr IV); weight &gt;2,000 g: 100,000 units/kg/24 hr divided q 6 hr IV (meningitis: 200,000 units/kg/24 hr divided q 6 hr IV)&lt;br&gt;Children: 100,000-250,000 units/kg/24 hr divided q 4-6 hr IV or IM (max dose: 400,000 units/kg/24 hr)&lt;br&gt;Adults: 2-24 million units/24 hr divided q 4-6 hr IV or IM</td>
<td>Cautions: β-Lactam safety profile (rash, eosinophilia), allergy, seizures with excessive doses particularly in patients with marked renal disease. Substantial pathogen resistance. Primarily renally eliminated. Drug interaction: Probenecid.</td>
</tr>
<tr>
<td><strong>Penicillin G, benzathine</strong>&lt;br&gt;Bicillin Injection</td>
<td>Long-acting repository form of penicillin effective in the treatment of infections responsive to persistent, low penicillin concentrations (1-4 wk), e.g., group A Streptococcus pharyngitis, rheumatic fever prophylaxis&lt;br&gt;Neonates: weight &gt;1,200 g: 50,000 units/kg IM once&lt;br&gt;Children: 300,000-1,200,000 units/kg q 3-4 wk IM (max dose: 1.2-2.4 million units/dose)&lt;br&gt;Adults: 1.2 million units IM q 3-4 wk</td>
<td>Cautions: β-Lactam safety profile (rash, eosinophilia). Allergy. Administer by IM injection only. Substantial pathogen resistance. Primarily renally eliminated. Drug interaction: Probenecid.</td>
</tr>
<tr>
<td><strong>Penicillin G, procaine</strong>&lt;br&gt;Crysticillin Injection</td>
<td>Repository form of penicillin providing low penicillin concentrations for 12 hr&lt;br&gt;Neonates: weight ≥1,200 g: 50,000 units/kg/24 hr IM&lt;br&gt;Children: 25,000-50,000 units/kg/24 hr IM for 10 days (max dose: 4.8 million units/dose)&lt;br&gt;Gonorrhea: 100,000 units/kg (max dose: 4.8 million units/24 hr) IM once with probenecid 25 mg/kg (max dose: 1 g)&lt;br&gt;Adults: 0.6-4.8 million units q 12-24 hr IM</td>
<td>Cautions: β-Lactam safety profile (rash, eosinophilia). Allergy. Seizures with excessive doses particularly in patients with marked renal disease. Substantial pathogen resistance. Primarily renally eliminated. Drug interaction: Probenecid.</td>
</tr>
<tr>
<td><strong>Penicillin V</strong>&lt;br&gt;Pen VK, V-Cillin K&lt;br&gt;Tablet: 125, 250, 500 mg&lt;br&gt;Suspension: 125 mg/5 mL, 250 mg/5 mL</td>
<td>Preferred oral dosing form of penicillin, active against most Gram-positive cocci; <em>S. pneumoniae</em> (resistance is increasing), other streptococci, and some Gram-negative bacteria (e.g., <em>N. gonorrhoeae, N. meningitidis</em>)&lt;br&gt;Children: 25-50 mg/kg/24 hr divided q 4-8 hr PO&lt;br&gt;Adults: 125-500 mg q 6-8 hr PO (max dose: 3 g/24 hr)</td>
<td>Cautions: β-Lactam safety profile (rash, eosinophilia). Allergy, seizures with excessive doses particularly in patients with renal disease. Substantial pathogen resistance. Primarily renally eliminated. Inactivated by penicillinase. Drug interaction: Probenecid.</td>
</tr>
<tr>
<td><strong>Piperacillin</strong>&lt;br&gt;Pipracil Injection</td>
<td>Extended-spectrum penicillin active against <em>E. coli, Enterobacter, Serratia, P. aeruginosa, and Bacteroides</em>&lt;br&gt;Neonates: Postnatal age ≤7 days 150 mg/kg/24 hr divided q 8-12 hr IV; &gt;7 days: 200 mg/kg divided q 6-8 hr IV&lt;br&gt;Children: 200-300 mg/kg/24 hr divided q 4-6 hr IV; cystic fibrosis: 350-500 mg/kg/24 hr IV&lt;br&gt;Adults: 2.4 g/dose q 4-6 hr (max dose: 24 g/24 hr IV)</td>
<td>Cautions: β-Lactam safety profile (rash, eosinophilia). Painful given intramuscularly; each gram contains 1.9 mEq sodium. Interferes with platelet aggregation/serum sickness-like reaction with high doses; increases in liver function tests. Renally eliminated. Inactivated by penicillinase. Drug interaction: Probenecid.</td>
</tr>
</tbody>
</table>

*In the Drug column, the generic drug name is in **bold**. In the Indications column, **bold** indicates major organisms targeted and mechanisms of action.*
Table 180-3  Antibacterial Medications (Antibiotics)—cont’d

<table>
<thead>
<tr>
<th>DRUG (TRADE NAMES, FORMULATIONS)</th>
<th>INDICATIONS (MECHANISM OF ACTION) AND DOSING</th>
<th>COMMENTS</th>
</tr>
</thead>
</table>
| **Piperacillin-tazobactam**  
Zosyn  
Injection | Extended-spectrum penicillin (piperacillin) combined with a β-lactamase inhibitor (tazobactam) active against *S. aureus*, *H. influenzae*, *E. coli*, *Enterobacter*, *Serratia*, *Acinetobacter*, *P. aeruginosa*, and *Bacteroides*  
Children: 300-400 mg/kg/24 hr divided q 6-8 hr IV or IM  
Adults: 3.375 g q 6-8 hr IV or IM | Cautions: β-Lactam safety profile (rash, eosinophilia); painful given intramuscularly; each gram contains 1.9 mEq sodium  
Interferes with platelet aggregation, serum sickness–like reaction with high doses, increases in liver function test results. Renally eliminated  
Drug interaction: Probencid |
| **Quinupristin/dalfopristin**  
Synercid  
IV injection: powder for reconstitution, 10 mL contains 150 mg quinupristin, 350 mg dalfopristin | Streptogramin antibiotic (quinupristin) active against vancomycin-resistant *E. faecium* (VRE) and methicillin-resistant *S. aureus* (MRSA). Not active against *E. faecalis*  
Children and adults: VRE: 7.5 mg/kg q 8 hr for VRE; skin infections: 7.5 mg/kg q 12 hr IV | Adverse events: Pain, edema, or phlebitis at injection site, nausea, diarrhea  
Drug interactions: Synercid is a potent inhibitor of CYP 3A4 |
| **Sulfadiazine**  
Tablet: 500 mg | Sulfonamide antibiotic primarily indicated for the treatment of lower urinary tract infections caused by *E. coli*, *P. mirabilis*, and *Klebsiella*  
Toxoplasmosis  
Neonates: 100 mg/kg/24 hr divided q 12 hr PO with pyrimethamine 1 mg/kg/24 hr PO (with folinic acid)  
Children: 120-200 mg/kg/24 hr divided q 6 hr PO with pyrimethamine 2 mg/kg/24 hr divided q 12 hr PO ≥3 days then 1 mg/kg/24 hr (max dose: 25 mg/24 hr) with folinic acid  
Rheumatic fever prophylaxis: weight ≤30 kg: 500 mg/24 hr q 24 hr PO; weight >30 kg: 1 g/24 hr q 24 hr PO | Cautions: Rash, Stevens-Johnson syndrome, nausea, leukopenia, crystalluria. Renal and hepatic elimination; avoid use with renal disease. Half-life ~10 hr  
Drug interactions: Protein displacement with warfarin, phenytoin, methotrexate |
| **Sulfamethoxazole**  
Gantanol  
Tablet: 500 mg  
Suspension: 500 mg/5 mL  
Ophthalmic solution, ointment | Sulfonamide antibiotic used for the treatment of otitis media, chronic bronchitis, and lower urinary tract infections due to susceptible bacteria  
Children: 50-60 mg/kg/24 hr divided q 12 hr PO  
Adults: 1 g/dose q 12 hr PO (max dose: 3 g/24 hr) | Cautions: Rash, Stevens-Johnson syndrome, nausea, leukopenia, crystalluria. Renal and hepatic elimination; avoid use with renal disease. Half-life 12 hr. Initial dose often a loading dose (doubled)  
Drug interactions: Protein displacement with warfarin, phenytoin, methotrexate |
| **Sulfisoxazole**  
Gantrisin  
Tablet: 500 mg  
Suspension: 500 mg/5 mL  
Ophthalmic solution, ointment | Sulfonamide antibiotic used for the treatment of otitis media, chronic bronchitis, and lower urinary tract infections caused by susceptible bacteria  
Children: 120-150 mg/kg/24 hr divided q 4-6 hr PO  
Adults: 4-8 g/24 hr divided q 4-6 hr PO | Cautions: Rash, Stevens-Johnson syndrome, nausea, leukopenia, crystalluria. Renal and hepatic elimination; avoid use with renal disease. Half-life ~7-12 hr. Initial dose often a loading dose (doubled)  
Drug interactions: Protein displacement with warfarin, phenytoin, methotrexate |
| **Ticarcillin**  
Ticar  
Injection | Extended-spectrum penicillin (ticarcillin) combined with a β-lactamase inhibitor (clavulanate) active against *S. aureus*, *H. influenzae*, *Enterobacter*, *E. coli*, *Serratia*, *P. aeruginosa*, *Acinetobacter*, and *Bacteroides*  
Children: 280-400 mg/kg/24 hr q 4-8 hr IV or IM  
Adults: 3.1 g q 4-8 hr IV or IM (max dose: 18-24 g/24 hr) | Cautions: β-Lactam safety profile (rash, eosinophilia); painful given intramuscularly; each gram contains 5-6 mEq sodium. Interferes with platelet aggregation, increases in liver function tests. Renally eliminated  
Drug interaction: Probencid |

*In the Drug column, the generic drug name is in **bold**. In the Indications column, **bold** indicates major organisms targeted and mechanisms of action.*
Resistance to penicillin is mediated by a variety of mechanisms (see Table 180-1). The production of β-lactamase is a common mechanism exhibited by many organisms that may be overcome, with variable success, by including a β-lactamase inhibitor with the penicillin. Such combination products (ampicillin-sulbactam, amoxicillin-clavulanate, piperacillin-tazobactam) are potentially very useful for management of resistant isolates, but only if the resistance is β-lactamase mediated. Notably, S. aureus and S. pneumoniae mediate β-lactam resistance through mechanisms other than β-lactamase production, rendering these combination agents of little value for the management of β-lactam–resistant S. aureus and S. pneumoniae infections.

Table 180-4 lists adverse reactions to penicillins.

**Cephalosporins**

Cephalosporins differ structurally from penicillins insofar as the β-lactam ring exists as a 6-member ring, compared to the 5-member ring structure of the penicillins. These agents are widely used in pediatric practice, both in oral and parenteral formulations (Table 180-5). The first-generation cephalosporins (e.g., cefazolin, a parenteral formulation, and cephalexin, an oral equivalent) are commonly used for management of skin and soft-tissue infections caused by susceptible strains of S. aureus and group A Streptococcus. The second-generation cephalosporins (e.g., cefuroxime, cefoxitin) have better activity against Gram-negative bacilli, especially E. coli, Klebsiella, Enterobacter, Serratia, Proteus, and Pseudomonas (e.g., cefuroxime, cefoxitin) have better activity against Gram-negative bacilli, especially E. coli, Klebsiella, Enterobacter, Serratia, Proteus, and Pseudomonas. Cautions: Pregnancy; children <8 yr of age; photosensitivity; hypersensitivity to tetracyclines; hepatic impairment (~60% hepatic clearance)

Drug interaction: Warfarin; mycophenolate mofetil

### Table 180-3 Antibacterial Medications (Antibiotics)—cont’d

<table>
<thead>
<tr>
<th>DRUG (TRADE NAMES, FORMULATIONS)</th>
<th>INDICATIONS (MECHANISM OF ACTION) AND DOSING</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tigecycline Tygacil Injection</td>
<td>Tetracycline-class antibiotic (glycylcycline) active against Enterobacteriaceae, including extended spectrum β-lactamase producers; streptococci (including VRE); staphylococci (including MRSA); and anaerobes</td>
<td>Cautions: Pregnancy; children &lt;8 yr of age; photosensitivity; hypersensitivity to tetracyclines; hepatic impairment (~60% hepatic clearance) Drug interaction: Warfarin; mycophenolate mofetil</td>
</tr>
<tr>
<td>Tobramycin Nebcin, Tobrex Injection Ophthalmic solution, ointment</td>
<td>Aminoglycoside antibiotic active against Gram-negative bacilli, especially E. coli, Klebsiella, Enterobacter, Serratia, Proteus, and Pseudomonas</td>
<td>Cautions: S. pneumoniae, other Streptococcus, and anaerobes are resistant. May cause ototoxicity and nephrotoxicity. Monitor renal function. Drug eliminated renally. Administered IV over 30-60 min Drug interactions: May potentiate other ototoxic and nephrotoxic drugs Target serum concentrations: Peak 6-12 mg/L; trough &lt;2 mg/L</td>
</tr>
<tr>
<td>Trimethoprim Proloprim, Trimpex Tablet: 100, 200 mg</td>
<td>Folic acid antagonist effective in the prophylaxis and treatment of E. coli, Klebsiella, P. mirabilis, and Enterobacter urinary tract infections; P. carinii pneumonia</td>
<td>Cautions: Megaloblastic anemia, bone marrow suppression, nausea, epigastric distress, rash Drug interactions: Possible interactions with phenytoin, cyclosporine, rifampin, warfarin</td>
</tr>
<tr>
<td>Vancomycin Vancocin, Lyphocin Injection Capsule: 125 mg, 250 mg Suspension</td>
<td>Glycopeptide antibiotic active against most Gram-positive pathogens including staphylococci (including MRSA and coagulase-negative staphylococci), S. pneumoniae including penicillin-resistant strains, Enterococcus (resistance is increasing), and C. difficile–associated colitis</td>
<td>Cautions: Ototoxicity and nephrotoxicity particularly when co-administered with other ototoxic and nephrotoxic drugs Infuse IV over 45-60 min. Flushing (red man syndrome) associated with rapid IV infusions, fever, chills, phlebitis (central line is preferred). Renally eliminated Target serum concentrations: Peak (1 hr after 1 hr infusion) 30-40 mg/L; trough 5-10 mg/L</td>
</tr>
</tbody>
</table>

*In the Drug column, the generic drug name is in **bold**. In the Indications column, **bold** indicates major organisms targeted and mechanisms of action.*
**Table 180-4** Adverse Reactions to Penicillins*

<table>
<thead>
<tr>
<th>TYPE OF REACTION</th>
<th>FREQUENCY (%)</th>
<th>OCCURS MOST FREQUENTLY WITH*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ALLERGIC</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immunoglobulin E antibody</td>
<td>0.004-0.4</td>
<td>Penicillin G</td>
</tr>
<tr>
<td>• Anaphylaxis (&lt;72 hr)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cytotoxic antibody</td>
<td>Rare</td>
<td>Penicillin G</td>
</tr>
<tr>
<td>• Hemolytic anemia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antibody–antibody complex disease</td>
<td>Rare</td>
<td>Penicillin G</td>
</tr>
<tr>
<td>• Serum sickness</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Delayed hypersensitivity</td>
<td>4-8</td>
<td>Ampicillin</td>
</tr>
<tr>
<td>• Contact dermatitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>IDIOPATHIC</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin rash</td>
<td>4-8</td>
<td>Ampicillin</td>
</tr>
<tr>
<td>Fever</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Late-onset urticaria</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>GASTROINTESTINAL</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>2-5</td>
<td>Ampicillin</td>
</tr>
<tr>
<td>Enterocolitis</td>
<td>2-5</td>
<td>Ampicillin</td>
</tr>
<tr>
<td>&lt;1</td>
<td></td>
<td>Ampicillin</td>
</tr>
<tr>
<td><strong>HEMATOLOGIC</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemolytic anemia</td>
<td>Rare</td>
<td>Penicillin G</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>1-4</td>
<td>Penicillin G, nafcillin, oxacillin, piperacillin</td>
</tr>
<tr>
<td>Platelet dysfunction</td>
<td>3</td>
<td>Ticarcillin</td>
</tr>
<tr>
<td><strong>HEPATIC</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elevated serum aspartate transaminase level</td>
<td>1-4</td>
<td>Flucloxacillin, nafcillin, oxacillin</td>
</tr>
<tr>
<td><strong>ELECTROLYTE DISTURBANCE</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sodium overload</td>
<td>Variable</td>
<td>Ticarcillin</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>Variable</td>
<td>Ticarcillin</td>
</tr>
<tr>
<td>Hyperkalemia—acute</td>
<td>Rare</td>
<td>Penicillin G</td>
</tr>
<tr>
<td><strong>NEUROLOGIC</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seizures</td>
<td>Rare</td>
<td>Penicillin G</td>
</tr>
<tr>
<td>Bizarre sensations</td>
<td></td>
<td>Procaine penicillin</td>
</tr>
<tr>
<td><strong>RENAL</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interstitial nephritis</td>
<td>&lt;1%</td>
<td>Any penicillin</td>
</tr>
</tbody>
</table>

*All the reactions can occur with any of the penicillins.


P. aeruginosa, making this a useful agent for febrile, neutropenic oncology patients. Ceftriaxone should not be mixed or reconstituted with a calcium-containing product, such as Ringer or Hartmann solution or parenteral nutrition containing calcium, because particulate formation can result. Cases of fatal reactions with ceftriaxone–calcium precipitates in lungs and kidneys in neonates have been reported. A fourth-generation cephalosporin, called cefepime, has activity against *P. aeruginosa* and retains good activity against methicillin-susceptible staphylococcal infections. A fifth-generation cephalosporin, ceftaro-line has been licensed. It is the active metabolite of the prodrug cefarolone fosamil and is a broad-spectrum cephalosporin with bactericidal activity against resistant Gram-positive organisms, including MRSA, and common Gram-negative pathogens. It has been licensed in adult patients for use in skin and soft-tissue infection and community-acquired bacterial pneumonia. It is indicated for MRSA only in the treatment of skin and soft-tissue infection and not MRSA pneumonia. Its activity is attributed to its ability to bind to penicillin-binding protein 2a with higher affinity than other β-lactams. Its role in pediatric practice remains to be defined. Another fifth-generation cephalosporin, ceftobiprole, has been approved for use in Canada and the European Union. Another novel cephalosporin with activity against *P. aeruginosa*, ceftolozane, is approaching licensure and will be combined with the β-lactamase inhibitor, tazobactam, in its final licensed formulation.

Table 180-6 lists adverse reactions to cephalosporins.

**Carbapenems**

The carbapenems include imipenem formulated in combination with cilastatin, meropenem, ertapenem, and doripenem. The basic structure of these agents is similar to that of β-lactam antibiotics, and these drugs have a similar mechanism of action. The carbapenems provide the broadest spectrum of antibacterial activity of any licensed class of antibiotics and are active against Gram-positive, Gram-negative, and anaerobic organisms. Among the carbapenems, meropenem is the only agent licensed for treatment of pediatric meningitis. At this time, ertapenem and doripenem are not approved for pediatric use. Importantly, MRSA and *E. faecium* are not susceptible to carbapenems. Carbapenems also tend to be poorly active against *Stenotrophomonas maltophilia*, rendering their use for cystic fibrosis patients who are infected with this organism problematic. Ertapenem is poorly active against *P. aeruginosa* and *Acinetobacter* species and should be avoided when these pathogens are encountered. Although imipenem–cilastatin is the first carbapenem approved for clinical use and the carbapenem with which there is the greatest clinical experience, this antibiotic unfortunately has a propensity to cause seizures in children, particularly in the setting of intercurrent meningitis. Accordingly, meropenem is typically more suitable for pediatric use, where meningitis is commonly a consideration.

Other carbapenems in various stages of clinical trials include panipenem, biapenem, razubem, tozopem, and tebipenem/pivoxil (the first oral carbapenem). Panipenem and biapenem are licensed in Japan, but there is minimal experience with pediatric dosing.

**Glycopeptides**

Glycopeptide antibiotics include vancomycin and teicoplanin, the less commonly available analog. These agents are bactericidal and act via inhibition of cell wall biosynthesis. The antimicrobial activity of the glycopeptides is limited to Gram-positive organisms, including *S. aureus*, coagulase-negative staphylococci, pneumococcus, enterococci, *Bacillus*, and *Corynebacterium*. Vancomycin is frequently employed in pediatric practice and is of particular value for serious infections, including meningitis, caused by MRSA and penicillin- and cephalosporin-resistant *S. pneumoniae*. Vancomycin is also commonly used for infections in the setting of fever and neutropenia in oncology patients, in combination with other antibiotics (see Chapter 178), and for infections associated with indwelling medical devices (see Chapter 179). Oral formulations of vancomycin are occasionally used to treat pseudomembranous colitis caused by *Clostridium difficile* infections; intrathecal therapy may also be used for selected CNS infections. Vancomycin must be administered with care because of its propensity to produce red man syndrome, which is a reversible adverse effect that is rare in young children and can typically be readily managed by slowing the rate of infusion of the drug. Newer glycopeptide antibiotics include oritavancin, dalbavancin, and the glycolipodepsipeptide agent, ramoplanin. Telavancin has been approved by FDA for the treatment of skin and soft-tissue infections suspected or known to be caused by MRSA for situations where other alternatives are not suitable.

**Aminoglycosides**

Aminoglycoside antibiotics include streptomycin, kanamycin, gentamicin, tobramycin, netilmicin, and amikacin. The most commonly used aminoglycosides in pediatric practice are gentamicin and tobramycin. They exert their mechanism of action via inhibition of bacterial protein synthesis. Although they are most commonly used to treat Gram-negative infections, the aminoglycosides are broad-spectrum agents: they have activity against *S. aureus* and provide synergistic activity against group B streptococcus, *L. monocytogenes*, viridans
**Table 180-5** Classification of Parenteral and Oral Cephalosporins

<table>
<thead>
<tr>
<th>CEPHALOSPORINS</th>
<th>FIRST GENERATION</th>
<th>SECOND GENERATION</th>
<th>CEPHAMYCINS</th>
<th>THIRD GENERATION</th>
<th>FOURTH GENERATION</th>
<th>FIFTH GENERATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parenteral</td>
<td>Cefazolin (Ancef, Kefzol)</td>
<td>Cefamandole (Mandol)</td>
<td>Cefmetazole (Zefazone)</td>
<td>Cefoperazone (Cefobid)</td>
<td>Cefepime (Maxipime)</td>
<td>Cefaroline (Teflaro)</td>
</tr>
<tr>
<td></td>
<td>Cephalothin (Keflin, Seffin)</td>
<td>Cefonicid (Monocid)</td>
<td>Cefotetan (Cefotan)</td>
<td>Cefotaxime (Claforan)</td>
<td>Cefpirome (Cefrom)</td>
<td>Cefobiprole (Zeftera)</td>
</tr>
<tr>
<td></td>
<td>Cepapirin (Cefadyl)</td>
<td>Cefuroxime (Kefurox, Zincacef)</td>
<td>Cefoxitin (Mefoxin)</td>
<td>Ceftazidime (Fortaz)</td>
<td>Cefotolozane (combined with tazobactam; CZA-101)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cephradine (Velosef)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral</td>
<td>Cefadroxil (Duricef, Ultracef)</td>
<td>Cefaclor (Ceclor)</td>
<td>Cefdinir (Omnicef)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cephalexin (Keflex, Biocef, Keftab)</td>
<td>Cefprozil (Cefzil)</td>
<td>Cefditoren (Spectracef)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cephradine (Velosef)</td>
<td>Cefuroxime-axetil (Ceftin)</td>
<td>Cefixime (Suprax)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Loracarbef (Lorabid)</td>
<td>Cefpodoxime (Vantin)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Cefitbuten (Cedax)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


streptococci, corynebacteria JK, *Pseudomonas, Staphylococcus epidermidis,* and *Enterococcus* when coadministered with a β-lactam agent. Aminoglycoside use has decreased with the development of newer alternatives, but they still play a key role in pediatric practice in the management of neonatal sepsis, urinary tract infections, Gram-negative sepsis, and complicated intraabdominal infections; infections in cystic fibrosis patients (including both parenteral and aerosolized forms of therapy); and in oncology patients with fever and neutropenia. Aminoglycosides, in particular streptomycin, are also important in the management of *Francisella tularensis, Mycobacterium tuberculosis,* and atypical mycobacterial infections. Toxicities of aminoglycoside therapy include nephrotoxicity and otootoxicity (cochlear and/or vestibular), and serum levels as well as renal function and hearing should be monitored for patients on long-term therapy. Toxicities of aminoglycosides may be reduced by the use of once-daily dosing regimens with appropriate monitoring of serum levels, Hypokalemia, volume depletion, hypomagnesemia, and other nephrotoxic drugs may increase the renal toxicity of aminoglycosides. A rare complication of aminoglycosides is neuromuscular blockade, which may occur in the presence of other neuromuscular blocking agents and in the setting of infant botulism.

**Tetracyclines**

The tetracyclines (tetracycline hydrochloride, doxycycline, demeclocycline, and minocycline) are bacteriostatic antibiotics that exhibit their antimicrobial effect by binding to the bacterial 30S ribosomal subunit, inhibiting protein translation. These agents have a broad spectrum of antimicrobial activity against Gram-positive and Gram-negative bacteria, rickettsia, and some parasites. The oral bioavailability of these agents facilitates oral dosing for many infections, including Rocky Mountain spotted fever, ehrlichiosis, Lyme disease, and malaria. Tetracyclines must be prescribed judiciously to children younger than 9 yr of age, because they can cause staining of teeth, hypoplasia of dental enamel, and abnormal bone growth in this age group. Tigecycline, a semisynthetic derivative of minocycline, is licensed in the United States. It is a parenteral agent of a new class of antibiotics (glycylcyclines). It has a broader spectrum of activity (bacteriostatic) than traditional tetracyclines, but retains the side–effect profile of tetracyclines. Tigecycline is active against tetracycline-resistant Gram-positive and Gram-negative pathogens, including MRSA, and possibly VRE, but not *Pseudomonas.*

Complications of tetracyclines include eosinophilia, leukopenia and thrombocytopenia (tetracycline), pseudotumor cerebri, anorexia, emesis and nausea, candidal superinfection, hepatitis, photosensitivity, and a hypersensitivity reaction (urticaria, asthma exacerbation, facial edema, dermatitis) as well as a systemic lupus erythematosus–like syndrome (minocycline). The FDA issued a black box warning regarding tigecycline in 2013 based on a meta-analysis of 10 studies that showed increased mortality among patients receiving this drug. A salutary side effect of demeclocycline has been identified: it is occasionally used as an off-label treatment of hyponatremia resulting from the syndrome of inappropriate antidiuretic hormone.

**Sulfonamides**

Trimethoprim and the sulfonamides are bacteriostatic agents that inhibit the bacterial folate synthesis pathway, in the process impairing both nucleic acid and protein synthesis. Sulfonamides interfere with the synthesis of dihydropteroic acid from paraaminobenzoic acid, whereas trimethoprim acts at a site further downstream, interfering with synthesis of tetrahydrofolic acid from dihydrofoleric acid. The sulfonamides are available in both parenteral and oral formulations. Although there have historically been a large number of sulfonamide antibiotics developed for clinical use, relatively few remain available for pediatric practice. The most important agent is the combination of trimethoprim–sulfamethoxazole (TMP-SMZ), which is commonly used for treatment of urinary tract infections. TMP-SMZ has also emerged as a commonly prescribed agent for staphylococcal skin and soft-tissue infections, since this antibiotic retains activity against MRSA. TMP-SMZ also plays a unique role in immunocompromised patients, as a prophylactic and therapeutic agent for *Pneumocystis jiroveci* infection. Other commonly used sulfonamides include sulfisoxazole, which is useful in the management of urinary tract infections, and sulfadiazine, which is a drug of choice in the treatment of toxoplasmosis.
Drug interactions are common with erythromycin and telithromycin and to a lesser extent with clarithromycin. These agents can inhibit the CYP 3A4 enzyme system, resulting in increased levels of certain drugs such as astemizole, cisapride, statins, pimozide, and theophylline. Itraconazole may increase macrolide levels, while rifampin, carbamazepine, and phenytoin may decrease macrolide levels. There are few reported adverse drug interactions with azithromycin. Cross-resistance may develop between a macrolide and the subsequent use of clindamycin.

**Lincosamides**

The prototype of the lincosamide class of antibiotics is clindamycin, which acts at the ribosomal level to exert its antimicrobial effect. The 50S subunit of the bacterial ribosome is the molecular target of this agent. Its spectrum of activity includes Gram-positive aerobes and anaerobes. Clindamycin has no significant activity against Gram-negative organisms. An important role for clindamycin has emerged in the management of MRSA infections. Because of its outstanding penetration into body fluids (excluding the CNS) and tissues and bone, clindamycin can be utilized for therapy of serious infections caused by MRSA. Clindamycin is also useful in the management of invasive group A Streptococcus infections and in the management of many anaerobic infections, often in combination with a β-lactam. There is a form of **inducible clindamycin resistance** exhibited by some strains of MRSA; therefore, consultation with the clinical microbiology laboratory is necessary before treating a serious MRSA infection with clindamycin. Pseudomembranous colitis, a complication of clindamycin therapy commonly encountered in adults, is seldom observed in pediatric patients. Clindamycin also plays an important role in the treatment of malaria and babesiosis (when coadministered with quinine), P. jiroveci pneumonia (when coadministered with primaquine), and toxoplasmosis.

**Quinolones**

The fluoroquinolones (ciprofloxacin, levofloxacin, moxifloxacin, gemifloxacin, besifloxacin) are antimicrobials that inhibit bacterial DNA replication by binding to the topoisomerases of the target pathogen, inhibiting the bacterial enzyme DNA gyrase. This class has very broad-spectrum activity against both Gram-positive and Gram-negative organisms. Some of the fluoroquinolones exhibit activity against penicillin-resistant S. pneumoniae as well as MRSA. These agents uniformly exhibit excellent activity against Gram-negative pathogens, including the Enterobacteriaceae and respiratory tract pathogens such as *M. catarrhalis* and *H. influenzae*. Quinolones are also very active against pathogens associated with atypical pneumonia, particularly *M. pneumoniae* and *L. pneumophila*.

Although these agents are not approved for use in children, there is a reasonable body of evidence that the fluoroquinolones are generally safe, well tolerated, and effective against a variety of bacterial infections commonly encountered in pediatric practice. Parenteral quinolones are appropriate for critically ill patients with Gram-negative infections. The use of oral quinolones in stable outpatients may also be reasonable for treatment of infections that would otherwise require parenteral antibiotics (*P. aeruginosa* soft-tissue infections such as osteochondritis) or selected genitourinary tract infections. However, they should be reserved for situations where no other oral antibiotic alternative is feasible. In 2013, the FDA announced that it was changing the warning labels for fluoroquinolones to more adequately describe the risk of permanent peripheral neuropathy associated with this class of antimicrobials. Additional risks include arrhythmias and retinal detachment. Moreover, in situations of overuse (such as typhoid fever and gonococcal infection), organisms have been demonstrated to rapidly develop resistance. Thus, the use of fluoroquinolones in pediatric practice should still be approached with continued caution, and consultation with an expert is recommended.

**Macrolides**

The macrolide antibiotics most commonly used in pediatric practice include erythromycin and the newer agents, clarithromycin and azithromycin. This class of antimicrobials exerts its antibiotic effect through binding to the 50S subunit of the bacterial ribosome, producing a block in elongation of bacterial polypeptides. Clarithromycin is metabolized to 14-hydroxy clarithromycin, and interestingly this active metabolite also has potent antimicrobial activity. The spectrum of antibacterial activity includes many Gram-positive bacteria. Unfortunately, resistance to these agents among *S. aureus* and group A *Streptococcus* is fairly widespread, limiting the usefulness of macrolides for many skin and soft-tissue infections and for streptococcal pharyngitis. Azithromycin and clarithromycin have demonstrated efficacy for otitis media. All of the members of this class have an important role in the management of pediatric respiratory infections, including atypical pathogens (*M. pneumoniae*, *Chlamydia pneumoniae*, and *Legionella pneumophila*, as well as infections caused by *Bordetella pertussis*).

Telithromycin is a ketolide antibiotic derived from erythromycin. It was initially approved by the FDA for the treatment in adults of mild to moderate community-acquired pneumonia, acute exacerbations of chronic bronchitis, and acute sinusitis, having good activity against the agents causing these infections (*S. pneumoniae*, *M. pneumoniae*, *C. pneumoniae*, and *L. pneumophila* for community-acquired pneumonia; *M. catarrhalis* and *H. influenzae* for sinusitis). Reports of liver failure and myasthenia gravis from telithromycin in particular prompted the withdrawal of the indication for sinusitis and bronchitis by the FDA.

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### Table 180-6: Potential Adverse Effects of Cephalosporins

<table>
<thead>
<tr>
<th>TYPE</th>
<th>SPECIFIC</th>
<th>FREQUENCY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypersensitivity</td>
<td>Rash</td>
<td>1-3%</td>
</tr>
<tr>
<td></td>
<td>Urticaria</td>
<td>&lt;1%</td>
</tr>
<tr>
<td></td>
<td>Serum sickness</td>
<td>&lt;1%</td>
</tr>
<tr>
<td></td>
<td>Anaphylaxis</td>
<td>0.01%</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Diarrhea</td>
<td>1-19%</td>
</tr>
<tr>
<td></td>
<td>Nausea, vomiting</td>
<td>1-6%</td>
</tr>
<tr>
<td></td>
<td>Transient transaminase</td>
<td>1-7%</td>
</tr>
<tr>
<td></td>
<td>elevation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Biliary sludge</td>
<td>20-46%*</td>
</tr>
<tr>
<td>Hematologic</td>
<td>Eosinophilia</td>
<td>1-10%</td>
</tr>
<tr>
<td></td>
<td>Neutropenia</td>
<td>&lt;1%</td>
</tr>
<tr>
<td></td>
<td>Thrombocytopenia</td>
<td>&lt;1-3%</td>
</tr>
<tr>
<td></td>
<td>Hypoprolactoaminemia</td>
<td>&lt;1%</td>
</tr>
<tr>
<td></td>
<td>Impaired platelet</td>
<td>&lt;1%</td>
</tr>
<tr>
<td></td>
<td>aggregation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hemolytic anemia</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Renal</td>
<td>Interstitial nephritis</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Central nervous</td>
<td>Seizures</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>system</td>
<td>Encephalopathy</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>False-positive</td>
<td>Coombs positive</td>
<td>3%</td>
</tr>
<tr>
<td>laboratory</td>
<td>Glucosuria</td>
<td>Rare</td>
</tr>
<tr>
<td></td>
<td>Serum creatinine</td>
<td>Rare</td>
</tr>
<tr>
<td>Other</td>
<td>Drug fever</td>
<td>Rare</td>
</tr>
<tr>
<td></td>
<td>Disulfiram-like reaction*</td>
<td>Rare</td>
</tr>
<tr>
<td></td>
<td>Superinfection</td>
<td>Rare</td>
</tr>
<tr>
<td></td>
<td>Phlebitis</td>
<td>Rare</td>
</tr>
<tr>
<td></td>
<td>Calcium-antibiotic</td>
<td>Unknown;</td>
</tr>
<tr>
<td></td>
<td>precipitation</td>
<td>associated</td>
</tr>
<tr>
<td></td>
<td>(ceftriaxone)</td>
<td>events</td>
</tr>
</tbody>
</table>

*Cephalosporins with thiomethyl tetrazole ring (MTT) side chain.

One such class that is especially useful for resistant Gram-positive infections is the streptogramins. The currently licensed agent in this category is dallopristin-quinupristin, which is available in a parenteral formulation. It is appropriate for treatment of MRSA, coagulase-negative staphylococci, penicillin-susceptible and penicillin-resistant *S. pneumoniae*, and vancomycin-resistant *E. faecium* but not *E. faecalis*.

Another licensed class of antibiotics for highly resistant Gram-positive infections is the oxazolidinone class. The prototype in this group is linezolid, which is available in both oral and parenteral formulations and is approved for use in pediatric patients. Its mechanism of action involves inhibition of ribosomal protein synthesis. It is indicated for MRSA, VRE, coagulase-negative staphylococci, and penicillin-resistant *S. pneumoniae*. There is little information on dallopristin-quinupristin and linezolid in treatment of CNS infections, and neither agent is approved for pediatric meningitis. Linezolid can cause anemia and thrombocytopenia and is a monoamine oxidase inhibitor.

**Daptomycin**

Daptomycin is a novel member of the cyclic lipopeptide class of antibiotics. Its spectrum of activity includes virtually all Gram-positive organisms, including *E. faecalis* and *E. faecium* (including VRE) and *S. aureus* (including MRSA). The structure of daptomycin is a 13-member amino acid peptide linked to a 10-carbon lipophilic tail, which results in a novel mechanism of action of disruption of the bacterial membrane through the formation of transmembrane channels. These channels cause leakage of intracellular ions, leading to depolarization of the cellular membrane and inhibition of macromolecular synthesis. A theoretical advantage of daptomycin for serious infections is its bactericidal activity against MRSA and enterococci. It is administered IV. Experience in children is limited. Myopathy and elevations in creatine phosphokinase have been described. An FDA warning has been issued linking some cases of eosinophilic pneumonitis to the use of daptomycin. Daptomycin is inactivated by surfactant and should not be used to treat pneumonia.

**Miscellaneous Agents**

Although rarely used today because of safety concerns and limited availability, chloramphenicol occasionally plays a role in the management of pediatric infections, particularly those involving the CNS. This agent binds peptidyl transferase, a component of the 50S ribosome, inhibiting bacterial protein synthesis. Metronidazole, which functions by disruption of DNA synthesis, has a unique role as an antianaerobic agent and also possesses antiparasitic and anthelmintic activity. Rifampin is a rifamycin antibiotic that inhibits bacterial RNA polymerase and has a major role in the management of tuberculosis. It is also of value in the management of other bacterial infections in pediatric patients, usually used as a second (synergistic) agent in the treatment of *S. aureus* infections or to eliminate nasopharyngeal colonization of *H. influenzae* type b or *N. meningitidis*. Rifaximin is a nonabsorbed rifamycin that has been used as an adjunct agent to treat patients with multiple recurrences of *C. difficile* infection. The emerging crisis in antimicrobial resistance has also necessitated the “rediscovery” of antimicrobial agents seldom used in clinical practice in recent decades, such as colistin (colistimethate sodium). This agent is a member of the polymyxin family of antibiotics (polymyxin E). Polymyxins have a general structure consisting of a cyclic peptide with hydrophobic tails. After binding to lipopolysaccharide in the outer membrane of Gram-negative bacteria, polymyxins disrupt both the outer and inner membranes, leading to cell death. Colistin is broadly active against the *Enterobacteriaceae* family, including *P. aeruginosa*. It is also active against extended-spectrum β-lactamase- and carbapenemase-producing strains. Toxicities are chiefly renal and neurologic.

*Bibliography is available at Expert Consult.*
Bibliography


Staphylococci are hardy, aerobic, Gram-positive bacteria that grow in pairs and clusters and are ubiquitous as normal flora of humans and present on fomites and in dust. They are resistant to heat and drying and may be recovered from nonbiologic environments weeks to months after contamination. Strains are classified as *Staphylococcus aureus* if they are coagulase positive or as 1 of the many species of coagulase-negative staphylococci (e.g., *Staphylococcus epidermidis*, *Staphylococcus saprophyticus*, *Staphylococcus haemolyticus*, etc.). Often, *S. aureus* produces a yellow or orange pigment and β-hemolysis on blood agar and *S. epidermidis* produces a white pigment with variable hemolysis results, although definitive species confirmation requires further testing. *S. aureus* has many virulence factors that mediate various serious diseases, whereas coagulase-negative staphylococci tend to be less pathogenic unless an indwelling foreign body (e.g., intravascular catheter) is present. Since 2000, *S. aureus* strains resistant to β-lactam antibiotics, commonly referred to as methicillin-resistant *S. aureus* (MRSA) have become a significant problem in both community and hospital settings. Vancomycin resistance is rare, but MRSA have been reported with an elevated vancomycin minimal inhibitory concentration (≥ 1.5 mg/L).

181.1 *Staphylococcus aureus*

*S. aureus* is the most common cause of pyogenic infection of the skin and soft tissues. Bacteremia (primary and secondary) is common and can be associated with or result in osteomyelitis, supplicative arthritis, pyomyositis, deep abscesses, pneumonia, empyema, endocarditis, pericarditis, and rarely meningitis. Toxin-mediated diseases, including food poisoning, staphylococcal scarlet fever, scalded skin syndrome, and toxic shock syndrome (TSS), are caused by certain *S. aureus* strains.

**ETIOLOGY**

Strains of *S. aureus* can be identified and characterized by the virulence factors they produce. These factors tend to play 1 or more of 4 pathogenic roles in human disease: *S. aureus* protecting the organism from host defenses, localizing infection, causing local tissue damage, and affecting noninfected sites through toxin elaboration.

Most strains of *S. aureus* possess factors that protect the organism from host defenses. Many staphylococci produce a loose polysaccharide capsule, or slime layer, which may interfere with opsonophagocytosis. Production of clumping factor and/or coagulase differentiates *S. aureus* from coagulase-negative staphylococci. Clumping factor interacts with fibrinogen to cause large clumps of organisms, interfering with effective phagocytosis. Coagulase causes plasma to clot by interacting with fibrinogen and this may have an important role in localization of infection (abscess formation). **Protein A** is present in most strains of *S. aureus* but not coagulase-negative staphylococci and reacts specifically with immunoglobulin G (IgG1, IgG2, and IgG3). It is
located on the outermost coat of the cell wall and can absorb serum immunoglobulins, preventing antibacterial antibodies from acting as opsonins and thus inhibiting phagocytosis. Other enzymes elaborated by staphylococci include catalase (inactivates hydrogen peroxide, promoting intracellular survival), penicillinase or β-lactamase (inactivates penicillin at the molecular level), and lipase (associated with skin infection).

Many strains of S. aureus produce substances that cause local tissue destruction. A number of immunologically distinct hemolysins that act on cell membranes and cause tissue necrosis have been identified (α-hemolysin, β-hemolysin, δ-hemolysin). Much attention has been given to the Panton-Valentine leukocidin, a protein that S. aureus combines with phospholipid in the leukocytic cell membrane, producing increased permeability and eventual death of the cell. Strains of S. aureus that produce Panton-Valentine leukocidin are associated with more-severe and invasive skin disease, pneumonia, and osteomyelitis. Many strains of S. aureus release 1 or more exotoxins. Exfoliatins A and B are serologically distinct proteins that produce localized (bullous impetigo) or generalized (scalded skin syndrome, staphylococcal scarlet fever) dermatologic manifestations (see Chapter 659). Exfoliatins produce skin separation by splitting the desmosome and altering the intracellular matrix in the stratum granulosum. S. aureus can produce more than 20 distinct enterotoxins (types A-V). Ingestion of preformed enterotoxin, particularly types A or B, can result in food poisoning, resulting in vomiting and diarrhea and, in some cases, profound hypotension. By 10 yr of age, almost all individuals have antibodies to at least 1 enterotoxin.

Toxic shock syndrome toxin-1 (TSST-1) is associated with TSS related to menstruation and focal staphylococcal infection. TSST-1 is a superantigen that induces production of interleukin-1 and tumor necrosis factor, resulting in hypotension, fever, and multisystem involvement. Enterotoxins A and B also may be associated with non-menstrual TSS. S. aureus also possesses intrinsic factors that can contribute to pathogenesis, including teichoic acid in the cell wall, which mediates adhesion to mucosal cells proteins that promote adhesion to fibronectin, fibropectin, collagen, and other human proteins. Expression of proteins that mediate antibiotic resistance is also of critical importance. Though historically sensitive to penicillin, S. aureus isolates now almost universally possess penicillinase, an enzyme that disrupts the β-lactam structure of penicillin. Production of altered penicillin-binding proteins (PBP's) in the bacterial cell wall mediates resistance to penicillin resistant antibiotics; an altered PBP-2A is responsible for the methicillin resistance of MRSA isolates. MRSA strains appear to be at least as virulent as their methicillin-resistant counterparts.

**EPIDEMIOLOGY**

Approximately 20-40% of normal individuals carry at least 1 strain of S. aureus in the anterior nares at any given time, with intermittent carriage occurring in up to 70% of individuals. The organisms may be transmitted from the nose to the skin, where colonization is more transient. Persistent umbilical, vaginal, and perianal carriage may also occur. Many neonates are colonized within the 1st wk of life. Rates of colonization with MRSA in the general population are typically less than 2% but have increased since 2000. MRSA colonization rates greater than 20-30% have been reported in higher risk populations with significant healthcare exposure.

Exposure to S. aureus generally occurs by autoinoculation or direct contact with the hands of other colonized individuals. Heavily colonized nasal carriers (often aggravated by a viral upper respiratory tract infection) are particularly effective disseminators. Spread via fomites is rare, though an outbreak occurring in a high school football team attributed to sharing towels. Infection control policies in healthcare facilities, particularly those emphasizing good hand hygiene, have been shown to decrease rates of nosocomial staphylococcal infection.

Outside of the hospital setting, outbreaks of staphylococcal disease, in particular disease due to methicillin-resistant strains, have been reported among athletes, military personnel, young children, veterinarians, injection drug users, and inmates in correctional facilities. Increased disease frequency is noted among household contacts of a MRSA colonized or infected individual. Skin infections caused by S. aureus are considerably more prevalent among persons living in low socioeconomic circumstances and particularly among those in tropical climates.

The burden of staphylococcal disease is significant. Most important is the role of S. aureus, including MRSA, in hospital acquired infections, including infections of the bloodstream, infection of surgical sites, and ventilator-associated pneumonia. S. aureus is a significant cause of morbidity and mortality in neonatal intensive care units. Two population-based studies suggested a decline in rates of MRSA-related hospital-acquired infection, possibly reflecting the benefits of aggressive infection control procedures.

Community-acquired staphylococcal infections are estimated to result in 14 million outpatient healthcare visits. In 2005 an estimated 478,000 hospitalizations were associated with S. aureus infection in the United States, over half of which were caused by MRSA.

**PATHOGENESIS**

Except in the case of food poisoning resulting from ingestion of preformed enterotoxins, disease associated with S. aureus typically begins with colonization as described above. Subsequent disease manifestations in susceptible individuals result either directly from tissue invasion or injury caused by various toxins and enzymes produced by the organism (Fig. 181-1).

The most significant risk factor for the development of infection is disruption of intact skin, including breaches from wounds, skin disease such as eczema, epidermolysis bullosa or burns, ventriculoperitoneal shunts, and indwelling intravascular or intrathecal catheters. Additional risk factors include corticosteroid treatment, malnutrition, and azotemia. Antibiotic therapy with a drug to which S. aureus is resistant favors colonization and the development of infection. Viral infections of the respiratory tract, especially influenza virus, may predispose to secondary bacterial infection with staphylococci in certain individuals.

Congenital defects in chemotaxis (Job syndrome, Chédiak-Higashi syndrome, Wiskott-Aldrich syndrome) and defective phagocytosis and killing (neutropenia, chronic granulomatous disease) increase the risk for staphylococcal infections. Patients with HIV infection have neutrophils that are defective in their ability to kill S. aureus in vitro. Patients with recurrent staphylococcal infection should be evaluated for immune defects, especially those involving neutrophil dysfunction.

Infants may acquire type-specific humoral immunity to staphylococci transplacentally. Older children and adults develop antibodies to staphylococci as a result of colonization or minor infections. Antibody to the various S. aureus toxins appears to protect against those specific toxin-mediated diseases, but humoral immunity does not necessarily protect against focal or disseminated S. aureus infection with the same organisms.

**Figure 181-1** Relationship of virulence factors and diseases associated with Staphylococcus aureus. TSST-1, toxic shock syndrome toxin-1.
CLINICAL MANIFESTATIONS
Signs and symptoms vary with the location of the infection, which is most commonly the skin but may be any tissue. Disease states of various degrees of severity are generally a result of local suppuration, systemic dissemination with metastatic infection, or systemic effects of toxin production.

Newborn
*S. aureus* is an important cause of neonatal infections (see Chapter 109.5).

Skin
*S. aureus* is an important cause of pyogenic skin infections, including impetigo contagiosa, erythema, bullous impetigo, folliculitis, hydradenitis, furuncles (boils), carbuncles (multiple coalesced boils), paronychia, staphylococcal scalded skin syndrome, and staphylococcal scarlet fever. Infection may also cause superinfection of other noninfectious skin disease, for example, eczema, or bug bites. Recurrent furunculosis is associated with repeated episodes of pyodermia over months to years. Recurrent skin and soft-tissue infections are commonly noted with community-associated MRSA and often affect the lower extremities and buttocks. *S. aureus* is also an important cause of traumatic and surgical wound infections and can cause deep soft-tissue involvement, including cellulitis and rarely necrotizing fasciitis.

Respiratory Tract
Infections of the upper respiratory tract (otitis media, sinusitis) caused by *S. aureus* are rare, in particular considering the frequency with which the anterior nares are colonized. *S. aureus* sinusitis is relatively common in children with cystic fibrosis or defects in leukocyte function and may be the only focus of infection in some children with TSS. Suppurative parotitis is a rare infection, but *S. aureus* is a common cause of this infection. A membranous tracheitis that complicates viral group may be a result of infection with *S. aureus*, but other organisms are also possible. Patients typically have high fever, leukocytosis, and evidence of severe upper airway obstruction. Direct laryngoscopy or bronchoscopy shows a normal epiglottis with subglottic narrowing and thick, purulent secretions within the trachea. Treatment requires careful airway management and appropriate antibiotic therapy.

Pneumonia (see Chapter 400) caused by *S. aureus* may be primary or secondary after a viral infection such as influenza. Hematogenous pneumonia may be secondary to septic emboli from right-sided endocarditis or septic thrombophlebitis, with or without the presence of intravascular devices. Inhalation pneumonia is caused by alteration of mucociliary clearance, leukocyte dysfunction, or bacterial adherence initiated by a viral infection. Common symptoms and signs include high fever, abdominal pain, tachypnea, dyspnea, and localized or diffuse bronchopneumonia or lobar disease. *S. aureus* often causes a necrotizing pneumonia that may be associated with early development of empyema, pneumatoceles, pyopneumothorax, and bronchopleural fistula.

Sepsis
*S. aureus* bacteremia and sepsis may be primary or associated with any localized infection. The onset may be acute and marked by nausea, vomiting, myalgia, fever, and chills. Organisms may localize subsequently at any site (usually a single deep focus) but are found especially in the heart valves, lungs, joints, bones, muscles, and deep tissue abscesses.

In some instances, especially in young adolescent males, disseminated *S. aureus* disease occurs, characterized by fever, persistent bacteremia despite antibiotics, and focal involvement of 2 or more separate tissue sites (skin, bone, joint, kidney, lung, liver, heart). In these cases, endocarditis and septic thrombophlebitis must be ruled out. All patients with primary *S. aureus* bacteremia, especially those with persistently positive blood cultures should be evaluated for endocarditis with transthoracic, and if that is negative, transesophageal, echocardiography.

Muscle
Localized staphylococcal abscesses in muscle sometimes without septicemia have been called pyomyositis. This disorder is reported most frequently from tropical areas and is termed tropical pyomyositis, but also occurs frequently in the United States in otherwise healthy children. Multiple abscesses occur in 30-40% of cases. History may include prior trauma at the site of the abscess. Surgical drainage and appropriate antibiotic therapy are essential.

Bones and Joints
*S. aureus* is the most common cause of osteomyelitis and supplicative arthritis in children (see Chapters 684 and 685).

Central Nervous System
Meningitis (see Chapter 603.1) caused by *S. aureus* is not common; it is associated with penetrating cranial trauma and neurosurgical procedures (craniotomy, cerebrospinal fluid [CSF] shunt placement), and less frequently with endocarditis, parameningeal foci (epidural or brain abscess), diabetes mellitus, or malignancy. The CSF profile of *S. aureus* meningitis is indistinguishable from that in other forms of bacterial meningitis.

Heart
*S. aureus* is a common cause of acute endocarditis (see Chapter 437) on native valves, and results in high rates of morbidity and mortality. Perforation of heart valves, myocardial abscesses, heart failure, conduction disturbances, acute hemopericardium, purulent pericarditis, and sudden death may ensue.

Kidney
*S. aureus* is a common cause of renal and perinephric abscess (see Chapter 538), usually of hematogenous origin. Pyelonephritis and cystitis caused by *S. aureus* are unusual.

Toxic Shock Syndrome
*S. aureus* is the principal cause of TSS (see Chapter 181.2), which should be suspected in anyone with fever, shock, and/or a scarlet fever-like rash.

Intestinal Tract
Staphylococcal enterocolitis rarely follows overgrowth of normal bowel flora by *S. aureus*, which can occur as a result of broad-spectrum oral antibiotic therapy. Diarrhea is associated with blood and mucus. Peritonitis associated with *S. aureus* in patients receiving long-term ambiulatory peritoneal dialysis usually involves the catheter tunnel. Removal of the catheter is required to achieve a bacteriologic cure.

Food poisoning (see Chapter 340) may be caused by ingestion of preformed enterotoxins produced by staphylococci in contaminated foods. The source of contamination is often colonized or infected food workers. Approximately 2-7 hr after ingestion of the toxin, sudden, severe vomiting begins. Watery diarrhea may develop, but fever is absent or low. Symptoms rarely persist longer than 12-24 hr. Rarely, shock and death may occur.

DIAGNOSIS
The diagnosis of *S. aureus* infection depends on isolation of the organism from nonpermissive sites such as cellulitis aspirates, abscess cavities, blood, bone or joint aspirates, or other sites of infection. Swab cultures of surfaces are not as useful, as they may reflect surface contamination rather than the true cause of infection. Tissue samples or fluid aspirates in a syringe provide the best culture material. Cellulitic lesions are ideally cultured using a needle aspirate from the most inflamed area, inoculated directly into a blood culture bottle; use of injected saline and targeting the leading edge are less effective. Isolation from the nose or skin does not necessarily imply causation because these sites may be normally colonized sites. Because of the high prevalence of MRSA, the increasing severity of *S. aureus* infections, and the fact that bacteremia is not universally present even in severe *S. aureus* infections, it is important to obtain a nonpermissive culture of any
potential focus of infection as well as a blood culture prior to starting antibiotic treatment. The organism can be grown readily in liquid and on solid media. After isolation, identification is made on the basis of Gram stain and coagulase, clumping factor, and protein A reactivity. Patterns of susceptibility to antibiotics should be assessed in serious cases, as antimicrobial resistance is increasingly common. Identification of MRSA infection or colonization has become increasingly important, from both a therapeutic and infection control standpoint. Inoculation of samples onto selective (e.g., cefoxitin-containing) media or use of latex agglutination to identify altered PBP-2a in positive cultures are 2 commonly used methods. Molecular (polymerase chain reaction) techniques are being used increasingly for the rapid identification of colonized patients on admission to the hospital or intensive care unit. Polymerase chain reaction for ribosomal RNA is emerging as an technique for identifying bacterial pathogens and may eventually complement or replace traditional culture methods.

Diagnosis of S. aureus food poisoning is usually made on the basis of epidemiologic and clinical findings. Food suspected of contamination may be cultured and can be tested for enterotoxin.

**Differential Diagnosis**

Many of the clinical entities discussed above can also be caused by other bacterial pathogens, and consideration of the differential is particularly important when making empiric antibiotic choices prior to definitive identification of the offending pathogen. Skin lesions caused by S. aureus may be indistinguishable from those caused by group A streptococci, although the former usually expand slowly, while the latter are prone to spread more rapidly and can be very aggressive. Fluctuant skin and soft-tissue lesions also can be caused by other organisms, including Mycobacterium tuberculosis, atypical mycobacteria, Bartonella henselae (cat-scratch disease), Francisella tularensis, and various fungi, among others. Noncavitary S. aureus pneumonia can be difficult to differentiate from more common etiologies, although children with S. aureus are generally more ill. S. aureus pneumonia is often suspected after failure to improve on standard treatment which does not cover Staphylococcus, or on the basis of chest roentgenograms that reveal pneumatoceles, pyopneumothorax, or lung abscess (Fig. 181-2). Other etiologies of cavitary pneumonias include Klebsiella pneumoniae and M. tuberculosis. In bone and joint infections, culture is the only reliable way to differentiate S. aureus from other less-common etiologies including group A streptococci and in young children, Kingella kingae.

**TREATMENT**

Antibiotic therapy alone is rarely effective in individuals with undrained abscesses or with infected foreign bodies. Loculated collections of purulent material should be relieved by incision and drainage. Foreign bodies should be removed, if possible. Therapy always should be initiated with an antibiotic consistent with the local staphylococcal susceptibility patterns as well as the severity of infection. For most patients with serious S. aureus infection, intravenous treatment is recommended until the patient has become afebrile and other signs of infection have improved. Oral therapy is often continued for a period of time, especially in patients with chronic infection or underlying host defense problems. Serious S. aureus infections, with or without abscesses, tend to persist and recur, necessitating prolonged therapy. The antibiotic used as well as the dose, route, and duration of treatment depend on the site and severity of infection, the response of the patient to treatment, and the susceptibility of the organisms recovered.

Treatment of S. aureus osteomyelitis (see Chapter 684), meningitis (see Chapter 603.1), and endocarditis (see Chapter 437) is discussed in the respective chapters on these diagnoses.

Initial treatment for serious infections thought to be caused by methicillin-susceptible S. aureus (MSSA) should include semisynthetic penicillin (e.g., nafcillin) or a first-generation cephalosporin (e.g., cefazolin). Penicillin and ampicillin are not appropriate, because more than 90% of all staphylococci isolated, regardless of source, are resistant to these agents. Addition of a β-lactamase inhibitor (clavulanic acid, sulbactam, tazobactam) to a penicillin-based drug also confers anti-staphyloccocal activity but has no effect on MRSA. The spectrum of these agents (which includes Gram-negative bacteria) can be an advantage when broad empiric coverage is needed, but more narrow coverage should be selected once S. aureus is identified. Antistaphylococcal penicillins and cephalosporins do not provide activity against MRSA. For initial treatment for penicillin-allergic individuals and those with suspected serious infections caused by MRSA, vancomycin can be used. Serum levels of vancomycin should be monitored, with serum trough concentrations of 10-20 µg/mL, depending on the case. Many, but not all MSSA and community-acquired MRSA strains are susceptible to clindamycin, and initial treatment with IV clindamycin, followed by a transition to oral clindamycin has been effective in bone, joint, and soft-tissue infection. Inducible clindamycin resistance in isolates initially reported as susceptible must be ruled out by D-test or molecular methods. Clindamycin is bacteriostatic and should not be used to treat endocarditis, brain abscess, or meningitis caused by S. aureus. Given that the mechanism of action of clindamycin involves inhibition or protein synthesis, many experts use clindamycin to treat S. aureus toxin–mediated illnesses (TSS) to inhibit toxin production.

MRSA is also resistant to carbapenems and is unreliably susceptible to the quinolones. Rare vancomycin intermediate and vancomycin-resistant strains of S. aureus have also been reported, mostly in patients being treated with vancomycin. Linezolid, daptomycin, and

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**Figure 181-2** Pneumatocele formation. **A**, A 5 yr old child with Staphylococcus aureus pneumonia initially demonstrated consolidation of the right middle and lower zones. **B**, Seven days later, multiple lucent areas are noted as pneumatoceles develop. **C**, Two weeks later, significant resolution is evident, with a rather thick-walled pneumatocele persisting in the right midzone associated with significant residual pleural thickening. (From Kuhn JP, Slovis TL, Haller JO: Caffey’s pediatric diagnostic imaging, ed 10. Philadelphia, 2004, Mosby, pp. 1003–1004.)
quinupristin-dalfopristin are useful for serious S. aureus infections highly resistant to other antibiotics (Table 181-1). Nonetheless, most S. aureus isolates with higher minimal inhibitory concentrations against vancomycin (≥1.5 mg/L) have been successfully treated with appropriate dosing of vancomycin. Cefaroline (IV), a broad-spectrum antistaphylococcal cephalosporin, is approved for MRSA skin infections in adults, but pediatric experience is limited. Three new FDA approved antibiotics for adults with skin and soft tissue MRSA infections are oritavancin, dalbavancin, and tedizolid. Rifampin or gentamicin may be added to a β-lactam or vancomycin for synergy in serious infections such as endocarditis, particularly when prosthetic valve material is involved.

In many infections, oral antimicrobials may be substituted to complete the course of treatment after an initial period of parenteral therapy and determination of antimicrobial susceptibilities, or be

utilized as initial treatment in less-severe infections. Dicloxacillin (50-100 mg/kg/24 hr divided 4 times per day PO) and cephalaxin (25-100 mg/kg/24 hr divided 3-4 times per day PO) are absorbed well orally and are effective against MSSA. Amoxicillin-clavulanate (40-80 mg amoxicillin/kg/24 hr divided 3 times per day PO) is also effective, as is clindamycin (30-40 mg/kg/24 hr divided 3-4 times per day PO). Trimethoprim-sulfamethoxazole may be an effective oral antibiotic for many strains of both MSSA and MRSA. Despite in vitro susceptibility of S. aureus to ciprofloxacin and other quinolone antibiotics, these agents should not be used in serious staphylococcal infections, because their use is associated with rapid development of resistance.

The duration of oral therapy depends on the response as determined by the clinical response and in some cases, roentgenographic and laboratory findings.

### Table 181-1 Parenteral Antimicrobial Agent(s) for Treatment of Bacteremia and Other Serious Staphylococcus aureus Infections

<table>
<thead>
<tr>
<th>SUSCEPTIBILITY</th>
<th>ANTIMICROBIAL AGENTS</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>I. INITIAL EMPIRIC THERAPY (ORGANISM OF UNKNOWN SUSCEPTIBILITY)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drugs of choice:</td>
<td>Vancomycin (15 mg/kg Q6-H + nafcillin or oxacillin)</td>
<td>For life-threatening infections (i.e., septicemia, endocarditis, CNS infection); linezolid could be substituted if the patient has received several recent courses of vancomycin</td>
</tr>
<tr>
<td></td>
<td>Vancomycin (15 mg/kg Q8H)</td>
<td>For non-life-threatening infection without signs of severe sepsis (e.g., skin infection, cellulitis, osteomyelitis, pyarthrosis) when rates of MRSA colonization and infection in the community are substantial</td>
</tr>
<tr>
<td></td>
<td>Clindamycin</td>
<td>For non-life-threatening infection without signs of severe sepsis when rates of MRSA colonization and infection in the community are substantial and prevalence of clindamycin resistance is low</td>
</tr>
<tr>
<td><strong>II. METHICILLIN-SUSCEPTIBLE, PENICILLIN-RESISTANT S. AUREUS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drugs of choice:</td>
<td>Nafcillin or oxacillin¹</td>
<td>Only for patients with a serious penicillin allergy and clindamycin-susceptible strain</td>
</tr>
<tr>
<td>Alternatives (depending on susceptibility results):</td>
<td>Cefazolin</td>
<td>Only for penicillin- and cephalosporin-allergic patients</td>
</tr>
<tr>
<td></td>
<td>Clindamycin</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Vancomycin</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ampicillin + sulbactam</td>
<td></td>
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<tr>
<td><strong>III. MRSA (OXACILLIN MIC, 4 µG/ML OR GREATER)</strong></td>
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<td></td>
</tr>
<tr>
<td><strong>A. Healthcare-Associated (Multidrug-Resistant)</strong></td>
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<td></td>
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<tr>
<td>Drugs of choice:</td>
<td>Vancomycin + gentamicin¹</td>
<td>Not recommended for people younger than 18 yr of age or as monotherapy</td>
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<tr>
<td>Alternatives:</td>
<td>Trimeprprin-sulfamethoxazole</td>
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<tr>
<td></td>
<td>Linezolid¹</td>
<td></td>
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<tr>
<td></td>
<td>Quinupristin-dalfopristin¹</td>
<td></td>
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<tr>
<td></td>
<td>Fluoroquinolones</td>
<td></td>
</tr>
<tr>
<td><strong>B. Community (Not Multidrug-Resistant)</strong></td>
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<td></td>
</tr>
<tr>
<td>Drugs of choice:</td>
<td>Vancomycin + gentamicin¹</td>
<td>For life-threatening infections</td>
</tr>
<tr>
<td></td>
<td>Clindamycin (if strain susceptible)</td>
<td>For pneumonia, septic arthritis, osteomyelitis, skin or soft tissue infections</td>
</tr>
<tr>
<td></td>
<td>Trimeprprin-sulfamethoxazole</td>
<td></td>
</tr>
<tr>
<td>Alternatives:</td>
<td>Vancomycin</td>
<td>For skin or soft tissue infections</td>
</tr>
<tr>
<td><strong>IV. VANCOMYCIN INTERMEDIATELY SUSCEPTIBLE OR S. AUREUS¹ (MIC, 4 TO 16 µG/ML)²</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drugs of choice:</td>
<td>Optimal therapy is not known</td>
<td>Dependent on in vitro susceptibility test results</td>
</tr>
<tr>
<td></td>
<td>Linezolid¹</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Daptomycin¹</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Quinupristin-dalfopristin²</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tigecycline¹</td>
<td></td>
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<tr>
<td>Alternatives:</td>
<td>Vancomycin + linezolid ± gentamicin</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Vancomycin + trimethopirin-sulfamethoxazole³</td>
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</tbody>
</table>

¹One of the adjunctive agents, gentamicin or rifampin, should be added to the therapeutic regimen for life-threatening infections such as endocarditis or CNS infection or infections with a vancomycin-intermediate S. aureus strain. Consultation with an infectious diseases specialist should be considered to determine which agent to use and duration of use.

²Linezolid, quinupristin-dalfopristin, and tigecycline are agents with activity in vitro and efficacy in adults with multidrug-resistant, Gram-positive organisms, including S. aureus. Because experience with these agents is limited, consultation with an infectious diseases specialist should be considered before use.

³Daptomycin is active in vitro against multidrug-resistant, Gram-positive organisms, including S. aureus, but has not been evaluated in children. Daptomycin is approved by the US FDA only for the treatment of complicated skin and skin structure infections and for S. aureus bloodstream infections. Daptomycin is ineffective for treatment of pneumonia and is not indicated for patients 18 yr of age and older.

CNS, central nervous system; MRSA, methicillin-resistant S. aureus; MIC, minimum inhibitory concentration.

**PROGNOSIS**

Un treated *S. aureus* septicemia is associated with a high fatality rate, which has been reduced significantly by appropriate antibiotic treatment. *S. aureus* pneumonia can be fatal at any age but is more likely to be associated with high morbidity and mortality in young infants or in patients whose therapy has been delayed. Prognosis also may be influenced by numerous host factors, including nutrition, immunologic competence, and the presence or absence of other debilitating diseases. In most cases with abscess formation, surgical drainage is necessary.

**PREVENTION**

*S. aureus* infection is transmitted primarily by direct contact. Strict attention to handwashing techniques is the most effective measure for preventing the spread of staphylococci from 1 individual to another (see Chapter 173). Use of a hand wash containing chlorhexidine or alcohol is recommended. In hospitals or other institutional settings, all persons with acute *S. aureus* infections should be isolated until they have been treated adequately. There should be constant surveillance for nosocomial *S. aureus* infections within hospitals. When MRSA is recovered, strict isolation of affected patients has been shown to be the most effective method for preventing nosocomial spread of infection. Thereafter, control measures should be directed toward identification of new isolates and strict isolation of newly colonized or infected patients. Clusters of cases may be defined by molecular typing. If associated with a singular molecular strain, it may also be necessary to identify colonized hospital personnel and attempt to eradicate carriage in affected individuals.

A number of protocols exist aimed at decolonization in patients with recurrent *S. aureus* skin infection, particularly in individuals colonized with MRSA. These often involve various combinations of decontaminating baths (hypochlorite, 1 teaspoon common bleach solution per gallon of water, or chlorhexidine 4% soap), an appropriate oral antibiotic, and nasal mupirocin. Although success is not universal, recurrent infections may be reduced, particularly when eradication is done in both patient and frequent or household contacts. Most cases of mild, recurrent disease will resolve in time without these measures.

Food poisoning (see Chapter 340) may be prevented by excluding individuals with *S. aureus* infections of the skin from the preparation and handling of food. Prepared foods should be eaten immediately or refrigerated appropriately to prevent multiplication of *S. aureus* with which the food may have been contaminated.

Bibliography is available at Expert Consult.

## 181.2 Toxic Shock Syndrome

*James T. Gaensbauer and James K. Todd*

Toxic shock syndrome (TSS) is an acute and potentially severe illness characterized by fever, hypotension, erythematous rash with subsequent desquamation on the hands and feet, and multisystem involvement, including vomiting, diarrhea, myalgias, nonfocal neurologic abnormalities, conjunctival hyperemia, and strawberry tongue.

### ETIOLOGY

TSS is caused by TSST-1–producing and some enterotoxin-producing strains of *S. aureus*, which may colonize the vagina or cause focal sites of staphylococcal infection.

### EPIDEMIOLOGY

TSS continues to occur in the United States in men, women, and children, with highest rates in menstruating women 15-25 yr of age. Nonmenstrual TSS is associated with *S. aureus* infected nasal packing and wounds, sinusitis, tracheitis, pneumonia, empyema, abscesses, burns, osteomyelitis, and primary bacteremia. Most strains of *S. aureus* associated with TSS are methicillin susceptible. While USA300, the predominant isolate of community-acquired MRSA in the United States, does not contain genes expressing the most common TSS superantigens, MRSA-associated TSS does occasionally occur.

### PATHOGENESIS

The primary toxin associated with TSS is TSST-1, though a significant proportion of nonmenstrual TSS is caused by 1 or more staphylococcal enterotoxins. These toxins act as superantigens, which trigger cytokine release causing massive loss of fluid from the intravascular space and end-organ cellular injury. Epidemiologic and in vitro studies suggest that these toxins are selectively produced in a clinical environment consisting of a neutral pH, a high PO2, and an “aerobic” PO2, which are the conditions found in abscesses and the vagina with tampon use during menstruation. The risk factors for symptomatic disease include a nonimmune host colonized with a toxin-producing organism, which is exposed to focal growth conditions (menstruation plus tampon use or abscess) that induce toxin production. It appears that some hosts may have a varied cytokine response to exposure to TSST-1, helping to explain a spectrum of severity of TSS that may include staphylococcal scarlet fever. The overall mortality rate of treated patients is 3-5% with early treatment.

Approximately 90% of adults have antibody to TSST-1 without a history of clinical TSS, suggesting that most individuals are colonized at some point with a toxin-producing organism at a site (anterior nares) where low-grade or inactive toxin exposure results in an immune response without disease.

### CLINICAL MANIFESTATIONS

The diagnosis of TSS is based on clinical manifestations (Table 181-2). The onset is abrupt, with high fever, vomiting, and diarrhea, and is accompanied by sore throat, headache, and myalgias. A diffuse erythematous macular rash (sunburn-like or scarlatiniform) appears within 24 hr and may be associated with hyperemia of pharyngeal, conjunctival, and vaginal mucous membranes. A strawberry tongue is common. Symptoms often include alterations in the level of consciousness, oliguria, and hypotension, which in severe cases may progress to shock and disseminated intravascular coagulation. Complications, including acute respiratory distress syndrome, myocardial dysfunction, and renal failure, are commensurate with the degree of shock. Recovery occurs within 7-10 days and is associated with

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**Table 181-2 Diagnostic Criteria of Staphylococcal Toxic Shock Syndrome**

<table>
<thead>
<tr>
<th>MAJOR CRITERIA (ALL REQUIRED)</th>
<th>MINOR CRITERIA (ANY 3 OR MORE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute fever; temperature &gt;38.8°C (101.8°F)</td>
<td>Mucous membrane inflammation (vaginal, oropharyngeal or conjunctival hyperemia, strawberry tongue)</td>
</tr>
<tr>
<td>Hypotension (orthostatic, shock; blood pressure below age-appropriate norms)</td>
<td>Vomiting, diarrhea</td>
</tr>
<tr>
<td>Rash (erythroderma with convalescent desquamation)</td>
<td>Liver abnormalities (bilirubin or transaminase greater than twice upper limit of normal)</td>
</tr>
<tr>
<td></td>
<td>Renal abnormalities (urea nitrogen or creatinine greater than twice upper limit of normal, or greater than 5 white blood cells per high-power field)</td>
</tr>
<tr>
<td></td>
<td>Muscle abnormalities (myalgia or creatinine phosphokinase greater than twice upper limit of normal)</td>
</tr>
<tr>
<td></td>
<td>Central nervous system abnormalities (alteration in consciousness without focal neurologic signs)</td>
</tr>
<tr>
<td></td>
<td>Thrombocytopenia (100,000/mm3 or less)</td>
</tr>
</tbody>
</table>

**EXCLUSIONARY CRITERIA**

Absence of another explanation

Negative blood cultures (except occasionally for *Staphylococcus aureus*)

Bibliography


desquamation, particularly of palms and soles; hair and nail loss have also been observed after 1-2 mo. Immunity to the toxins is slow to develop, so recurrences can occur, especially if there is inadequate antibiotic treatment and/or recurrent tampon use. Many cases of apparent scarlet fever without shock may be caused by TSST-1-producing S. aureus strains.

**DIAGNOSIS**

There is no specific laboratory test, and diagnosis is dependent on meeting certain clinical and laboratory criteria in the absence of an alternate diagnosis (see Fig. 181-2). Appropriate tests reveal involvement of multiple organ systems, including the hepatic, renal, muscular, gastrointestinal, cardiopulmonary, and central nervous systems. Bacterial cultures of the associated focus (vagina, abscess) before administration of antibiotics usually yield S. aureus, although this is not a required element of the definition.

**Differential Diagnosis**

Group A Streptococcus can cause a similar TSS-like illness, termed streptococcal TSS (see Chapter 183), which is often associated with severe streptococcal sepsis or a focal streptococcal infection such as cellulitis, necrotizing fasciitis, or pneumonia.

Kawasaki disease closely resembles TSS clinically but is usually not as severe or rapidly progressive. Both conditions are associated with fever unresponsive to antibiotics, hyperemia of mucous membranes, and an erythematous rash with subsequent desquamation. However, many of the clinical features of TSS are usually absent or rare in Kawasaki disease, including diffuse myalgia, vomiting, abdominal pain, diarrhea, azotemia, hypotension, acute respiratory distress syndrome, and shock (see Chapter 166). Kawasaki disease typically occurs in children younger than 5 yr. Scarlet fever, Rocky Mountain spotted fever, leptospirosis, toxic epidermal necrolysis, sepsis, and measles must also be considered in the differential diagnosis.

**TREATMENT**

Recommended antibiotic therapy for TSS should include the combination of a β-lactamase-resistant antistaphylococcal antibiotic (nafcillin, oxacillin, or a first-generation cephalosporin) plus clindamycin to reduce toxin production. Though TSS is most commonly caused by MSSA, clinicians should consider use of vancomycin in place of the β-lactam in areas where MRSA rates are very high, when hospital acquired MRSA is suspected, and when the clinical picture overlaps with staphylococcal sepsis. Drainage of the vagina by removal of any retained tampons in menstrual TSS and of focially infected sites in nonmenstrual TSS is important for successful treatment. Antistaphylococcal therapy and avoidance of tampon use may also reduce the risk for recurrence in menstrual TSS.

TSS often requires intensive supportive care, including aggressive fluid replacement to prevent or treat hypotension, renal failure, and cardiovascular collapse. Inotropic agents may be needed to treat shock; corticosteroids and intravenous immunoglobulin may be helpful in severe cases.

**PREVENTION**

The risk for acquiring menstrual TSS (1-2 cases/100,000 menstruating women) is low. Changing tampons at least every 8 hr is recommended. If a fever, rash, or dizziness develops during menstruation, any tampon should be removed immediately and medical attention should be sought.

Bibliography is available at Expert Consult.

### 181.3 Coagulase-Negative Staphylococci

*James K. Todd*

At present, there are approximately 30 species of coagulase negative staphylococci (CoNS) affecting or colonizing humans. *Staphylococcus epidermidis*, and less commonly *Staphylococcus hominis*, *Staphylococcus haemolyticus*, and others, are widely distributed on the skin and are significant causes of nosocomial infection, particularly in the bloodstream of neonatal and immunocompromised hosts, in surgical patients and those with indwelling catheters and other medical devices. *S. saprophyticus* is a common cause of urinary tract infection. *Staphylococcus lugdunensis* has been increasingly recognized as cause of potentially severe infection.

**EPIDEMIOLOGY**

In the United States, CoNS are the most common cause of hospital acquired infection, particularly in neonatal units. In many instances, growth of CoNS from clinical specimens represents contamination from skin, rather than a cause of true disease, posing significant challenges for clinicians and infection control specialists. CoNS are normal inhabitants of the human skin, throat, mouth, vagina, and urethra. *S. epidermidis* is the most common and persistent species, representing 65-90% of staphylococci present on the skin and mucous membranes. Colonization, sometimes with strains acquired from hospital staff, precedes infection; alternatively, direct inoculation during surgery may initiate infection of CSF shunts, prosthetic valves, or indwelling vascular lines. For epidemiologic purposes, CoNS can be identified on the basis of molecular DNA methods.

**PATHOGENESIS**

CoNS produce an *exopolysaccharide* protective biofilm, or slime layer, that surrounds the organism and may enhance adhesion to foreign surfaces, resist phagocytosis, and impair penetration of antibiotics. However, the low virulence of CoNS usually requires the presence of another factor for development of clinical disease. Of these, the most significant is the presence of an indwelling catheter or other medical device, including hemodialysis shunts and grafts, CSF shunts (meningitis), peritoneal dialysis catheters (peritonitis), pacemaker wires and electrodes (local infection), prosthetic cardiac valves (endocarditis), and prostatic joints (arthritis). Other risk factors for the development of infection include immature or compromised immunnity and significant exposure to antibiotics.

**CLINICAL MANIFESTATIONS**

**Bacteremia**

CoNS, specifically *S. epidermidis*, are the most common cause of nosocomial bacteremia, usually in association with central vascular catheters. In neonates, CoNS bacteremia, with or without a central venous catheter, may be manifested as apnea, bradycardia, temperature instability, abdominal distention, hematochezia, meninitis and the absence of CSF pleocytosis, and cutaneous abscesses. Persistence of positive blood cultures despite adequate antimicrobial therapy is common, particularly when catheters are not removed. In older children, CoNS bacteremia is indolent and is not usually associated with overwhelming septic shock.

**Endocarditis**

Infection of native heart valves or the right atrial wall secondary to an infected thrombosis at the end of a central line may produce endocarditis. *S. epidermidis* and other CoNS may rarely produce native valve subacute endocarditis in previously normal patients without a central venous catheter. CoNS is a common cause of prosthetic valve endocarditis, presumably a result of inoculation at the time of surgery. Infection of the valve sewing ring, with abscess formation and dissection, produces valve dysfunction, dehiscence, arrhythmias, or valve obstruction (see Chapter 437). *S. lugdunensis* has been increasingly associated with severe endocardial infection in adults, but its role as a significant pediatric pathogen is unclear.

**Central Venous Catheter Infection**

Central venous catheters become infected through the exit site and subcutaneous tunnel, which provide a direct path to the bloodstream. *S. epidermidis* is the most frequent pathogen, owing in part to its high rate of cutaneous colonization. Line sepsis is usually manifested as
Bibliography
fever and leukocytosis; tenderness and erythema may be present at the exit site or along the subcutaneous tunnel. Catheter thrombosis may complicate line sepsis. Disease severity with CoNS is often less severe than other etiologies of line infection.

**Cerebrospinal Fluid Shunts**

CoNS, introduced at the time of surgery, is the most common pathogen associated with CSF shunt meningitis. Most (70-80%) infections occur within 2 mo of the operation and are manifested by signs of meningeal irritation, fever, increased intracranial pressure (headache), or peritonitis from the intraabdominal position of the distal end of the shunt tubing.

**Urinary Tract Infection**

*S. saprophyticus* is a common cause of primary urinary tract infections in sexually active females. Manifestations are similar to those characteristics of urinary tract infection caused by *Escherichia coli* (see Chapter 538). CoNS also cause asymptomatic urinary tract infection in hospitalized patients with urinary catheters and after urinary tract surgery or transplantation.

**DIAGNOSIS**

Because *S. epidermidis* is a common skin inhabitant and may contaminate poorly collected blood cultures, differentiating bacteremia from contamination is often difficult. True bacteremia should be suspected if blood cultures grow rapidly (within 24 hr), ≥2 blood cultures are positive with the same CoNS strain, cultures from both line and peripheral sites are positive, and clinical and laboratory signs and symptoms compatible with CoNS sepsis are present and subsequently resolve with appropriate therapy. No blood culture that is positive for CoNS in a neonate or patient with intravascular catheter should be considered contaminated without careful assessment of the foregoing criteria and examination of the patient. Before initiating presumptive antimicrobial therapy in such patients, it is always prudent to draw 2 separate blood cultures to facilitate subsequent interpretation if CoNS is grown.

**TREATMENT**

Most CoNS strains are resistant to methicillin. *Vancomycin is the drug of choice for methicillin-resistant strains*. The addition of rifampin to vancomycin may increase antimicrobial efficacy. Other antibiotics with good in vitro activity against CoNS may be considered in certain circumstances. These include linezolid, quinupristin-dalfopristin, and daptomycin. Antibiotics with potential activity include teicoplanin, clindamycin, and trimethoprim-sulfamethoxazole. Removal of an infected catheter is ideal. However, this is not always possible owing to the therapeutic requirements of the underlying disease (nutrition for short bowel syndrome, chemotherapy for malignancy). A trial of intravenous vancomycin is indicated to attempt to preserve the use of the central line as long as systemic manifestations of infection are not severe. Antibiotic therapy given through an infected central venous catheter (alternating lumens if multiple), and the use of antibiotic locks in conjunction with systemic therapy may increase the likelihood of curing CoNS line sepsis without line removal. In many cases of CoNS infection associated with foreign bodies, the catheter, valve, or shunt must be removed to ensure a cure. Prosthetic heart valves and CSF shunts usually have to be removed to treat the infection adequately.

Peritonitis caused by *S. epidermidis* in patients on continuous ambulatory peritoneal dialysis is an infection that may be treated with intravenous or intraperitoneal antibiotics without removing the dialysis catheter. If the organism is resistant to methicillin, vancomycin adjusted for renal function is appropriate therapy. Unlike most CoNS, *S. saprophyticus* is usually methicillin susceptible, and urinary tract infection can typically be treated with a first-generation cephalosporin (cephalexin), amoxicillin-clavulanic acid, or trimethoprim-sulfamethoxazole.

**PROGNOSIS**

Most episodes of CoNS bacteremia respond successfully to antibiotics and removal of any foreign body that is present. Poor prognosis is associated with malignancy, neutropenia, and infected prosthetic or native heart valves. CoNS increases morbidity, the duration of hospitalization, and mortality rates among patients with underlying complicated illnesses.

**PREVENTION**

Iatrogenic morbidity and resource utilization caused by contaminated blood cultures, can be reduced by the use of gloves, good skin preparation techniques, and through the use of trained, dedicated personnel to draw blood cultures. Prevention of CoNS infection of indwelling lines include basic techniques such as good hand hygiene, adequate decontamination of hubs and ports prior to access, minimizing frequency of access, and frequent replacement of external connections/infusion materials. Antibiotic impregnated catheters, antiseptic impregnated dressings, and the use of antibiotic or ethanol locks are being evaluated for reducing line-associated bloodstream infections.

*Bibliography is available at Expert Consult.*
Bibliography


Infectious Diseases

Chapter 182

Streptococcus pneumoniae (Pneumococcus)

James B. Wood and Timothy R. Peters

Streptococcus pneumoniae (pneumococcus) is a very important pathogen that kills more than 1 million children each year. Childhood pneumococcal disease is prevalent and commonly severe, causes numerous clinical syndromes, and is a major cause of life-threatening pneumonia, bacteremia, and meningitis. Antimicrobial resistance in pneumococcus is a major public health problem, with 15-30% of isolates worldwide classified as multidrug-resistant (MDR; resistant to ≥3 classes of antibiotics). Pneumococcal polysaccharide-protein conjugate vaccines (PCVs) developed for infants have been highly successful in the control of disease caused by virulent vaccine-specific serotypes. Epidemiologic surveillance reveals a dynamic pneumococcal ecology with emergence of highly virulent, MDR serotypes. Ongoing vaccine development and distribution efforts remain our best approach to control of this threat to childhood health.

ETIOLOGY

S. pneumoniae is a Gram-positive, lancet-shaped, polysaccharide encapsulated diplococcus, occurring occasionally as individual cocci or in chains. More than 90 serotypes have been identified by typespecific capsular polysaccharides. Antisera to some pneumococcal polysaccharides crossreact with other pneumococcal types, defining serogroups (e.g., 6A and 6B). Encapsulated strains cause most serious disease in humans. Capsular polysaccharides impede phagocytosis. Virulence is related in part to capsular size, but pneumococcal types with capsules of the same size can vary widely in virulence.

On solid media, S. pneumoniae forms unpigmented, umbilicated colonies surrounded by a zone of incomplete (α) hemolysis. S. pneumoniae is bile soluble (i.e., 10% deoxycholate) and Optochin-sensitive. S. pneumoniae is closely related to the viridans groups of Streptococcus mitis, which typically overlap phenotypically with pneumococci. The conventional laboratory definition of pneumococci continues to rely on bile and Optochin sensitivity, although considerable confusion occurs in distinguishing pneumococci and other α-hemolytic streptococci. Pneumococcal capsules can be microscopically visualized and typed by exposing organisms to type-specific antisera that combine with their unique capsular polysaccharide, rendering the capsule
Streptococcus pneumoniae  

1323  

Children at Increased Risk of Invasive Pneumococcal Infection

<table>
<thead>
<tr>
<th>RISK GROUP</th>
<th>CONDITION</th>
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<tr>
<td>Immunocompetent children</td>
<td>Chronic heart disease*</td>
</tr>
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<td></td>
<td>Chronic lung disease†</td>
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<tr>
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<td>Diabetes mellitus</td>
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<td></td>
<td>Cerebrospinal fluid leaks</td>
</tr>
<tr>
<td></td>
<td>Cochlear implant</td>
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<tr>
<td>Children with functional or anatomic asplenia</td>
<td>Sickle cell disease and other hemoglobinopathies</td>
</tr>
<tr>
<td></td>
<td>Congenital or acquired asplenia, or splenic dysfunction</td>
</tr>
<tr>
<td>Children with immunocompromising conditions</td>
<td>HIV infection</td>
</tr>
<tr>
<td></td>
<td>Chronic renal failure and nephrotic syndrome</td>
</tr>
<tr>
<td></td>
<td>Diseases associated with treatment with immunosuppressive drugs or radiation therapy, including malignant neoplasms, leukemias, lymphomas and Hodgkin disease; or solid-organ transplantation</td>
</tr>
<tr>
<td></td>
<td>Congenital immunodeficiency†</td>
</tr>
</tbody>
</table>

*Particularly cyanotic congenital heart disease and cardiac failure.  
†Including asthma if treated with high-dose oral corticosteroid therapy.  
‡Including B-humoral or T-lymphocyte deficiency; complement deficiencies, particularly C1,C2,C3, and C4 deficiency; and phagocytic disorders (excluding chronic granulomatous disease).  


**EPIDEMIOLOGY**

Most healthy individuals carry various *S. pneumoniae* serotypes in their upper respiratory tract; more than 90% of children between 6 mo and 5 yr of age harbor *S. pneumoniae* in the nasopharynx at some time. A single serotype usually is carried by a given individual for an extended period (45 days to 6 mo). Carriage does not consistently induce local or systemic immunity sufficient to prevent later reacquisition of the same serotype. Rates of pneumococcal carriage peak during the 1st and 2nd yr of life and decline gradually thereafter. Carriage rates are highest in institutional settings and during the winter, and rates are lowest in summer. Nasopharyngeal carriage of pneumococci is common among young children attending out-of-home care, with rates of 21-59% in point prevalence studies.

Prior to the introduction of heptavalent pneumococcal conjugate vaccine (PCV7) in 2000, serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F caused most invasive childhood pneumococcal infections in the United States. The introduction of PCVs resulted in a marked decrease in invasive pneumococcal infections (IPIs) in children. However, by 2005 IPIs began to increase slightly as a result of an increase in non-PCV7 serotypes, particularly serotype 19A (Fig. 182-1). The occurrence of “serotype replacement” can result from expansion of existing nonvaccine serotypes, as well as from vaccine type pneumococci acquiring the polysaccharide capsule of a nonvaccine serotype (serotype switching). Since the introduction of PCV13 in 2010 in the United States, there has been a decline in IPIs caused by new vaccine serotypes, including 19A. Indirect protection of unvaccinated persons has occurred since PCV introduction, and this herd protection is likely a result of decreases in nasopharyngeal carriage of virulent pneumococcal vaccine serotypes.

*S. pneumoniae* is the most frequent cause of bacteremia, bacterial pneumonia, otitis media, and bacterial meningitis in children. The decreased ability in children younger than 2 yr of age to produce antibody against the T-cell–independent polysaccharide antigens and the high prevalence of colonization may explain an increased susceptibility to pneumococcal infection and the decreased effectiveness of polysaccharide vaccines. Children at increased risk of pneumococcal infections include those with sickle cell disease, asplenia, deficiencies in humoral (B cell) and complement-mediated immunity, HIV infection, certain malignancies (e.g., leukemia, lymphoma), chronic heart, lung, or renal disease (particularly nephrotic syndrome), cerebrospinal fluid leak, and cochlear implants. Table 182-1 lists other high-risk groups. Some American Indian, Alaska Native, and African-American children may also be at increased risk. Children younger than 5 yr of age in out-of-home daycare are at increased risk (approximately 2-fold higher) of experiencing IPIs than other children. Males are more commonly affected than females.

Pneumococcal disease usually occurs sporadically but can be spread from person to person by respiratory droplet transmission. *S. pneumoniae* is an important cause of secondary bacterial pneumonia in patients with influenza. During influenza epidemics and pandemics, most deaths result from bacterial pneumonia, and *Pneumococcus* is the predominant bacterial pathogen isolated in this setting. Pneumococcal copathogenicity may be important in disease caused by other respiratory viruses as well.

**PATHOGENESIS**

Invasion of the host is affected by a number of factors. Nonspecific defense mechanisms, including the presence of other bacteria in the nasopharynx, may limit multiplication of pneumococci. Aspiration of secretions containing pneumococci is hindered by the epiglottic reflex and by respiratory epithelial cell cilia, which move infected mucus toward the pharynx. Similarly, normal ciliary flow of fluid from the middle ear through the eustachian tube and sinuses to the nasopharynx usually prevents infection with nasopharyngeal flora, including pneumococci. Interference with these normal clearance mechanisms by allergy, viral infection, or irritants (e.g., smoke) may allow colonization and subsequent infection with these organisms in otherwise normally sterile sites.

Virulent pneumococci are intrinsically resistant to phagocytosis by alveolar macrophages. Pneumococcal disease frequently is facilitated by viral respiratory tract infection, which may produce mucosal injury, diminish epithelial cell ciliary activity, and depress the function of alveolar macrophages and neutrophils. Phagocytosis may be impaired by respiratory secretions and alveolar exudate. In the lungs and other tissues, the spread of infection is facilitated by the antiphagocytic
The signs and symptoms of pneumococcal infection are related to the clinical manifestations after the introduction of highly active antiretroviral therapy. Although rates of invasive pneumococcal disease decreased with the AIDS epidemic, children with HIV infection also have deficits in the antibody-independent properdin (alternative) pathway of complement activation, in addition to functional asplenia. Both complement pathways contribute to antibody-independent and antibody-dependent opsonophagocytosis of pneumococci. With advancing age (e.g., >5 yr), children with sickle cell disease produce anticapsular antibody, augmenting antibody-dependent opsonophagocytosis and greatly reducing, but not eliminating, the risk of severe pneumococcal disease. Deficiency of many of the complement components (e.g., C2 and C3) is associated with recurrent pyogenic infection, including S. pneumoniae infection. The efficacy of phagocytosis also is diminished in patients with B- and T-cell immunodeficiency syndromes (e.g., agammaglobulinemia, severe combined immune deficiency) or loss of immune globulin (e.g., nephrotic syndrome) and is largely caused by a deficiency of opsonic anticapsular antibody. These observations suggest that opsonization of pneumococci depends on the alternative complement pathway in antibody-deficient persons and that recovery from pneumococcal disease depends on the development of anticapsular antibodies that act as opsonins, enhancing phagocytosis and killing of pneumococci. Children with HIV infection also have high rates of IPI similar to or greater than rates in children with sickle cell disease, although rates of invasive pneumococcal disease decreased after the introduction of highly active antiretroviral therapy.

**Clinical Manifestations**

The signs and symptoms of pneumococcal infection are related to the anatomic site of disease. Common clinical syndromes include otitis media (see Chapter 640), sinusitis (see Chapter 380), pneumonia (Fig. 182-2) (see Chapter 400), and sepsis (see Chapter 70). Before routine use of PCVs, pneumococci caused >80% of bacteremia episodes in infants 3-36 mo of age with fever without an identifiable source (i.e., occult bacteremia). Bacteremia may be followed by meningitis (see Chapter 603), osteomyelitis (see Chapter 684), suppurative arthritis (see Chapter 685), endocarditis (see Chapter 437), and, rarely, brain abscess (see Chapter 604). Primary peritonitis (see Chapter 371) may occur in children with peritoneal effusions due to nephrotic syndrome and other conditions. Local complications of infection may occur, causing empyema, pericarditis, mastoiditis, epidural abscess, periorbital cellulitis, or meningitis. Hemolytic-uremic syndrome (see Chapter 484.4) and disseminated intravascular coagulation also occur as rare complications of pneumococcal infections. Epidemic conjunctivitis caused by nonencapsulated or encapsulated pneumococci occurs as well.

**Diagnosis**

The diagnosis of pneumococcal infection is established by recovery of S. pneumoniae from the site of infection or the blood/sterile body fluid. Although pneumococci may be found in the nose or throat of patients with otitis media, pneumonia, septicemia, or meningitis, cultures of these locations are generally not helpful for diagnosis, as they are not indicative of causation. Blood cultures should be obtained in children with pneumonia, meningitis, arthritis, osteomyelitis, peritonitis, pericarditis, or gangrenous skin lesions. Because of the implementation of universal vaccination with PCVs, there has been a substantial decrease in the incidence of occult bacteremia, but blood cultures should still be considered in febrile patients with clinical toxicity or significant leukocytosis. Leukocytosis often is pronounced, with total white blood cell counts frequently >15,000/µL. In severe cases of pneumococcal disease, white blood cell count may be low.

Pneumococci can be identified in body fluids as Gram-positive, lancet-shaped diplococci. Early in the course of pneumococcal meningitis, many bacteria may be seen in relatively acellular cerebrospinal fluid. With current methods of continuously monitored blood culture systems, the average time to isolation of pneumococcal organisms is 14-15 hr. Pneumococcal latex agglutination tests for urine or other body fluids suffer from poor sensitivity and add little to Gram-stained fluids and standard cultures.

**Treatment**

Antimicrobial resistance among S. pneumoniae continues to be a serious healthcare concern, especially for the widely used β-lactams, macrolides and fluoroquinolones. Serotypes 6A, 6B, 9V, 14, 19A, 19F, and 23F are the most common serotypes associated with resistance to penicillin. Consequently, the introduction of the 7- and 13-valent...
pneumococcal conjugate vaccines (PCV7 and PCV13) has altered antimicrobial resistance patterns.

Resistance in pneumococcal organisms to penicillin and the extended-spectrum cephalosporins cefotaxime and ceftriaxone is defined by the minimum inhibitory concentration (MIC), as well as clinical syndrome. Pneumococci are considered susceptible, intermediate, or resistant to various antibacterial agents based on specific MIC breakpoints. For patients with pneumococcal meningitis, penicillin-susceptible strains have an MIC $\leq 0.06 \mu g/mL$ and penicillin-resistant strains have an MIC $\geq 1 \mu g/mL$. For patients with nonmeningeal pneumococcal infections, breakpoints are higher; in particular, penicillin susceptible strains have an MIC $\leq 2 \mu g/mL$, and penicillin resistant strains have an MIC $\geq 8 \mu g/mL$. For patients with meningitis, cefotaxime and ceftriaxone susceptible strains have an MIC $\leq 0.5 \mu g/mL$ and resistant strains have an MIC $\geq 2.0 \mu g/mL$. For patients with nonmeningeal pneumococcal disease, breakpoints are higher, and cefotaxime- and ceftriaxone-susceptible strains have an MIC $\leq 1 \mu g/mL$ and resistant strains have an MIC $\geq 4 \mu g/mL$. In cases where the pneumococcus is resistant to erythromycin but sensitive to clindamycin, a D-test should be performed to determine whether clindamycin resistance can be induced; if the D-test is positive, clindamycin should not be used to complete treatment of the patient. More than 30% of pneumococcal isolates are resistant to trimethoprim-sulfamethoxazole; levofloxacin resistance is low, but has also been reported. All isolates from children with severe infections should be tested for antibiotic susceptibility given widespread pneumococcal MDR strains. Resistance to vancomycin has not been seen to as of the writing of this chapter, but vancomycin-tolerant pneumococci that are killed at a slower rate have been reported, and these tolerant pneumococci may be associated with a worse clinical outcome. Linezolid is an oxazolidinone antibacterial with activity against MDR Gram-positive organisms, including Pneumococcus, and has been used in the treatment of MDR pneumococcal pneumonia, meningitis, and severe otitis. Despite early favorable studies, use of this drug is limited by myelosuppression and high cost, and linezolid resistance in Pneumococcus is reported.

Children 1 mo of age or older with suspected pneumococcal meningitis should be treated with combination therapy using vancomycin (60 mg/kg/24 hr divided q 6 hr IV), and high-dose cefotaxime (300 mg/kg/24 hr divided q 8 hr IV) or ceftriaxone (100 mg/kg/24 hr divided q 12 hr IV). Proven pneumococcal meningitis can be treated with penicillin alone, or cefotaxime or ceftriaxone alone, if the isolate is penicillin-susceptible. If the organism is nonsusceptible (i.e., intermediate or full resistance) to penicillin but susceptible to cefotaxime and ceftriaxone, pneumococcal meningitis can be treated with cefotaxime or ceftriaxone alone. However, if the organism is nonsusceptible to penicillin and to cefotaxime or ceftriaxone, pneumococcal meningitis should be treated with combination vancomycin plus cefotaxime or ceftriaxone, not with vancomycin alone, and consideration should be given to the addition of rifampin. Some experts recommend use of corticosteroids in pneumococcal meningitis early in the course of disease, but data demonstrating clear benefit in children is lacking.

In 2011 the Infectious Diseases Society of America published guidelines for the management of community-acquired pneumonia in infants and children. Per these guidelines, amoxicillin may be used as first-line therapy for previously healthy, appropriately immunized infants and preschool children with mild to moderate uncomplicated community-acquired pneumonia. Amoxicillin or penicillin G may be administered to the fully immunized infant or school-age child admitted to a hospital ward with uncomplicated community-acquired pneumonia, when local epidemiologic data document lack of substantial high-level penicillin resistance for invasive S. pneumoniae. Empiric therapy with a third-generation parenteral cephalosporin (ceftriaxone or cefotaxime) should be prescribed for hospitalized infants and children who are not fully immunized, in regions where local epidemiology of invasive pneumococcal strains documents widespread penicillin resistance, or for infants and children with life-threatening infection, including those with empyema. Non-β-lactam agents, such as vancomycin, have not been shown to be more effective than third-generation cephalosporins in the treatment of pneumococcal pneumonia, given the degree of drug resistance currently seen in the United States.

For individuals who are allergic to penicillin, clindamycin, erythromycin (or related macrolides, e.g., azithromycin or clarithromycin), cefotaxime and ceftriaxone (standard dosing), and trimethoprim-sulfamethoxazole may provide effective alternative therapy for susceptible strains, depending on the site of infection (e.g., clindamycin may be effective for pneumococcal infections other than meningitis). Higher doses of amoxicillin (80-100 mg/kg/24 hr) have been successful in the treatment of otitis media caused by penicillin-non susceptible strains. Empirical treatment of pneumococcal disease should be based on knowledge of susceptibility patterns in specific communities.

**PROGNOSIS**

Prognosis depends on the integrity of host defenses, virulence and numbers of the infecting organism, the age of the host, the site and extent of the infection, and the adequacy of treatment. The mortality rate for pneumococcal meningitis is approximately 10% in most studies. Pneumococcal meningitis results in sensorineural hearing loss in 20-30% of patients and can cause other serious neurologic sequelae, including paralysis, epilepsy, blindness, and intellectual deficits.

**PREVENTION**

The highly successful PCVs have resulted in a marked decrease in IPIs in children. PCVs (Table 182-2) provoke protective antibody responses in 90% of infants given these vaccines at 2, 4, and 6 mo of age, and greatly enhanced responses (e.g., immunologic memory) are apparent after vaccine doses given at 12-15 mo of age. In a large clinical trial, PCV7 was shown to reduce invasive disease caused by vaccine serotypes by up to 97% and to reduce invasive disease caused by all serotypes, including serotypes not in the vaccine, by 89%. Children who received PCV7 had 7% fewer episodes of acute otitis media and underwent 20% fewer tympanostomy tube placements than did unvaccinated children. In preliminary studies following PCV 13, a 42% reduction in IPIs caused by vaccine serotypes has been seen. The greatest reduction in the number of cases occurred in children younger than 24 mo of age. Mastoiditis cases, which have been especially associated with serotype 19A isolates, had the greatest percentage decrease. In addition, pneumococcal conjugate vaccines significantly reduce nasopharyngeal carriage of vaccine serotypes. PCVs have significantly decreased rates of invasive pneumococcal disease in children with sickle cell disease, and studies suggest substantial protection for HIV-infected children and splenectomized adults. Adverse events after the administration of PCV have included local swelling and redness and slightly

**Table 182-2** Comparison of Pneumococcal Vaccines Licensed in United States

<table>
<thead>
<tr>
<th>CARRIER PROTEIN</th>
<th>PNEUMOCOCCAL CAPSULAR POLYSACCHARIDES</th>
<th>MANUFACTURER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diptheria CRM197 protein</td>
<td>4, 6B, 9V, 14, 18C, 19F, 23F</td>
<td>Wyeth Lederle (PCV7, Prevnar)</td>
</tr>
<tr>
<td>Diptheria CRM197 protein</td>
<td>1, 3, 4, 5, 6A, 6B, 6F, 7F, 9V, 14, 18C, 19A, 19F, 23F</td>
<td>Wyeth Lederle (PCV13, Prevnar 13)</td>
</tr>
<tr>
<td>None</td>
<td>1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F, 33F</td>
<td>Sanofi Pasteur MSD (PPSV23, Pneumovax II)</td>
</tr>
</tbody>
</table>

*PCV7 serotypes in bold.*
increased rates of fever, when used in conjunction with other childhood vaccines. Immunologic responsiveness and efficacy following administration of pneumococcal polysaccharide vaccines (PPSV23) is unpredictable in children younger than 2 yr of age. PPSV23 contains purified polysaccharide of 23 pneumococcal serotypes responsible for more than 95% of cases of invasive disease. The clinical efficacy of PPSV23 is controversial and studies have yielded conflicting results.

Immunization with PCV13 is recommended for all infants on a schedule for primary immunization, in previously unvaccinated infants, and for transition for those partially vaccinated with PCV7 (Tables 182-3 and 182-4). High-risk children 2 yr of age and older, such as those with asplenia, sickle cell disease, some types of immune deficiency (e.g., antibody deficiencies), HIV infection, cochlear implant, cerebrospinal fluid leak, diabetes mellitus, and chronic lung, heart, or kidney disease (including nephrotic syndrome), may benefit also from PPSV23 administered after 2 yr of age following priming with the scheduled doses of PCV13. Thus, it is recommended that children 2 yr of age and older with these underlying conditions receive supplemental

vaccination with PPSV23. A 2nd dose of PPSV23 is recommended 5 yr after the 1st dose of PPSV23 for persons age 2 yr or older who are immunocompromised, have sickle cell disease, or functional or anatomic asplenia. Additional recommendations have been made for at-risk children between 6-18 yr (Table 182-5).

Immunization with pneumococcal vaccines also may prevent pneumococcal disease caused by nonvaccine serotypes that are serotypically related to a vaccine strain. However, because current vaccines do not eliminate all pneumococcal invasive infections, penicillin prophylaxis is recommended for children at high risk of invasive pneumococcal disease, including children with asplenia or sickle cell disease. Oral penicillin V potassium (125 mg bid for children <3 yr; 250 mg bid for children ≥3 yr) decreases the incidence of pneumococcal sepsis in children with sickle cell disease. Once-monthly intramuscular benzathine penicillin G (600,000 units q 3-4 wk for children weighing <60 lb; 1,200,000 units q 3-4 wk for children weighing ≥60 lb) may also provide prophylaxis. Erythromycin may be used in children with penicillin allergy, but its efficacy is unproved. Prophylaxis in sickle cell disease has been safely discontinued after the 5th birthday in children who have received all recommended pneumococcal vaccine doses and who had not experienced invasive pneumococcal disease. Prophylaxis is often administered for at least 2 yr after splenectomy or up to 5 yr of age. Efficacy in children older than 5 yr of age and adolescents is unproved. If oral antibiotic prophylaxis is used, strict compliance must

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**Table 182-3**

<table>
<thead>
<tr>
<th>AGE AT 1ST DOSE (MO)</th>
<th>PRIMARY PCV13 SERIES*</th>
<th>PCV13 BOOSTER DOSE†</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-6</td>
<td>3 doses</td>
<td>1 dose at age 12-15 mo</td>
</tr>
<tr>
<td>7-11</td>
<td>2 doses</td>
<td>1 dose at age 12-15 mo</td>
</tr>
<tr>
<td>12-23</td>
<td>2 doses</td>
<td>—</td>
</tr>
<tr>
<td>24-59 (healthy children)</td>
<td>1 dose</td>
<td>—</td>
</tr>
<tr>
<td>24-71 (children with certain chronic diseases or immunocompromising conditions)</td>
<td>2 doses</td>
<td>—</td>
</tr>
</tbody>
</table>

*Minimum interval between doses is 8 wk except for children vaccinated at age <12 mo for whom minimum interval between doses is 4 wk. Minimum age for administration of 1st dose is 6 wk.†Given at least 8 wk after the previous dose.


**Table 182-4**

<table>
<thead>
<tr>
<th>INFANT SERIES</th>
<th>BOOSTER DOSE</th>
<th>SUPPLEMENTAL PCV13 DOSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 mo</td>
<td>4 mo</td>
<td>≥12 mo‡</td>
</tr>
<tr>
<td>PCV7</td>
<td>PCV13</td>
<td>PCV13</td>
</tr>
<tr>
<td>PCV7</td>
<td>PCV7</td>
<td>PCV13</td>
</tr>
<tr>
<td>PCV7</td>
<td>PCV7</td>
<td>PCV7</td>
</tr>
<tr>
<td>PCV7</td>
<td>PCV7</td>
<td>PCV7</td>
</tr>
</tbody>
</table>

*No additional PCV13 doses are indicated for children age 12-23 mo who have received 2 or 3 doses of PCV before age 12 mo and at least 1 dose of PCV13 at age ≥12 mo.†For children with underlying medical conditions (see Table 182-1), a single supplemental PCV13 dose is recommended through age 71 mo.


**Table 182-5**

<table>
<thead>
<tr>
<th>RISK GROUP</th>
<th>UNDERLYING MEDICAL CONDITION</th>
<th>PCV13 RECOMMENDED</th>
<th>PPSV23 RECOMMENDED</th>
<th>REVACCINATION 5 YR AFTER 1ST DOSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immunocompetent persons</td>
<td>Chronic heart disease§</td>
<td>✓</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Chronic lung disease§</td>
<td>✓</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Diabetes mellitus</td>
<td>✓</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cerebrospinal fluid leaks</td>
<td>✓</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cochlear implants</td>
<td>✓</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Alcoholism</td>
<td>✓</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Chronic liver disease</td>
<td>✓</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cigarette smoking</td>
<td>✓</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Persons with functional or anatomic asplenia</td>
<td>Sickle cell disease/other hemoglobinopathies</td>
<td>✓</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Congenital or acquired asplenia</td>
<td>✓</td>
<td>✓</td>
<td></td>
</tr>
</tbody>
</table>

### Table 182-5  Medical Conditions or Other Indications for Administration of PCV13,* and Indications for PPSV23† Administration, and Revaccination for Children Age 6–18 Years‡—cont’d

<table>
<thead>
<tr>
<th>RISK GROUP</th>
<th>UNDERLYING MEDICAL CONDITION</th>
<th>PCV13 RECOMMENDED</th>
<th>PPSV23 RECOMMENDED</th>
<th>REVACCINATION 5 YR AFTER 1ST DOSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immunocompromised persons</td>
<td>Congenital or acquired immunodeficiencies§</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td>Human immunodeficiency virus infection</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td>Chronic renal failure</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td>Nephrotic syndrome</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td>Leukemia</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td>Lymphoma</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td>Hodgkin disease</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td>Generalized malignancy</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td>Iatrogenic immunosuppression**</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td>Solid organ transplant</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td>Multiple myeloma</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

---

*13-valent pneumococcal conjugate vaccine.
†23-valent pneumococcal polysaccharide vaccine.
‡Children age 2-5 yr with chronic conditions (e.g., heart disease or diabetes), immunocompromising conditions (e.g., HIV), functional or anatomic asplenia (including sickle cell disease), cerebrospinal fluid leaks, or cochlear implants, and who have not previously received PCV13, have been recommended to receive PCV13 since 2010.
§Including congestive heart failure and cardiomyopathies.
¶Including chronic obstructive pulmonary disease, emphysema, and asthma.
**Diseases requiring treatment with immunosuppressive drugs, including long-term systemic corticosteroids and radiation therapy.


be encouraged. Given the rapid emergence of penicillin-resistant pneumococci, especially in children receiving long-term, low-dose therapy, prophylaxis cannot be relied on to prevent disease. High-risk children with fever should be promptly evaluated and treated regardless of vaccination or penicillin prophylaxis history.

Bibliography is available at Expert Consult.
Group A streptococcus (GAS), also known as *Streptococcus pyogenes*, is a very common cause of infections of the upper respiratory tract (pharyngitis) and the skin (impetigo, pyoderma) in children and less frequently causes perianal cellulitis, vaginitis, septicemia, pneumonia, endocarditis, pericarditis, osteomyelitis, suppurative arthritis, myositis, cellulitis, and omphalitis. This organism also causes distinct clinical entities (scarlet fever and erysipelas), as well as streptococcal toxic shock syndrome and necrotizing fasciitis. GAS is also the cause of 2 potentially serious nonsuppurative complications: rheumatic fever (see Chapters 183.1 and 438) and acute glomerulonephritis (see Chapter 511.1).

**ETIOLOGY**

Group A streptococci are Gram-positive coccoid-shaped bacteria that tend to grow in chains. They are broadly classified by their hemolytic activity on mammalian (typically sheep) red blood cells. The zone of complete hemolysis that surrounds colonies grown on blood agar distinguishes β-hemolytic (complete hemolysis) from α-hemolytic (green or partial hemolysis) and γ (nonhemolytic) species. The β-hemolytic streptococci can be divided into groups by a group-specific polysaccharide (Lancefield C carbohydrate) located in the bacterial cell wall. More than 20 serologic groups are identified, designated by the letters A through V. Serologic grouping by the Lancefield method is precise, but group A organisms can be identified more readily by any one of a number of latex agglutination, coagglutination, or enzyme immunoassay procedures. Group A strains can also be distinguished from other groups by differences in sensitivity to bacitracin. A disk containing 0.04 units of bacitracin inhibits the growth of most group A strains, whereas other groups are generally resistant to this antibiotic. This method is approximately 95% accurate. GAS can be subdivided into more than 220 serotypes on the basis of the M protein antigen, which is located on the cell surface and in fimbriae that project from the outer surface of the cell. Currently, a molecular approach to M typing GAS isolates using the polymerase chain reaction is based on sequencing the terminal portion of the *emm* gene of GAS that encodes the M protein. More than 220 distinct M types have been identified using *emm* typing, and there is excellent correlation between known serotypes and *emm* types.

Immunity is largely based upon type-specific opsonic anti-M antibody. M serotyping is valuable for epidemiologic studies; specific GAS diseases tend to be associated with certain M types. Types 1, 12, 28, 4, 3, and 2 (in that order) are the most common causes of uncomplicated streptococcal pharyngitis in the United States. M types commonly associated with pharyngitis rarely cause skin infections, and the M types commonly associated with skin infections rarely cause pharyngitis. Types 1, 3, 5, 6, 18, 29), but no skin strains, are associated with acute rheumatic fever in North America. Rheumatogenic potential is not solely dependent on serotype but is likely a characteristic of specific strains within several serotypes.

**EPIDEMIOLOGY**

Humans are the natural reservoir for GAS. These bacteria are highly communicable and can cause disease in normal individuals of all ages who do not have type-specific immunity against the particular serotype involved. Disease in neonates is uncommon in developed countries, probably because of maternally acquired antibody. The incidence of pharyngeal infections is highest in children 5-15 yr of age, especially in young school-age children. These infections are most common in the northern regions of the United States, especially during winter and early spring. Children with untreated acute pharyngitis spread GAS by...
airborne salivary droplets and nasal discharge. Transmission is favored by close proximity; therefore, schools, military barracks, and homes are important environments for spread. The incubation period for pharyngitis is usually 2-5 days. GAS has the potential to be an important upper respiratory tract pathogen and to produce outbreaks of disease in the daycare setting. Foods containing GAS occasionally cause explosive outbreaks of pharyngotonsillitis. Children are usually no longer infectious 24 hr after appropriate antibiotic therapy has been started. Chronic pharyngeal carriers of GAS rarely transmit this organism to others.

Streptococcal pyoderma (impetigo, pyoderma) occurs most frequently during the summer in temperate climates, or year round in warmer climates, when the skin is exposed and abrasions and insect bites are more likely to occur (see Chapter 665). Colonization of healthy skin by GAS usually precedes the development of impetigo. Because GAS cannot penetrate intact skin, impetigo usually occurs at the site of open lesions (insect bites, traumatic wounds, burns). Although impetigo serotypes may colonize the throat, spread is usually from skin to skin, not via the respiratory tract. Fingernails and the perianal region can harbor GAS and play a role in disseminating impetigo. Multiple cases of impetigo in the same family are common. Both impetigo and pharyngitis are more likely to occur among children living in crowded homes and in poor hygienic circumstances.

The incidence of severe invasive GAS infections, including bacteremia, streptococcal toxic shock syndrome, and necrotizing fasciitis, has increased in recent decades. The incidence appears to be highest in the very young and in the elderly. Prior to the routine use of varicella vaccine, varicella was the most commonly identified risk factor for invasive GAS infection in children. Other risk factors include diabetes mellitus, HIV infection, intravenous drug use, and chronic pulmonary or chronic cardiac disease. The portal of entry is unknown in almost 50% of cases of severe invasive GAS infection; in most cases, it is believed to be skin or mucous membrane. Severe invasive disease rarely follows clinically apparent GAS pharyngitis.

**PATHOGENESIS**

Virulence of GAS depends primarily on the M protein, and strains rich in M protein resist phagocytosis in fresh human blood, whereas M-negative strains do not. M protein stimulates the production of protective opsonophagocytic antibodies that are type-specific, protecting against infection with a homologous M type but much less so against other M types. Therefore, multiple GAS infections attributable to various M types are common during childhood and adolescence. By adult life, individuals are probably immune to several or many of the common M types in the environment. GAS produces a large variety of extracellular enzymes and toxins, including erythrogenic toxins (known as streptococcal pyrogenic exotoxins). Streptococcal pyrogenic exotoxins A, B, and C are responsible for the rash of scarlet fever and are elaborated by streptococci that contain a particular bacteriophage. These exotoxins stimulate the formation of specific antigen antibodies that provide immunity against the scarlatiniform rash but not against other streptococcal infections. GAS can produce up to 12 different pyrogenic exotoxins, and repeat attacks of scarlet fever are possible. Streptococcal pyrogenic exotoxins A, B, and C, as well as several newly discovered exotoxins, appear to be involved in the pathogenesis of invasive GAS disease, including the streptococcal toxic shock syndrome.

The importance of other streptococcal toxins and enzymes in human disease is not yet established. Many of these extracellular substances are antigenic and stimulate antibody production after an infection. However, these antibodies do not confer immunity. Their measurement is useful for establishing evidence of a recent streptococcal infection to aid in the diagnosis of postinfectious illnesses. Tests for antibodies against streptolysin O (antistreptolysin O) and DNAse B (anti–DNAse B) are the most commonly used antibody determinations. Because the immune response to extracellular antigens varies among individuals as well as with the site of infection, it is sometimes necessary to measure other streptococcal antibodies.

**CLINICAL MANIFESTATIONS**

The most common infections caused by GAS involve the respiratory tract and the skin and soft tissues.

**Respiratory Tract Infections**

GAS is an important cause of acute pharyngitis (see Chapter 381) and pneumonia (see Chapter 400).

**Scarlet Fever**

Scarlet fever is an upper respiratory tract infection associated with a characteristic rash, which is caused by an infection with pyrogenic exotoxin (erythrogenic toxin)—producing GAS in individuals who do not have antitoxin antibodies. It is now encountered less commonly and is less virulent than in the past, but the incidence is cyclic, depending on the prevalence of toxin-producing strains and the immune status of the population. The modes of transmission, age distribution, and other epidemiologic features are otherwise similar to those for GAS pharyngitis.

The rash appears within 24-48 hr after onset of symptoms, although it may appear with the first signs of illness (Fig. 183-1A). It often begins around the neck and spreads over the trunk and extremities. The rash is a diffuse, finely papular, erythematous eruption producing bright red discoloration of the skin, which blanches on pressure. It is often accentuated in the creases of the elbows, axillae, and groin. The skin has a goose-pimple appearance and feels rough. The cheeks are often erythematous with pallor around the mouth. After 3-4 days, the rash begins to fade and is followed by desquamation, initially on the face, progressing downward, and often resembling a mild sunburn. Occasionally, sheet-like desquamation may occur around the free margins of the fingernails, the palms, and the soles. Examination of the pharynx of a patient with scarlet fever reveals essentially the same findings as with GAS pharyngitis. In addition, the tongue is usually coated and the papillae are swollen (Fig. 183-1B). After desquamation, the reddened papillae are prominent, giving the tongue a strawberry appearance (Fig. 183-1C).

Typical scarlet fever is not difficult to diagnose; the milder form with equivocal pharyngeal findings can be confused with viral exanthems, Kawasaki disease, and drug eruptions. Staphylococcal infections are occasionally associated with a scarlatiniform rash. A history of recent exposure to a GAS infection is helpful. Identification of GAS in the pharynx confirms the diagnosis.

**Impetigo**

Impetigo (or pyoderma) has traditionally been classified into 2 clinical forms: bullous and nonbullous (see Chapter 665). Nonbullous impetigo is the more common form and is a superficial infection of the skin that appears first as a discrete papulovesicular lesion surrounded by a localized area of redness. The vesicles rapidly become purulent and covered with a thick, confluent, amber-colored crust that gives the appearance of having been stuck onto the skin. The lesions may occur anywhere but are most common on the face and extremities. If untreated, nonbullous impetigo is a mild but chronic illness, often spreading to other parts of the body, but occasionally self-limited. Regional lymphadenitis is common. Nonbullous impetigo is generally not accompanied by fever or other systemic signs or symptoms. Impetiginized excoriations around the nares are seen with active GAS infections of the nasopharynx particularly in young children. However, impetigo is not usually associated with an overt streptococcal infection of the upper respiratory tract.

**Bullous impetigo** is less common and occurs most often in neonates and young infants. It is characterized by flaccid, transparent bullae usually <3 cm in diameter on previously untraumatized skin. The usual distribution involves the face, buttocks, trunk, and perineum. Although Staphylococcus aureus has traditionally been accepted as the sole pathogen responsible for bullous impetigo, there has been confusion about the organism responsible for nonbullous impetigo. In most episodes of nonbullous impetigo, either GAS or S. aureus, or both, is isolated. Earlier investigations suggested that GAS was the causative agent in most cases of nonbullous impetigo and that S. aureus was only
Definition of Streptococcal Toxic Shock Syndrome or necrotizing fasciitis and includes the group of focal and systemic infections that do not meet the criteria for toxic shock syndrome. The 3rd is severe invasive disease involving the deeper layers of the skin and the underlying connective tissue. The skin in the affected area is swollen, red, and very tender. Superficial blebs may be present. The most characteristic finding is a sharply defined, slightly elevated border. At times, reddish streaks of lymphangitis project out from the margins of the lesion. The onset is abrupt, and signs and symptoms of a systemic infection, such as high fever, are often present. Cultures obtained by needle aspirate of the advancing margin of the inflamed area often reveal the causative agent.

**Perianal Dermatitis**
Perianal dermatitis, also called perianal cellullitis or perianal streptococcal disease, is a distinct clinical entity characterized bywell-demarcated, perianal erythema associated with anal pruritus, painful defecation, and occasionally blood-streaked stools. Physical examination reveals flat, pink to beefy-red perianal erythema with sharp margins extending as far as 2 cm from the anus. Erythema may involve the vulva and vagina. Lesions may be very tender and, particularly when chronic, may fissure and bleed. Systemic symptoms and fever are unusual. Culture or a rapid strep test of a perianal swab will yield group A streptococci or detect antigen.

**Vaginitis**
GAS is a common cause of vaginitis in prepubertal girls (see Chapter 549). Patients usually have a serous discharge with marked erythema and irritation of the vulvar area, accompanied by discomfort in walking and in urination.

**Severe Invasive Disease**
Invasive GAS infection is defined by isolation of GAS from a normally sterile body site and includes 3 overlapping clinical syndromes. The 1st is GAS toxic shock syndrome, which is differentiated from other types of invasive GAS infections by the presence of shock and multiorgan system failure early in the course of the infection (Table 183-1). The 2nd is GAS necrotizing fasciitis characterized by extensive local necrosis of subcutaneous soft tissues and skin. The 3rd is the group of focal and systemic infections that do not meet the criteria for toxic shock syndrome or necrotizing fasciitis and includes bacteremia with no identified focus, meningitis, pneumonia, peritonitis, puerperal sepsis, osteomyelitis, suppurative arthritis, myositis, and surgical wound infections. GAS toxic shock syndrome, necrotizing fasciitis, and focal and systemic infections can be present in any combination.

The pathogenic mechanisms responsible for severe, invasive GAS infections, including streptococcal toxic shock syndrome and necrotizing fasciitis, have yet to be defined completely, but an association with streptococcal pyrogenic exotoxins is strongly suspected. The 3 original streptococcal pyrogenic exotoxins (A, B, C), the newly discovered streptococcal pyrogenic exotoxin, and potentially other as yet unidentified toxins produced by GAS act as superantigens, which stimulate intense activation and proliferation of T lymphocytes and macrophages, resulting in the production of large quantities of proinflammatory cytokines. These cytokines are capable of inducing shock and tissue injury and appear to mediate many of the clinical manifestations of severe, invasive GAS infections.

**DIAGNOSIS**
When deciding whether to perform a diagnostic test on a patient presenting with acute pharyngitis, the clinical and epidemiologic findings should be considered. A history of close contact with a well-documented case of GAS pharyngitis is helpful, as is an awareness of a high prevalence of GAS infections in the community. The signs and symptoms of streptococcal and nonstreptococcal pharyngitis overlap too broadly to allow the requisite diagnostic precision on clinical grounds alone. The
clinical diagnosis of GAS pharyngitis cannot be made with reasonable accuracy even by the most experienced physicians, and bacteriologic confirmation is required. The only exception to this statement are those patients with overt viral signs and symptoms such as rhinorrhea, cough, mouth ulcers, and hoarseness, who generally do not need a diagnostic test performed.

Culture of a throat swab on a sheep blood agar plate is effective for documenting the presence of GAS in the upper respiratory tract and for confirming the clinical diagnosis of acute GAS pharyngitis. When performed correctly, a single throat swab cultured on a sheep blood-agar plate has a sensitivity of 90-95% for detecting the presence of GAS in the pharynx.

A significant disadvantage of culturing a throat swab on a blood-agar plate is the delay (overnight or longer) in obtaining the culture result. Rapid antigen detection tests are available for the identification of GAS directly from throat swabs. Although these rapid tests are more expensive than the blood-agar culture, the advantage they offer over the traditional procedure is the speed with which they can provide results, often less than 10-15 minutes. Rapid identification and treatment of patients with streptococcal pharyngitis can reduce the risk for spread of GAS, allowing the patient to return to school or work sooner, and can reduce the acute morbidity of this illness.

Almost all currently available rapid antigen detection tests have excellent specificity of >95% when compared with blood-agar plate cultures. False-positive test results are quite unusual, and, therefore, therapeutic decisions can be made with confidence on the basis of a positive test result. Unfortunately, the sensitivity of most of these tests is 80-90%, sometimes lower, when compared with blood-agar plate culture. Therefore, a negative rapid test does not completely exclude the presence of GAS, and a confirmatory throat culture should be performed in children and adolescents but not necessarily in adults, who are at exceptionally low risk for developing acute rheumatic fever.

Definitive studies to determine whether some rapid antigen detection tests are significantly more sensitive than others, and, whether any of these tests are sensitive enough to be used routinely in children and adolescents without throat culture confirmation of negative test results, are not available. Some experts believe that physicians who use a rapid antigen detection test without culture backup should compare the results with that specific test to those of throat cultures to confirm adequate sensitivity in their practice.

Nucleic acid amplification tests including isothermal loop amplification are also available to detect GAS pharyngitis with a high degree of specificity and sensitivity as well as a rapid turn-around time. GAS infection can also be diagnosed retrospectively on the basis of an elevated or increasing streptococcal antibody titer. The antistreptolysin O assay is the streptococcal antibody test most commonly used. Because streptolysin O is also produced by groups C and G streptococci, the test is not specific for group A infection. The antistreptolysin O response can be feeble following streptococcal skin infection. In contrast, the anti-DNase B responses are generally present after either skin or throat infections. A significant antibody increase is usually defined as an increase in titer of 2 or more dilution increments (24-fold rise) between the acute phase and convalescent phase specimens, regardless of the actual height of the antibody titer. Physicians frequently misinterpret streptococcal antibody titers because of a failure to appreciate that the normal levels of these antibodies are substantially higher among school-age children compared to adults. Both the traditional antistreptolysin O and anti-DNase B tests are neutralization assays. Newer tests use latex agglutination or nephelometric assays. Unfortunately, these newer tests often have not been well-standardized against the traditional neutralization assays. Physicians should be aware of these potential problems when interpreting the results of streptococcal serologic testing.

A commercially available slide agglutination test for the detection of antibodies to several streptococcal antigens is the Streptozyme test (Wampole Laboratories, Stamford, CT). This test is much-less well-standardized and less reproducible than other antibody tests, and it should not be used as a test for evidence of a preceding GAS infection.

**Differential Diagnosis**

Viruses are the most common cause of acute pharyngitis in children. Respiratory viruses such as influenza virus, parainfluenza virus, rhinovirus, coronavirus, adenovirus, and respiratory syncytial virus are frequent causes of acute pharyngitis. Other viral causes of acute pharyngitis include enteroviruses and herpes simplex virus. Epstein-Barr virus is a frequent cause of acute pharyngitis that is often accompanied by other clinical findings of infectious mononucleosis (e.g., splenomegaly, generalized lymphadenopathy). Systemic infections with other viral agents including cytomegalovirus, rubella virus, measles virus, and HIV may be associated with acute pharyngitis.

GAS is by far the most common cause of bacterial pharyngitis, accounting for 15-30% of cases of acute pharyngitis in children and a lower proportion in adults. Groups C and G β-hemolytic streptococcus (see Chapter 185) also cause acute pharyngitis, typically in teens and young adults. Arcanobacterium haemolyticum and Fusobacterium necrophorum are additional less common causes. Neisseria gonorrhoeae can occasionally cause acute pharyngitis in sexually active adolescents. Other bacteria, such as *Francisella tularensis* and *Yersinia enterocolitica*, as well as mixed infections with anaerobic bacteria (Vincent angina), are rare causes of acute pharyngitis. *Chlamydia pneumoniae* and Mycoplasma pneumoniae have been implicated as causes of acute pharyngitis, particularly in adults. *Corynebacterium diphtheriae* (see Chapter 187) is a serious cause of pharyngitis but is rare because of universal immunization. Although other bacteria, such as *S. aureus, Haemophilus influenzae*, and *Streptococcus pneumoniae*, are frequently cultured from the throats of children with acute pharyngitis, their etiologic role in pharyngitis has not been established.

GAS pharyngitis is the only common cause of acute pharyngitis for which antibiotic therapy is definitely indicated. Therefore, when confronted with a patient with acute pharyngitis, the clinical decision that usually needs to be made is whether or not the pharyngitis is attributable to GAS.

**TREATMENT**

Antibiotic therapy for patients with GAS pharyngitis can prevent acute rheumatic fever, shorten the clinical course of the illness, reduce transmission of the infection to others, and prevent supplicative complications. For the patient with classic scarlet fever, antibiotic therapy should be started immediately, but for the vast majority of patients who present with much less distinctive findings, treatment should be withheld until there is some form of bacteriologic confirmation, either by throat culture or rapid antigen detection test. Rapid antigen detection tests, because of their high degree of specificity, have made it possible to initiate antibiotic therapy immediately for one with a positive test result. GAS is exquisitely sensitive to penicillin and cephalosporins, and resistant strains have never been encountered. Penicillin or amoxicillin is therefore the drug of choice (except in patients who are allergic to penicillins) for pharyngeal infections as well as for suppurative complications. Oral penicillin V (250 mg/dose bid-tid for children weighing ≤60 lb and 500 mg/dose bid-tid for children weighing >60 lb PO) is recommended but must be taken for a full 10 days even though there is symptomatic improvement within 3-4 days. Penicillin V (phenoxyethylpenicillin) is preferred over penicillin G because it may be given without regard to mealtime. The major concern with all forms of oral therapy is the risk that the drug will be discontinued before the 10-day course has been completed. Therefore, when oral treatment is prescribed, the necessity of completing a full course of therapy must be emphasized. If the parents seem unlikely to comply with oral therapy because of family disorganization, difficulties in comprehension, or other reasons, parenteral therapy with a single intramuscular injection of benzathine penicillin G (600,000 IU for children weighing ≤60 lb and 1.2 million IU for children weighing >60 lb, IM) is the most efficacious and often the most practical method of treatment. Disadvantages include soreness at the site of injection, which may last for several days, and potential for injection into nerves or blood vessels if not administered correctly. The local reaction is diminished when benzathine penicillin G is combined in a single injection with procaine.
penicillin G, although it is necessary to ensure that an adequate dose of benzathine penicillin G is administered.

In several comparative clinical trials, once-daily amoxicillin (50 mg/kg, maximum: 1,000 mg) for 10 days has been demonstrated to be effective in treating GAS pharyngitis. This somewhat broader-spectrum agent has the advantage of once-daily dosing, which may enhance adherence. In addition, amoxicillin is relatively inexpensive and is considerably more palatable than penicillin V suspension.

A 10-day course of a narrow spectrum oral cephalosporin is recommended for most penicillin-allergic individuals. It has been suggested that a 10-day course with an oral cephalosporin is superior to 10 days of oral penicillin in eradicating GAS from the pharynx. Analysis of these data suggests that the difference in eradication is mainly the result of a higher rate of eradication of carriers included unintentionally in these clinical trials. Some penicillin-allergic persons (up to 10%) are also allergic to cephalosporins, and these agents should be avoided in patients with immediate (anaphylactic-type) hypersensitivity to penicillin. Most oral broad-spectrum cephalosporins are considerably more expensive than penicillin or amoxicillin, and the former agents are more likely to select for antibiotic-resistant flora.

Oral clindamycin is an appropriate agent for treating penicillin-allergic patients, and resistance to clindamycin among GAS isolates in the United States is currently only approximately 1%. An oral macro-lide (erythromycin or clarithromycin) or azalide (azithromycin) is also an appropriate agent for patients allergic to penicillins. Ten days of therapy is indicated except for azithromycin, which is given at 12 mg/kg once daily for 5 days. Erythromycin is associated with substantially higher rates of gastrointestinal side effects than the other agents. In recent years, macrolide resistance rates among pharyngeal isolates of GAS in most areas of the United States have been approximately 5-8%. Sulfonamides and the tetracyclines are not indicated for treatment of GAS infections.

Most oral antibiotics must be administered for the conventional 10 days to achieve maximal pharyngeal eradication rates of GAS and prevention of rheumatic fever, but certain newer agents are reported to achieve comparable bacteriologic and clinical cure rates when given for 5 days or less. However, definitive results from comprehensive studies are not available to allow full evaluation of these proposed shorter courses of oral antibiotic therapy. Therefore, they cannot be recommended at this time. In addition, these antibiotics have a much broader spectrum than penicillin and are generally more expensive, even when administered for short courses.

The majority of patients with GAS pharyngitis respond clinically to antimicrobial therapy, and GAS is eradicated from the pharynx. Post-treatment throat cultures are indicated only in the relatively few patients who remain symptomatic. Whose symptoms recur, or who have had rheumatic fever or rheumatic heart disease and are, therefore, at unusually high risk for recurrence.

Antibiotic therapy for a patient with nonbubbling impetigo can prevent local extension of the lesions, spread to distant infectious foci, and transmission of the infection to others. However, the ability of antibiotic therapy to prevent poststreptococcal glomerulonephritis has not been demonstrated. Patients with a few superficial, isolated lesions and no systemic signs can be treated with topical antibiotics. Mupirocin is a safe and effective agent that has become the topical treatment of choice. If there are widespread lesions or systemic signs, oral therapy with coverage for both GAS and S. aureus is needed. With the rapid emergence of methicillin-resistant S. aureus in many communities, consideration should be given to using clindamycin alone or a combination of trimethoprim-sulfamethoxazole and amoxicillin as first-line therapy. Oral ceftoxime is an effective treatment of perianal streptococcal disease.

Theoretical considerations and experimental data suggest that intravenous clindamycin is a more effective agent for the treatment of severe, invasive GAS infections than intravenous penicillin. However, because a small proportion (approximately 1%) of GAS isolates in the United States are resistant to clindamycin, clindamycin initially should be used in combination with penicillin for these infections until susceptibility to clindamycin has been established. If necrotizing fasciitis is suspected, immediate surgical exploration or biopsy is required to identify a deep soft-tissue infection that should be debrided immediately. Patients with streptococcal toxic shock syndrome require rapid and aggressive fluid replacement, management of respiratory or cardiac failure, if present, and anticipatory management of multigorgan system failure. Limited data suggest that intravenous immunoglobulin is effective as adjunctive therapy in the management of streptococcal toxic shock syndrome.

COMPLICATIONS

Suppurative complications from the spread of GAS to adjacent structures were extremely common in the preantibiotic era. Cervical lymphadenitis, peritonsillar abscess, retropharyngeal abscess, otitis media, mastoiditis, and sinusitis still occur in children in whom the primary illness has gone unnoticed or in whom treatment of the pharyngitis has been inadequate. GAS pneumonia can also occur.

Acute rheumatic fever (see Chapter 183.1) and acute poststreptococcal glomerulonephritis (see Chapter 511.1) are both nonsuppurative sequelae of infections with GAS that occur after an asymptomatic latent period. They are both characterized by disease remote from the site of the primary GAS infection. Acute rheumatic fever and acute glomerulonephritis differ in their clinical manifestations, epidemiology, and potential morbidity. In addition, acute glomerulonephritis follows a GAS infection of either the upper respiratory tract or the skin, but acute rheumatic fever only follows an infection of the upper respiratory tract.

Poststreptococcal Reactive Arthritis

Poststreptococcal reactive arthritis (PSRA) has been used to describe a syndrome characterized by the onset of acute arthritis following an episode of GAS pharyngitis in a patient whose illness does not fulfill the Jones criteria for the diagnosis of acute rheumatic fever. It is still unclear whether this entity represents a distinct syndrome or is a variant of acute rheumatic fever. Although PSRA usually involves the large joints like the arthritis of acute rheumatic fever, it may involve small peripheral joints, as well as the axial skeleton, and is typically nonmigratory, characteristics distinct from the arthritis of acute rheumatic fever. The latent period between the antecedent episode of GAS pharyngitis and PSRA may be considerably shorter (usually <10 days) than that typically seen with acute rheumatic fever (usually 14-21 days). In contrast to the arthritis of acute rheumatic fever, PSRA does not respond dramatically to therapy with aspirin or other nonsteroidal antiinflammatory agents. In addition, PSRA is usually not migratory, and fewer patients have a fever >38°C (100.4°F). Even though no more than half of patients with PSRA who have a throat culture performed have GAS isolated, all have serologic evidence of a recent GAS infection. Because a very small proportion of patients with PSRA have been reported to develop valvular heart disease subsequently, these patients should be carefully observed for several months for clinical evidence of carditis. Some recommend that these patients receive secondary prophylaxis for up to 1 yr. If clinical evidence of carditis is not observed, the prophylaxis can then be discontinued. If valvular disease is detected, the patient should be classified as having had acute rheumatic fever and should continue to receive secondary prophylaxis.

Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcus pyogenes

Pediatric autoimmune neuropsychiatric disorders associated with Streptococcus pyogenes (PANDAS) is a term proposed for a group of neuropsychiatric disorders (particularly obsessive-compulsive disorder, tic disorder, and Tourette syndrome) for which a possible relationship with GAS infections has been hypothesized (see Chapter 24). This relationship has not been proven. It has been proposed that this subset of patients with obsessive-compulsive and tic disorders may produce autoimmune antibodies in response to a GAS infection that cross-react with brain tissue similar to the autoimmune response believed to be responsible for the manifestations of Sydenham chorea. It has also been
suggested that secondary prophylaxis that prevents recurrences of rheumatic fever, including Sydenham chorea, might also be effective in preventing exacerbations of obsessive-compulsive and tic disorders in these patients, but clinical trials have not confirmed this. It has also been proposed that these patients may benefit from immunoregulatory therapy such as plasma exchange or intravenous immunoglobulin therapy, but these unproven modalities should only be utilized in a clinical research trial. That PANDAS may represent an extension of the spectrum of acute rheumatic fever is intriguing, but it should be considered only as a yet-unproven hypothesis. Until carefully designed and well-controlled studies have established a causal relationship between neurobehavioral abnormalities and GAS infections, routine diagnostic laboratory testing for GAS and antistreptococcal antibodies, long-term antistreptococcal prophylaxis, or immunoregulatory therapy (e.g., intravenous immunoglobulin, plasma exchange) to treat exacerbations of this disorder clearly are not recommended (see Chapter 24). It has also been suggested that a broad spectrum of infectious agents may have the ability to trigger exacerbations in children with these neurobehavioral disorders.

**PROGNOSIS**

The prognosis for appropriately treated GAS pharyngitis is excellent, and complete recovery is the rule. When therapy is instituted within 9 days of the onset of symptoms and continued for the full course, acute rheumatic fever is almost always prevented. There is no comparable evidence that acute poststreptococcal glomerulonephritis can be prevented once pharyngitis or pyoderma with a nephritogenic strain of GAS has occurred. In rare instances, particularly in neonates or in children whose response to infection is compromised, fulminant pneumonia, septicemia, and death may occur despite usually adequate therapy.

**PREVENTION**

The only specific indication for long-term use of an antibiotic to prevent GAS infections is for patients with a history of acute rheumatic fever and/or rheumatic heart disease. Mass prophylaxis is generally not feasible except to reduce the number of infections during epidemics of impetigo and to control epidemics of pharyngitis in military populations and in schools. Because the ability of antimicrobial agents to prevent GAS infections is limited, a group A streptococcal vaccine offers the possibility of a more effective approach.

Several candidate vaccines are in development, including a 30-valent M protein-based recombinant vaccine, another recombinant vaccine that includes several conserved non-M protein epitopes that induce protective antibody, and a M-protein vaccine that includes an epitope in a very conserved region of M protein to provide broad immunity. All of these vaccines are in relatively early stages of development.

Bibliography is available at Expert Consult.

### 183.1 Rheumatic Fever

**Stanford T. Shulman**

**ETIOLOGY**

Considerable evidence supports the link between antecedent GAS upper pharyngitis tract infections and acute rheumatic fever and rheumatic heart disease. As many as two-thirds of patients with an acute episode of rheumatic fever have history of an upper respiratory tract infection several weeks before, and the peak age and seasonal incidence of acute rheumatic fever closely parallel that of GAS pharyngitis. Patients with acute rheumatic fever almost always have serologic evidence of a recent GAS infection. Their antibody titers are usually considerably higher than those seen in patients with uncomplicated GAS infections. Outbreaks of GAS pharyngitis in closed communities, such as boarding schools or military bases, may be followed by outbreaks of acute rheumatic fever. Antimicrobial therapy that eliminates GAS from the pharynx also prevents initial episodes of acute rheumatic fever, and long-term, continuous antibiotic prophylaxis that prevents GAS pharyngitis also prevents recurrences of acute rheumatic fever.

Not all serotypes of GAS can cause rheumatic fever. When some GAS strains (e.g., M type 4) caused acute pharyngitis in a very susceptible rheumatic population, no recurrences of rheumatic fever occurred. In contrast, episodes of pharyngitis caused by other serotypes in the same population led to frequent recurrences of acute rheumatic fever, suggesting that the latter organisms were rheumatogenic. The concept of rheumatogenicity is further supported by the observation that although serotypes of GAS frequently associated with skin infection can often be isolated also from the upper respiratory tract, they rarely cause recurrences of rheumatic fever in individuals with a previous history of rheumatic fever or first episodes of rheumatic fever. In addition, certain serotypes of GAS (M types 1, 3, 5, 6, 18, 29) are more frequently isolated from patients with acute rheumatic fever than are other serotypes.

**EPIDEMIOLOGY**

The annual incidence of acute rheumatic fever in some developing countries exceeds 50 per 100,000 children, and very high rates are also seen in ethnic minority populations within Australia and New Zealand. Worldwide, rheumatic heart disease remains the most common form of acquired heart disease in all age groups, accounting for as much as 50% of all cardiovascular disease and as much as 50% of all cardiac admissions in many developing countries. Striking differences in the incidence of acute rheumatic fever and rheumatic heart disease among different ethnic groups are evident within the same country; these differences are partially related to differences in socioeconomic status, and there is a genetic basis for increased susceptibility.

In the United States at the beginning of the 20th century, acute rheumatic fever was a leading cause of death among children and adolescents, with annual incidence rates of 100-200 per 100,000 population. In addition, rheumatic heart disease was a leading cause of heart disease among adults younger than 40 yr of age. At that time, as many as 25% of hospital beds in the United States were occupied by patients with acute rheumatic fever or its complications. By the 1940s, the annual incidence of acute rheumatic fever had decreased to 50 per 100,000 population, and over the next 4 decades, the decline in incidence accelerated rapidly. By the early 1980s, the annual incidence in some areas of the United States was as low as 0.5 per 100,000 population. This sharp decline in the incidence of acute rheumatic fever has been observed in other industrialized countries as well.

The explanation for this dramatic decline in the incidence of acute rheumatic fever and rheumatic heart disease in the United States and other industrialized countries is not clear but is likely related in large part to decline in circulating rheumatogenic strains causing acute pharyngitis. Historically, acute rheumatic fever was associated with poverty and overcrowding, particularly in urban areas. Much of the decline in the incidence of acute rheumatic fever in industrialized countries during the preantibiotic era is probably the result of improved living conditions. Of the various manifestations of poverty, crowding, which facilitates spread of GAS infections, is most closely associated with the incidence of acute rheumatic fever. The decline in incidence of acute rheumatic fever in industrialized countries over the past 4 decades is also attributable to the greater availability of medical care and to the widespread use of antibiotics. Antibiotic therapy of GAS pharyngitis is important in preventing initial attacks and, particularly, recurrences of the disease. In addition, the decline in the United States is attributed to a shift in the prevalent strains of GAS from rheumatogenic to nonrheumatogenic strains.

A dramatic outbreak of acute rheumatic fever in the Salt Lake City area began in early 1985, and 198 cases were reported by the end of 1989. Other outbreaks were reported between 1984 and 1988 in Columbus and Akron, OH; Pittsburgh, PA; Nashville and Memphis, TN; New York, NY; Kansas City, MO; Dallas, TX; and among Navy
Chapter 183  •  Group A Streptococcus 1332.e1

Bibliography
Guidelines for the Diagnosis of Initial or Recurrent Attack of Rheumatic Fever (Jones Criteria, Updated 2015)

PATHOGENESIS

The details of the pathogenic link between a GAS infection of the upper respiratory tract and an attack of acute rheumatic fever, characterized by organ and tissue involvement at sites far removed from the pharynx, is still not clear. A major obstacle to understanding the pathogenesis of acute rheumatic fever and rheumatic heart disease has been the inability to establish an animal model. Several theories of pathogenesis have been proposed, notably the cytotoxicity theory and immunologic theories.

The cytotoxicity theory suggests that a GAS toxin is involved in the pathogenesis of acute rheumatic fever and rheumatic heart disease. GAS produces a number of enzymes that are cytotoxic for mammalian cardiac cells, such as streptolysin O, which has a direct cytotoxic effect on mammalian cells in tissue culture. Most proponents of the cytotoxicity theory have focused on this enzyme. However, a major problem with the cytotoxicity hypothesis is its inability to explain the substantial latent period (approximately 2-4 wk) between GAS pharyngitis and the onset of acute rheumatic fever.

An immune-mediated pathogenesis for acute rheumatic fever and rheumatic heart disease has been suggested by its clinical similarity to other illnesses with an immunopathogenesis and by the latent period between the GAS infection and acute rheumatic fever. The antigenicity of several GAS cellular and extracellular epitopes and their immunologic crossreactivity with cardiac antigenic epitopes also lends support to the hypothesis of molecular mimicry. Common epitopes are shared between certain GAS components (e.g., M protein, cell membrane, group A cell wall carbohydrate, capsular hyaluronate) and specific mammalian tissues (e.g., heart valve, sarcomere, brain, joint). For example, certain rheumatogenic M proteins (M1, M5, M6, and M19) share epitopes with human myocardial proteins such as tropomyosin and myosin. Additionally, the involvement of GAS superantigens such as pyrogenic exotoxins in the pathogenesis of acute rheumatic fever has been proposed.

A more recently proposed pathogenetic hypothesis is that the binding of an M protein N-terminus domain to a region of collagen type IV leads to an antibody response to the collagen, resulting in ground substance inflammation especially subendothelial areas like cardiac valves and myocardium.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Because no clinical or laboratory finding is pathognomonic for acute rheumatic fever, T. Duckett Jones, in 1944, proposed guidelines to aid in diagnosis and to limit overdiagnosis. The Jones Criteria, as revised in 2015 by the American Heart Association (AHA) (Table 183-2), is now intended for diagnosis of the initial attack of acute rheumatic fever and recurrent attacks. There are 5 major and 4 minor criteria and a requirement of evidence of recent GAS infection. The 2015 revision now includes separate criteria for Low-Risk populations (defined as those with incidence ≤2 per 100,000 school-age children per year or all-age rheumatic heart disease prevalence of ≤1 per thousand population) and Moderate/High-Risk populations (defined as those with higher incidence or prevalence rates). Virtually all of the United States, Canada, and Western Europe are Low Risk, whereas Moderate/High-Risk populations include Maoris in New Zealand, aborigines in Australia, Pacific Islanders, and most developing countries. Diagnosis of a first attack or recurrent attack of acute rheumatic fever can be established when a patient fulfills 2 major or 1 major and 2 minor criteria and has evidence of preceding GAS infection. Diagnosis of recurrent acute rheumatic fever can also be made only in the Moderate/High Risk population by presence of 3 minor criteria with evidence of preceding GAS infection. In the 2015 Jones Criteria revision, a major change from previous versions expands the definition of the major criterion—carditis—to include subclinical evidence (i.e., in the absence of a murmur, echocardiographic evidence of mitral regurgitation [MR] meeting specific criteria to distinguish physiologic from pathologic MR) (Table 183-3). Areas in which the Jones Criteria differ in Low-Risk populations from Moderate/High-Risk populations relate to the major criterion of arthritis and in the minor criteria of arthralgia, definition of fever, and of elevated inflammatory markers (see Table 183-2).

Table 183-2: Guidelines for the Diagnosis of Initial or Recurrent Attack of Rheumatic Fever (Jones Criteria, Updated 2015)\(^5\)

<table>
<thead>
<tr>
<th>MAJOR MANIFESTATIONS</th>
<th>MINOR MANIFESTATIONS</th>
<th>SUPPORTING EVIDENCE OF ANTECEDENT GROUP A STREPTOCOCCAL INFECTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carditis</td>
<td>Clinical features:</td>
<td>Positive throat culture or rapid streptococcal antigen test</td>
</tr>
<tr>
<td>Polyarthritis</td>
<td>Arthralgia</td>
<td>Elevated or increasing streptococcal antibody titer</td>
</tr>
<tr>
<td>Erythema marginatum</td>
<td>Fever</td>
<td></td>
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<tr>
<td>Subcutaneous nodules</td>
<td>Laboratory features:</td>
<td></td>
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<tr>
<td>Chorea</td>
<td>Elevated acute phase reactants:</td>
<td></td>
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<tr>
<td></td>
<td>Erythrocyte sedimentation rate</td>
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<td></td>
<td>C-reactive protein</td>
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<td>Prolonged P-R interval</td>
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1. Initial attack: 2 major manifestations, or 1 major and 2 minor manifestations, plus evidence of recent GAS infection. Recurrent attack: 2 major, or 1 major and 2 minor, or 3 minor manifestations (the latter only in the Moderate/High-Risk population), plus evidence of recent GAS infection (see text).

2. Low-Risk population is defined as ARF incidence ≤2 per 100,000 school-age children per year, or all-age RHD prevalence of <1 per 1000 population. Moderate/High-Risk population is defined as ARF incidence >2 per 100,000 school-age children per year, or all-age RHD prevalence of >1 per 1000 population.

3. Carditis is now defined as clinical and/or subclinical (echocardiographic valvulitis). See Table 183-3.

4. Arthritis (major) refers only to polyarthritis in Low-Risk populations, but also to monoarthritis or polyarthralgia in Moderate/High-Risk populations.

5. Minor criteria for Moderate/High-Risk populations only include monoarthalgia (polyarthralgia for Low-Risk populations), fever of >38°C (>38.5°C in Low-Risk populations), ESR >50 mm/hr (>60 mm/hr in Low-Risk populations).
and text below). These changes are designed to make it easier to fulfill the Jones Criteria in patients from Moderate/High-Risk populations. Even with strict application of the Jones criteria, overdiagnosis as well as underdiagnosis of acute rheumatic fever may occur. There are 3 circumstances in which the diagnosis of acute rheumatic fever can be made without strict adherence to the Jones criteria: (1) when chorea occurs as the only major manifestation of acute rheumatic fever, (2) when indolent carditis is the only manifestation in patients who first come to medical attention only months after the apparent onset of acute rheumatic fever, and (3) in a limited number of patients with recurrences of acute rheumatic fever in particularly high-risk populations.

The 5 Major Criteria
Migratory Polyarthritis
Arthritis occurs in approximately 75% of patients with acute rheumatic fever and typically involves larger joints, particularly the knees, ankles, wrists, and elbows. Involvement of the spine, small joints of the hands and feet, or hips is uncommon. Rheumatic joints are classically hot, red, swollen, and exquisitely tender, with even the friction of bedclothes being uncomfortable. The pain can precede and can appear to be disproportionate to the objective findings. The joint involvement is characteristically migratory in nature; that is, a severely inflamed joint can become normal within 1-3 days without treatment, even as 1 or more other large joints become involved. Severe arthritis can persist for several weeks in untreated patients. Monoarticular arthritis is unusual unless antiinflammatory therapy is initiated prematurely, aborting the progression of the migratory polyarthritis. If a child with fever and arthritis is suspected to have acute rheumatic fever, it is frequently useful to withhold salicylates and observe for migratory progression. A dramatic response to even low doses of salicylates is another characteristic feature of the arthritis, and the absence of such a response should suggest an alternative diagnosis. Rheumatic arthritis is almost never deforming. Synovial fluid in acute rheumatic fever usually has 10,000-100,000 white blood cells/µL with a predominance of neutrophils, a protein level of approximately 4 g/dL, a normal glucose level, and forms a good mucin clot. Frequently, arthritis is the earliest manifestation of acute rheumatic fever and may correlate temporally with peak antistreptococcal antibody titers. There is often an inverse relationship between the severity of arthritis and the severity of cardiac involvement. In Moderate/High-Risk populations only, monoarthritis in the absence of prior inflammatory therapies or even polyarthralgia without frank objective signs of arthritis can fulfill this major criterion. Before polyarthralgia should be considered a major criterion in the Moderate/High-Risk population, other potential causes should be excluded.

Carditis
A major change in the 2015 revision of the Jones Criteria is the acceptance of subclinical carditis (defined as without a murmur of valvulitis but with echocardiographic evidence of valvulitis) or clinical carditis (with a valvulitis murmur) as fulfilling the major criterion of carditis in all populations. The echocardiographic features of subclinical carditis must meet those included in Table 183-3 in order to distinguish pathologic from physiologic degrees of valve regurgitation. Subclinical (echocardiographic) evidence of pathologic mitral regurgitation requires that a jet is seen in at least 2 views, the jet length is ≥2 cm in at least one view, peak jet velocity is >3 meters/second, and the peak systolic jet is in at least one envelope. Subclinical pathologic evidence of aortic regurgitation is similar except that the jet length is ≥2 cm in at least one view. Carditis and resultant chronic rheumatic heart disease are the most serious manifestations of acute rheumatic fever and account for essentially all of the associated morbidity and mortality. Rheumatic carditis is characterized by pancarditis, with active inflammation of myocardium, pericardium, and endocardium (see Chapter 438). Cardiac involvement during acute rheumatic fever varies in severity from fulminant, potentially fatal exudative pancarditis to mild, transient cardiac involvement. Endocarditis (valvulitis) is a universal finding in rheumatic carditis, whereas the presence of pericarditis or myocarditis is variable. Myocarditis and/or pericarditis without clinical evidence of endocarditis almost never is rheumatic carditis; alternate etiologies (especially viral) need to be sought. Most rheumatic heart disease is isolated mitral valvular disease or combined aortic and mitral valvular disease. Isolated aortic or right-sided valvular involvement is quite uncommon. Serious and long-term illness is related entirely to the severity of valvular heart disease as a consequence of a single attack or recurrent attacks of acute rheumatic fever. Valvular insufficiency is characteristic of both acute and convalescent stages of acute rheumatic fever, whereas mitral and/or aortic valvular stenosis usually appears years or even decades after the acute illness. However, in developing countries where acute rheumatic fever often occurs at a younger age, mitral stenosis and aortic stenosis may develop sooner after acute rheumatic fever than in developed countries and can occur in young children.

Acute rheumatic carditis usually presents as tachycardia and cardiac murmurs, with or without evidence of myocardial or pericardial involvement. Moderate to severe rheumatic carditis can result in cardiogely and heart failure with hepatomegaly and peripheral and pulmonary edema. Echocardiographic findings are not diagnostic but include pericardial effusion, decreased ventricular contractility, and aortic and/or mitral regurgitation. Mitral regurgitation is characterized typically by a high-pitched apical holosystolic murmur radiating to the axilla. In patients with significant mitral regurgitation, this may be associated with an apical mid-diastolic murmur of relative mitral stenosis. Aortic insufficiency is characterized by a high-pitched decrescendo diastolic murmur at the left sternal border.

Carditis occurs in approximately 50-60% of all cases of acute rheumatic fever. Recurrent attacks of acute rheumatic fever in patients who had carditis with their initial attack are associated with high rates of carditis with increasing severity of cardiac disease. The major consequence of acute rheumatic carditis is chronic, progressive valvular disease, particularly valvular stenosis, which can require valve replacement.

Chorea
Sydenham chorea occurs in approximately 10-15% of patients with acute rheumatic fever and usually presents as an isolated, frequently subtle, movement disorder. Emotional lability, incoordination, poor school performance, uncontrollable movements, and facial grimacing, all exacerbated by stress and disappearing with sleep, are characteristic. Chorea occasionally is unilateral (hemichorea). The latent period from acute GAS infection to chorea is usually substantially longer than for arthritis or carditis and can be months. Onset can be insidious, with symptoms being present for several months before recognition. Clinical maneuvers to elicit features of chorea include (1) demonstration of milkmaid’s grip (irregular contractions and relaxations of the muscles of the fingers while squeezing the examiner’s fingers), (2) spooning and pronation of the hands when the patient’s arms are extended, (3) wormian darting movements of the tongue upon protrusion, and (4) examination of handwriting to evaluate fine motor movements. Diagnosis is based on clinical findings with supportive evidence of GAS antibodies. However, in the usual patient with a long latent period from the inciting streptococcal infection to onset of chorea, antibody levels have often declined to normal. Although the acute illness is distressing, chorea rarely, if ever, leads to permanent neurologic sequelae.

<table>
<thead>
<tr>
<th>Table 183-3</th>
<th>Echocardiographic Findings in Rheumatic Valvulitis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PATHOLOGIC MITRAL REGRUGITATION (ALL 4 MET)</strong></td>
<td><strong>PATHOLOGIC AORTIC REGRUGITATION (ALL 4 MET)</strong></td>
</tr>
<tr>
<td>1. Seen in at least 2 views</td>
<td>1. Seen in at least 2 views</td>
</tr>
<tr>
<td>2. Jet length ≥2 cm in at least 1 view</td>
<td>2. Jet length ≥2 cm in at least 1 view</td>
</tr>
<tr>
<td>3. Peak velocity &gt;3 meters/second</td>
<td>3. Peak velocity &gt;3 meters/second</td>
</tr>
<tr>
<td>4. Pan-systolic jet in at least 1 envelope</td>
<td>4. Pan-diastolic jet in at least 1 envelope</td>
</tr>
</tbody>
</table>
Differential Diagnosis of Acute Rheumatic Fever

<table>
<thead>
<tr>
<th>ARTHRITIS</th>
<th>CARDITIS</th>
<th>CHOREA</th>
</tr>
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<tr>
<td>Juvenile idiopathic arthritis</td>
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<td>Pyogenic arthritis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poststreptococcal reactive arthritis</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Erythema Marginatum

Erythema marginatum is a rare (approximately 1% of patients with acute rheumatic fever) but characteristic rash of acute rheumatic fever. It consists of erythematous, serpiginous, macular lesions with pale centers that are not pruritic (Fig. 183–2). It occurs primarily on the trunk and extremities, but not on the face, and it can be accentuated by warming the skin.

Subcutaneous Nodules

Subcutaneous nodules are a rare (<1% of patients with acute rheumatic fever) finding and consist of firm nodules approximately 1 cm in diameter along the extensor surfaces of tendons near bony prominences. There is a correlation between the presence of these nodules and significant rheumatic heart disease.

Minor Criteria

These are more nonspecific than major criteria, and the 2015 revised Jones Criteria have included some changes from previous criteria. The first of the 2 clinical minor criteria involve joint manifestations (only if arthritis is not used as a major criterion) and is defined as polyarthritis in Low-Risk populations and monoarthritis in Moderate/High-Risk populations. The second clinical minor manifestation is fever, defined as at least 38.5°C in Low-Risk populations and at least 38.0°C in Moderate/High-Risk populations. The 2 laboratory minor criteria are (1) elevated acute phase reactants (defined as ESR at least 60 mm/hr and/or CRP at least 3.0 mg/dl [30 mg/L] in Low-Risk populations, and ESR at least 30 mm/hr and/or CRP at least 3.0 mg/dl [30 mg/L] in Moderate/High-Risk populations) and (2) prolonged P-R interval on ECG (unless carditis is a major criterion). However, a prolonged P-R interval alone does not constitute evidence of carditis or predict long-term cardiac sequelae.

Recent Group A Streptococcus Infection

An absolute requirement for the diagnosis of acute rheumatic fever is supporting evidence of a recent GAS infection. Acute rheumatic fever typically develops 2–4 wk after an acute episode of GAS pharyngitis at a time when clinical findings of pharyngitis are no longer present and when only 10–20% of patients still harbor GAS in the throat. One-third of patients with acute rheumatic fever have no history of an antecedent pharyngitis. Therefore, evidence of an antecedent GAS infection is usually based on elevated or rising serum antistreptococcal antibody titers. A slide agglutination test (Streptozyme) purports to detect antibodies against 5 different GAS antigens. Although this test is rapid, relatively simple to perform, and widely available, it is less standardized and less reproducible than other tests and is not recommended as a diagnostic test for evidence of an antecedent GAS infection. If only a single antibody is measured (usually antistreptolysin O), only 80–85% of patients with acute rheumatic fever have an elevated titer; however, 95–100% have an elevation if 3 different antibodies (antistreptolysin O, antidi–DNase B, antihyaluronidase) are measured. Therefore, when acute rheumatic fever is suspected clinically, multiple antibody tests should be performed. Except for chorea, the clinical findings of acute rheumatic fever generally coincide with peak antistreptococcal antibody responses. Most patients with chorea have elevation of antibodies to at least 1 GAS antigen. However, in patients with a long latent period from the inciting GAS infection, antibody levels may have declined to within the normal range. The diagnosis of acute rheumatic fever should not be made in those patients with elevated or increasing streptococcal antibody titers who do not fulfill the Jones criteria.

Differential Diagnosis

The differential diagnosis of rheumatic fever includes many infectious as well as noninfectious illnesses (Table 183–4). When children present with arthritis, a collagen vascular disease must be considered. Juvenile idiopathic arthritis in particular must be distinguished from acute rheumatic fever. Children with rheumatoid arthritis tend to be younger and usually have less joint pain relative to their other clinical findings than those with acute rheumatic fever. Spiking fevers, nonmigratory arthritis, lymphadenopathy, and splenomegaly are more suggestive of rheumatoid arthritis than acute rheumatic fever. The response to salicylate therapy is also much less dramatic with rheumatoid arthritis than with acute rheumatic fever. Systemic lupus erythematosus can usually be distinguished from acute rheumatic fever by antinuclear antibodies in systemic lupus erythematosus. Other causes of arthritis such as pyogenic arthritis, malignancies, serum sickness, Lyme disease, sickle cell disease, and reactive arthritis related to gastrointestinal infections (e.g., Shigella, Salmonella, Yersinia) should also be considered. Poststreptococcal reactive arthritis has been discussed earlier (see “Poststreptococcal Reactive Arthritis” above).

When carditis is the sole major manifestation of suspected acute rheumatic fever, viral myocarditis, viral pericarditis, Kawasaki disease, and infective endocarditis should also be considered. Patients with infective endocarditis may present with both joint and cardiac manifestations. These patients can usually be distinguished from patients with acute rheumatic fever by blood cultures and the presence of extra-cardiac findings (e.g., hematuria, splenomegaly, splinter hemorrhages). When chorea is the sole major manifestation of suspected acute rheumatic fever, Huntington chorea, Wilson disease, systemic lupus erythematosus, and various encephalitides should also be considered.

Table 183-4  Differential Diagnosis of Acute Rheumatic Fever

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</table>
TREATMENT
All patients with acute rheumatic fever should be placed on bed rest and monitored closely for evidence of carditis. They can be allowed to ambulate when the signs of acute inflammation have subsided. However, patients with carditis require longer periods of bed rest.

Antibiotic Therapy
Once the diagnosis of acute rheumatic fever has been established and regardless of the throat culture results, the patient should receive 10 days of orally administered penicillin or amoxicillin or a single intramuscular injection of benzathine penicillin to ensure eradication of GAS from the upper respiratory tract. If penicillin-allergic, 10 days of erythromycin, azithromycin (5 days) or clindamycin is indicated. After this initial course of antibiotic therapy, long-term antibiotic prophylaxis should be instituted.

Antiinflammatory Therapy
Antiinflammatory agents (e.g., salicylates, corticosteroids) should be withheld if arthralgia or atypical arthritis is the only clinical manifestation of presumed acute rheumatic fever. Premature treatment with 1 of these agents may interfere with the development of the characteristic migratory polyarthritis and thus obscure the diagnosis of acute rheumatic fever. Acetaminophen can be used to control pain and fever while the patient is being observed for more definite signs of acute rheumatic fever or for evidence of another disease.

Patients with typical migratory polyarthritis and those with carditis without cardiomegaly or congestive heart failure should be treated with oral salicylates. The usual dose of aspirin is 50-70 mg/kg/day in 4 divided doses PO for 3-5 days, followed by 50 mg/kg/day in 4 divided doses PO for 3 wk and half that dose for another 2-4 wk. Determination of the serum salicylate level is not necessary unless the arthritis does not respond or signs of salicylate toxicity (tinnitus, hyperventilation) develop. There is no evidence that nonsteroidal antiinflammatory agents are any more effective than salicylates.

Patients with carditis and more than minimal cardiomegaly and/or congestive heart failure should receive corticosteroids. The usual dose of prednisone is 2 mg/kg/day in 4 divided doses for 2-3 wk followed by half the dose for 2-3 wk and then tapering of the dose by 5 mg/24 hr every 2-3 days. When prednisone is being tapered, aspirin should be started at 50 mg/kg/day in 4 divided doses for 6 wk to prevent rebound of inflammation. Supportive therapies for patients with moderate to severe carditis include digoxin, fluid and salt restriction, diuretics, and oxygen. The cardiac toxicity of digoxin is enhanced with myocarditis.

Termination of the antiinflammatory therapy may be followed by the reappearance of clinical manifestations or of elevated erythrocyte sedimentation rate and C-reactive protein (rebound). It may be prudent to increase salicylates or steroids until near-normalization is achieved.

Sydenham Chorea
Because chorea often occurs as an isolated manifestation after the resolution of the acute phase of the disease, antiinflammatory agents are usually not indicated. Sedatives may be helpful early in the course of chorea; phenobarbital (16-32 mg every 6-8 hr PO) is the drug of choice. If phenobarbital is ineffective, then haloperidol (0.01-0.03 mg/kg/24 hr divided bid PO) or chlorpromazine (0.5 mg/kg every 4-6 hr PO) should be initiated. Some patients may benefit from a few-week course of corticosteroids.

COMPLICATIONS
The arthritis and chorea of acute rheumatic fever resolve completely without sequelae. Therefore, the long-term sequelae of rheumatic fever are essentially limited to the heart (see Chapter 438).

The AHA has published updated recommendations regarding the use of prophylactic antibiotics to prevent infective endocarditis (see Chapter 437). The AHA recommendations no longer suggest routine prophylaxis for patients with rheumatic heart disease. However, the maintenance of optimal oral healthcare remains an important component of an overall healthcare program. For the relatively few patients with rheumatic heart disease in whom infective endocarditis prophylaxis remains recommended, such as those with a prosthetic valve or prosthetic material used in valve repair, the current AHA recommendations should be followed (see Chapter 437). These recommendations advise using an agent other than a penicillin to prevent infective endocarditis in those receiving penicillin prophylaxis for rheumatic fever because oral α-hemolytic streptococci are likely to have developed resistance to penicillin.

PROGNOSIS
The prognosis for patients with acute rheumatic fever depends on the clinical manifestations present at the time of the initial episode, the severity of the initial episode, and the presence of recurrences. Approximately 50-70% of patients with carditis during the initial episode of acute rheumatic fever recover with no residual heart disease; the more severe the initial cardiac involvement, the greater the risk is for residual heart disease. Patients without carditis during the initial episode are less likely to have carditis with recurrent attacks, but there is a stepwise increase in cardiac involvement as the number of episodes increases. In contrast, patients with carditis during the initial episode are very likely to have carditis with recurrences, and the risk for permanent heart damage increases with each recurrence. Patients who have had acute rheumatic fever are susceptible to recurrent attacks following reinfection of the upper respiratory tract with GAS, with approximately 50% risk with each GAS pharyngitis. Therefore, these patients require long-term continuous chemoprophylaxis.

Before antibiotic prophylaxis was available, 75% of patients who had an initial episode of acute rheumatic fever had one or more recurrences during their lifetimes. These recurrences were a major source of morbidity and mortality. The risk of recurrence is highest in the 1st 5 yr after the initial episode and decreases with time.

Approximately 20% of patients who present with “pure” chorea who are not given secondary prophylaxis develop rheumatic heart disease within 20 yr. Therefore, patients with chorea, even in the absence of other manifestations of rheumatic fever, require long-term antibiotic prophylaxis (see Table 183-5).

PREVENTION
Prevention of both initial and recurrent episodes of acute rheumatic fever depends on controlling GAS infections of the upper respiratory tract. Prevention of initial attacks (primary prevention) depends on identification and eradication of GAS causing acute pharyngitis. Individuals who have already suffered an attack of acute rheumatic fever are particularly susceptible to recurrences of rheumatic fever with any subsequent GAS upper respiratory tract infection, whether or not they are symptomatic. Therefore, these patients should receive continuous antibiotic prophylaxis to prevent recurrences (secondary prevention).

Primary Prevention
Appropriate antibiotic therapy instituted before the 9th day of symptoms of acute GAS pharyngitis is highly effective in preventing first attacks of acute rheumatic fever. However, approximately 30% of patients with acute rheumatic fever do not recall a preceding episode of pharyngitis and did not seek therapy.

Secondary Prevention
Secondary prevention is directed at preventing acute GAS pharyngitis in patients at substantial risk of recurrent acute rheumatic fever. Secondary prevention requires continuous antibiotic prophylaxis, which should begin as soon as the diagnosis of acute rheumatic fever has been made and immediately after a full course of antibiotic therapy has been completed. Because patients who have had carditis with their initial episode of acute rheumatic fever are at higher risk for having carditis with recurrences and for sustaining additional cardiac damage, they should receive long-term antibiotic prophylaxis well into adulthood and perhaps for life.

Patients who did not have carditis with their initial episode of acute rheumatic fever have a relatively low risk for carditis with recurrences.
Antibiotic prophylaxis should continue in these patients until the patient reaches 21 yr of age or until 5 yr have elapsed since the last rheumatic fever attack, whichever is longer. The decision to discontinue prophylactic antibiotics should be made only after careful consideration of potential risks and benefits and of epidemiologic factors such as the risk for exposure to GAS infections.

The regimen of choice for secondary prevention is a single intramuscular injection of benzathine penicillin G (600,000 IU for children weighing ≤60 lb and 1.2 million IU for those weighing >60 lb) every 4 wk (Table 183-5). In certain high-risk patients, and in certain areas of the world where the incidence of rheumatic fever is particularly high, use of benzathine penicillin G every 3 wk may be necessary because serum concentrations of penicillin may decrease to marginally effective levels after 3 wk. In the United States, the administration of benzathine penicillin G every 3 wk is recommended only for those who have recurrent acute rheumatic fever despite adherence to a 4 wk regimen. In compliant patients, continuous oral antimicrobial prophylaxis can be used. Penicillin V 250 mg twice daily and sulfadiazine or sulfasoxazole 500 mg for those weighing ≤60 pounds or 1,000 mg for those weighing >60 pounds given once daily are equally effective when used in such patients. For the exceptional patient who is allergic to both penicillin and sulfonamides, a macrolide (erythromycin or clarithromycin) or azalide (azithromycin) may be used. Table 183-6 notes the duration of secondary prophylaxis.

Bibliography is available at Expert Consult.
Bibliography


Group B streptococcus (GBS), or *Streptococcus agalactiae*, is a major cause of neonatal bacterial sepsis in the United States. Although advances in prevention strategies have led to a decline in the incidence of neonatal disease, GBS remains a major pathogen for neonates, pregnant women, and nonpregnant adults.

**ETIOLOGY**

Group B streptococci are facultative anaerobic Gram-positive cocci that form chains or diplococci in broth and small gray-white colonies on solid medium. GBS is definitively identified by demonstration of the Lancefield group B carbohydrate antigen, such as with latex agglutination techniques widely used in clinical laboratories. Presumptive identification can be established on the basis of a narrow zone of β-hemolysis on blood agar, resistance to bacitracin and trimethoprim-sulfamethoxazole, lack of hydrolysis of bile esculin, and elaboration of CAMP factor (named for the discoverers, Christie, Atkins, and Munch-Petersen), an extracellular protein that, in the presence of the β toxin of *Staphylococcus aureus*, produces a zone of enhanced hemolysis on sheep’s blood agar. Individual GBS strains are serologically classified according to the presence of 1 of the structurally distinct capsular polysaccharides, which are important virulence factors and stimulators of antibody-associated immunity. Ten GBS capsular types have been identified: types Ia, Ib, II, III, IV, V, VI, VII, VIII, and IX.

**EPIDEMIOLOGY**

GBS emerged as a prominent neonatal pathogen in the late 1960s. For the next 2 decades, the incidence of neonatal GBS disease remained fairly constant, affecting 1.0-5.4/1,000 liveborn infants in the United States. Two patterns of disease were seen: early-onset disease, which presents at <7 days of age, and late-onset disease, which presents at 7 days of age or later. Since the early 1990s, widespread implementation of maternal intrapartum chemoprophylaxis has led to a striking decrease in the incidence of early-onset neonatal GBS disease in the United States, decreasing from 1.7 per 1,000 live births to 0.25 per 1,000 live births in recent years. This strategy has not had a significant effect on the incidence of late-onset disease, which has remained stable at approximately 0.3-0.4 per 1,000 live births (Fig. 184-1). The incidence of neonatal GBS disease is higher in premature and low-birthweight infants, although most cases occur in full-term infants. Rates of both early- and late-onset disease are higher in black infants.

Colonization by GBS in healthy adults is common. Vaginal or rectal colonization occurs in up to approximately 30% of pregnant women and is the usual source for GBS transmission to newborn infants. In the absence of maternal chemoprophylaxis, approximately 50% of infants born to colonized women acquire GBS colonization, and 1-2% of infants born to colonized mothers develop early-onset disease.
Heavy maternal colonization increases the risk for infant colonization and development of early-onset disease. Additional risk factors for early-onset disease include prolonged rupture of membranes, intrapartum fever, prematurity, maternal bacteriuria during pregnancy, or previous delivery of an infant who developed GBS disease. Risk factors for late-onset disease are less-well defined. Whereas late-onset disease may follow vertical transmission, horizontal acquisition from nursery or other community sources has also been described.

GBS is also an important cause of invasive disease in adults. GBS may cause urinary tract infections, bacteremia, endometritis, chorioamnionitis, and wound infection in pregnant and parturient women. In nonpregnant adults, especially those with underlying medical conditions such as diabetes mellitus, cirrhosis, or malignancy, GBS may cause serious infections such as bacteremia, skin and soft-tissue infections, bone and joint infections, endocarditis, pneumonia, and meningitis. In the era of maternal chemoprophylaxis, most invasive GBS infections occur in nonpregnant adults. Unlike neonatal disease, the incidence of invasive GBS disease in adults has increased substantially, doubling between 1990 and 2007.

The serotypes most commonly associated with neonatal GBS disease are types Ia, III, and V; Ib and IL are less frequent. Strains of serotype III are isolated in more than 50% of cases of late-onset disease and of meningitis associated with early- or late-onset disease. The serotype distribution of colonizing and invasive isolates from pregnant women is similar to that from infected newborns. In Japan, serotypes VI and VII have been reported as common maternal colonizing serotypes, and case reports indicate that type VIII strains may cause neonatal disease indistinguishable from that caused by other serotypes.

**PATHOGENESIS**

A major risk factor for the development of early-onset neonatal GBS infection is maternal vaginal or rectal colonization by GBS. Infants acquire GBS via ascending infection or during passage through the birth canal. Fetal aspiration of infected amniotic fluid may occur. The incidence of early-onset GBS infection increases with the duration of rupture of membranes. Infection may also occur through seemingly intact membranes. In cases of late-onset infection, GBS may be vertically transmitted or acquired later from maternal or nonmaternal sources.

Several bacterial factors are implicated in the pathophysiology of invasive GBS disease. Foremost among these is the type-specific capsular polysaccharide. Strains that are associated with invasive disease in humans elaborate more capsular polysaccharide than do colonizing isolates. All GBS capsular polysaccharides are high-molecular-weight polymers and contain a short side chain terminating in N-acetylmuramic acid (sialic acid). Studies in type III GBS show that the sialic acid component of the capsular polysaccharide prevents activation of the alternative complement pathway in the absence of type-specific antibody. Sialylated capsular polysaccharide on the GBS surface also interacts with sialic acid-binding lectins or siglecs on human leukocytes to dampen inflammatory gene activation. Thus, the capsular polysaccharide appears to exert a virulence effect by protecting the organism from opsonophagocytosis in the nonimmune host and by downregulating leukocyte activation. In addition, type-specific virulence attributes are suggested by the fact that type III strains are implicated in most cases of late-onset neonatal GBS disease and meningitis. Type III strains are taken up by brain endothelial cells more efficiently in vitro than are strains of other serotypes, although studies using acapsular mutant strains demonstrate that it is not the capsule itself that facilitates cellular uptake. A single clone of type III GBS is highly associated with late-onset disease and meningitis. This clonal group, ST-17, produces a surface-anchored protein called hypervirulent GBS adhesin (HvgA) that is not present in other GBS isolates. HvgA contributes to GBS adherence to intestinal and endothelial cells and mediates invasion into the central nervous system in an experimental infection model in mice. Other putative GBS virulence factors include GBS surface proteins, which may play a role in adhesion to host cells; C5a peptidase, which is postulated to inhibit the recruitment of polymorphonuclear cells into sites of infection; β-hemolysin, which has been associated with cell injury in vitro; and hyaluronidase, which has been postulated to act as a spreading factor in host tissues.

In a classic study among pregnant women colonized with type III GBS, those who gave birth to healthy infants had higher levels of capsular polysaccharide-specific antibody than those who gave birth to infants who developed invasive disease. In addition, there is a high correlation of antibody titer to GBS type III in mother–infant paired sera. These observations indicate that placental transfer of maternal antibody is critically involved in neonatal immunity to GBS. Optimal immunity to GBS also requires an intact complement system. The classical complement pathway is an important component of GBS immunity in the absence of specific antibody; in addition, antibody-mediated opsonophagocytosis may proceed via the alternative complement pathway. These and other results indicate that anticapsular antibody can overcome the prevention of C3 deposition on the bacterial surface by the sialic acid component of the type III capsule.

The precise steps between GBS colonization and invasive disease remain unclear. In vitro studies showing GBS entry into alveolar epithelial cells and pulmonary vasculature endothelial cells suggest that GBS may gain access to the bloodstream via invasion from the alveolar space, perhaps following intrapartum aspiration of infected fluid. β-Hemolysin/cytolyisin may facilitate GBS entry into the bloodstream following inoculation into the lungs. However, highly encapsulated GBS strains enter eukaryotic cells poorly in vitro compared with capsule-deficient organisms are associated with virulence clinically and in experimental infection models.

GBS induces the release of proinflammatory cytokines. The group B antigen and the peptidoglycan component of the GBS cell wall are potent inducers of tumor necrosis factor-α release in vitro, whereas purified type III capsular polysaccharide is not. Even though the capsule plays a central role in virulence through avoidance of immune clearance, the capsule does not directly contribute to cytokine release and the resultant inflammatory response.

The complete genome sequences of types Ia, III, and V GBS strains have been reported, emphasizing a genomic approach to better understanding GBS. Analysis of these sequences shows that GBS is closely related to *Streptococcus pyogenes* and *Streptococcus pneumoniae*. Many known and putative GBS virulence genes are clustered in pathogenicity islands that also contain mobile genetic elements, suggesting that interspecies acquisition of genetic material plays an important role in genetic diversity.
**Table 184-1** Characteristics of Early- and Late-Onset Group B Streptococcus Disease

<table>
<thead>
<tr>
<th></th>
<th>EARLY-ONSET DISEASE</th>
<th>LATE-ONSET DISEASE</th>
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</thead>
<tbody>
<tr>
<td>Age at onset</td>
<td>0-6 days</td>
<td>7-90 days</td>
</tr>
<tr>
<td>Increased risk after obstetric complications</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Common clinical manifestations</td>
<td>Sepsis, pneumonia, meningitis</td>
<td>Bacteremia, meningitis, other focal infections</td>
</tr>
<tr>
<td>Common serotypes</td>
<td>Ia, Ib, II, III, V</td>
<td>III predominates</td>
</tr>
<tr>
<td>Case fatality rate</td>
<td>4.7%</td>
<td>2.8%</td>
</tr>
</tbody>
</table>


**CLINICAL MANIFESTATIONS**

Two syndromes of neonatal GBS disease are distinguishable on the basis of age at presentation, epidemiologic characteristics, and clinical features (Table 184-1). **Early-onset neonatal GBS disease** presents within the 1st 6 days of life and is often associated with maternal obstetric complications, including choioamnionitis, prolonged rupture of membranes, and premature labor. Infants may appear ill at the time of delivery, and most infants become ill within the 1st 24 hr of birth. In utero infection may result in septic abortion. More than 80% of early-onset GBS disease presents as sepsis; pneumonia and meninitis are other common manifestations. Asymptomatic bacteremia is uncommon but can occur. In symptomatic patients, nonspecific signs such as hypothermia or fever, irritability, lethargy, apnea, and bradycardia may be present. Respiratory signs are prominent regardless of the presence of pneumonia and include cyanosis, apnea, tachypnea, grunting, flaring, and retractions. A fulminant course with hemodynamic abnormalities, including tachycardia, acidosis, and shock, may ensue. Persistent fetal circulation may develop. Clinically and radiographically, pneumonia associated with early-onset GBS disease is difficult to distinguish from respiratory distress syndrome. Patients with meninitis often present with nonspecific findings, as described for sepsis or pneumonia, with more specific signs of central nervous system involvement initially being absent.

**Late-onset neonatal GBS disease** occurs on or after 7 days of life and most commonly manifests as bacteremia (45-65%) and meninitis (25-35%). Focal infections involving bone and joints, skin and soft tissue, the urinary tract, or lungs may also be seen. Cellulitis and adenitis are often localized to the submandibular or parotid regions. In contrast to early-onset disease, maternal obstetric complications are not risk factors for the development of late-onset GBS disease. Infants with late-onset disease are often less severely ill on presentation than infants with early-onset disease, and the disease is often less fulminant.

Invasive GBS disease in children beyond early infancy is uncommon. Bacteremia without a focus is the most common syndrome associated with childhood GBS disease beyond early infancy. Focal infections may include meninitis, pneumonia, endocarditis, and bone and joint infections.

**DIAGNOSIS**

A major challenge is distinguishing between respiratory distress syndrome and invasive neonatal GBS infection in preterm infants because the 2 illnesses share clinical and radiographic features. Severe apnea, early onset of shock, abnormalities in the peripheral leukocyte count, and greater lung compliance may be more likely in infants with GBS disease. Other neonatal pathogens, including *Escherichia coli* and *Listeria monocytogenes*, may cause illness that is clinically indistinguishable from that caused by GBS.

The diagnosis of invasive GBS disease is established by isolation and identification of the organism from a normally sterile site, such as blood, urine, or cerebrospinal fluid (CSF). Isolation of GBS from gastric or tracheal aspirates or from skin or mucous membranes indicates colonization and is not diagnostic of invasive disease. CSF should be examined in all neonates suspected of having sepsis, because specific central nervous system signs are often absent in the presence of meningitis, especially in early-onset disease. Antigen detection methods that use group B polysaccharide-specific antiserum, such as latex particle agglutination, are available for testing of urine, blood, and CSF, but these tests are less sensitive than culture. Moreover, antigen is often detected in urine samples collected by bag from otherwise healthy neonates who are colonized with GBS on the perineum or rectum.

**LABORATORY FINDINGS**

Frequently present are abnormalities in the peripheral white blood cell count, including an increased or decreased absolute neutrophil count, an elevated band count, an elevated ratio of bands to total neutrophils, or leukopenia. Elevation in the C-reactive protein level has been investigated as a potential early marker of GBS sepsis but is unreliable. Findings on chest radiograph are often indistinguishable from those of respiratory distress syndrome and may include reticulogranular patterns, patchy infiltrates, generalized opacification, pleural effusions, or increased interstitial markings.

**TREATMENT**

Penicillin G is the treatment of choice of confirmed GBS infection. Empirical therapy of neonatal sepsis that could be caused by GBS generally includes ampicillin and an aminoglycoside, both for the need for broad coverage pending organism identification and for synergistic bactericidal activity. Once GBS has been definitively identified and a good clinical response has occurred, therapy may be completed with penicillin alone. Especially in cases of meningitis, high doses of penicillin (450,000-500,000 units/kg/day) or ampicillin (300 mg/kg/day) are recommended because of the relatively high mean inhibitory concentration of penicillin for GBS as well as the potential for a high initial CSF inoculum. The duration of therapy varies according to the site of infection (Table 184-2) and should be guided by clinical circumstances. Extremely ill near-term patients with respiratory failure have been successfully treated with extracorporeal membrane oxygenation.

In cases of GBS meningitis, some experts recommend that additional CSF be sampled at 24-48 hr to determine whether sterility has been achieved. Persistent GBS growth may indicate an unsuspected intracranial focus or an insufficient antibiotic dose.

**Table 184-2** Recommended Duration of Therapy for Manifestations of Group B Streptococcus Disease

<table>
<thead>
<tr>
<th>TREATMENT</th>
<th>DURATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacteremia without a focus</td>
<td>10 days</td>
</tr>
<tr>
<td>Meningitis</td>
<td>2-3 wk</td>
</tr>
<tr>
<td>Ventriculitis</td>
<td>At least 4 wk</td>
</tr>
<tr>
<td>Septic arthritis or osteomyelitis</td>
<td>3-4 wk</td>
</tr>
</tbody>
</table>

For recurrent neonatal GBS disease, standard intravenous antibiotic therapy followed by attempted eradication of GBS mucosal colonization has been suggested. This suggestion is based on the findings in several studies that invasive isolates from recurrent episodes are usually identical to each other and to colonizing isolates from the affected infant. Rifampin has most frequently been used for this purpose, but 1 report demonstrates that eradication of GBS colonization in infants is not reliably achieved by rifampin therapy. Optimal management of this uncommon situation remains unclear.

**PROGNOSIS**

Studies from the 1970s and 1980s showed that up to 30% of infants surviving GBS meningitis had major long-term neurologic sequelae, including developmental delay, spastic quadriplegia, microcephaly, seizure disorder, cortical blindness, or deafness; less severe neurologic complications may be present in other survivors. A study of infants who survived GBS meningitis diagnosed from 1998 through 2006 found that 19% had severe neurologic impairment and 25% had mild to moderate impairment at long-term follow-up. Periventricular leukomalacia and severe developmental delay may result from GBS disease and accompanying shock in premature infants, even in the absence of meningitis. The outcome of focal GBS infections outside of the central nervous system, such as bone or soft-tissue infections, is generally favorable.

In the 1990s, the case fatality rates associated with early- and late-onset neonatal GBS disease were 4.7% and 2.8%, respectively. Mortality is higher in premature infants; 1 study reported a case fatality rate of 30% in infants whose gestational age was <33 wk and 2% in infants whose gestational age was ≥37 wk. The case fatality rate in children aged 3 mo to 14 yr was 9%, and in nonpregnant adults was 11.5%.

**PREVENTION**

Persistent morbidity and mortality from perinatal GBS disease despite advances in neonatal care has spurred intense investigation into modes of prevention. Two basic approaches to GBS prevention have been investigated: (1) elimination of colonization from the mother or infant (chemoprophylaxis), and (2) induction of protective immunity (immunoprophylaxis).

**Chemoprophylaxis**

Administration of antibiotics to pregnant women before the onset of labor does not reliably eradicate maternal GBS colonization and is not an effective means of preventing neonatal GBS disease. Interruption of neonatal colonization is achievable through administration of antibiotics to the mother during labor (see Chapter 109). Infants born to GBS-colonized women with premature labor or prolonged rupture of membranes who were given intrapartum chemoprophylaxis had a substantially lower rate of GBS colonization (9% vs 51%) and early-onset disease (0% vs 6%) than did the infants born to women who were not treated. Maternal postpartum febrile illness was also decreased in the treatment group.

In the mid-1990s, guidelines for chemoprophylaxis were issued that specified administration of intrapartum antibiotics to women identified as high-risk by either culture-based or risk factor–based criteria. These guidelines were revised in 2002 after epidemiologic data indicated the superior protective effect of the culture-based approach in the prevention of neonatal GBS disease, and further revised guidelines were issued in 2010. According to current recommendations, vaginorectal GBS screening cultures should be performed for all pregnant women at 35-37 wk gestation, except for those with GBS bacteriuria during the current pregnancy or a previous infant with invasive GBS disease. Any woman with a positive prenatal screening culture, GBS bacteriuria during pregnancy, or a previous infant with invasive GBS disease should receive intrapartum antibiotics. Women whose culture status is unknown (culture not done, incomplete, or results unknown) and who deliver prematurely (<37 wk gestation), experience prolonged rupture of membranes (≥18 hr), experience intrapartum fever (≥38°C [100.4°F]) or have a positive nucleic acid amplification test for GBS should also receive intrapartum chemoprophylaxis. Routine intrapartum prophylaxis is not recommended for women with GBS colonization undergoing planned cesarean delivery who have not begun labor or had rupture of membranes.

Penicillin remains the preferred agent for maternal chemoprophylaxis because of its narrow spectrum and the universal penicillin susceptibility of GBS isolates associated with human infection. Ampicillin is an acceptable alternative. If amnionitis is suspected, broad-spectrum antibiotic therapy that includes an agent active against GBS should replace GBS prophylaxis. Occasional GBS isolates have demonstrated reduced in vitro susceptibility to penicillin and other β-lactam antibiotics in association with mutations in penicillin-binding proteins. However, such strains have not been reported in invasive infection. Because of recent reports indicating frequent resistance of GBS to clindamycin (up to 20%), cefazolin should be used in most cases of intrapartum chemoprophylaxis for penicillin-intolerant women. For penicillin-allergic women at high risk for anaphylaxis, clindamycin should be used, if isolates are demonstrated to be susceptible. Vancomycin should be used if isolates are resistant to, or demonstrate inducible resistance to, clindamycin or if clindamycin susceptibility is unknown.

The Centers for Disease Control and Prevention (CDC) guidelines also provide recommendations for secondary prevention of early onset GBS disease among newborns (Fig. 184-2). Extent of newborn evaluation and decision to institute empiric antibiotics is guided by clinical evaluation of the infant as well as gestational age, maternal risk factors, and receipt of intrapartum prophylaxis. In the era of maternal chemoprophylaxis, most cases of early onset disease are seen in infants born to women with negative prenatal screening cultures. Data from a large epidemiologic study indicate that the administration of maternal intrapartum antibiotics does not change the clinical spectrum or delay the onset of clinical signs in infants who developed GBS disease despite maternal prophylaxis.

A significant concern with maternal intrapartum prophylaxis has been that large-scale antibiotic use among parturient women might lead to increased rates of antimicrobial resistance or infection in infants with organisms other than GBS. To date, an increase in the incidence of non-GBS early-onset neonatal infections has been seen only in premature, low-birthweight, and very-low-birthweight infants in whom risk factors other than maternal chemoprophylaxis may play a role. At present, the substantial decline in early-onset neonatal GBS disease favors continued broad-spectrum intrapartum chemoprophylaxis, but continued surveillance is required.

A limitation of the maternal chemoprophylaxis strategy is that intrapartum antibiotic use is unlikely to have an impact on late-onset neonatal disease, miscarriages or stillbirths attributed to GBS, or adult GBS disease. In addition, with wider implementation of maternal chemoprophylaxis, an increasing percentage of early-onset neonatal disease has been in patients born to women with negative cultures, that is, false-negative screens.

**Maternal Immunization**

Human studies demonstrate that transplacental transfer of naturally acquired maternal antibody to the GBS capsular polysaccharide protects newborns from invasive GBS infection and that efficient transplacental passage of vaccine-induced GBS antibodies occurs. Conjugate vaccines composed of the GBS capsular polysaccharides coupled to carrier proteins have been produced for human use. In early clinical trials, conjugate GBS vaccines were well tolerated and induced levels of functional antibodies well above the range believed to be protective in greater than 90% of recipients. A vaccine containing type III polysaccharide coupled to tetanus toxoid was safely administered to pregnant women and elicited functionally active type-specific antibody that was efficiently transported to the fetus. Administration of a multivalent polysaccharide-protein vaccine before or during pregnancy should lead to transplacental passage of vaccine-induced antibody that protects the fetus and newborn against infection by several GBS serotypes. Such a vaccine would eliminate the need for cumbersome cultures during pregnancy, would circumvent the various risks associated with large-scale antibiotic prophylaxis, and would likely have an impact on
both early- and late-onset disease. Intrapartum chemoprophylaxis will likely remain an important aspect of prevention, particularly for women in whom opportunities for GBS immunization are missed and for infants born so early that levels of transplacentally acquired antibodies may not be high enough to be protective.

*Bibliography is available at Expert Consult.*
Chapter 184 • Group B Streptococcus

Bibliography


The genus *Streptococcus* is exceptionally diverse and includes the major human pathogens *Streptococcus pyogenes* (group A streptococcus), *Streptococcus agalactiae* (group B streptococcus) and *Streptococcus pneumoniae* (Table 185-1). Other important pathogens include large-colony species bearing groups C and G Lancefield antigens and numerous small-colony variants that may or may not express Lancefield carbohydrate antigen included among the viridians streptococci (Table 185-1). This chapter focuses on *Streptococcus dysgalactiae* subspecies *equisimilis*, commonly known as “group C and G streptococci,” while Chapter 182 discusses *S. pneumoniae*, and Chapter 186 discusses enterococci, formerly classified among the streptococci but now comprising their own genus.

All members of the genus *Streptococcus* are Gram-positive, catalase-negative organisms. Lancefield carbohydrate antigen, hemolytic activity, and colony morphology have classically been used to further distinguish and classify streptococci. These features provide a useful framework for the clinician and are still the most commonly used classification schema. However, grouping based on these phenotypic features does not precisely correlate with genetic relatedness, and it is becoming clear that disease propensity is better correlated with sequence homology than Lancefield grouping or hemolytic activity. As a consequence, the streptococci are undergoing taxonomic reclassification as genome sequence information becomes available.

In this chapter, groups C and G streptococci refer exclusively to the large colony-forming organisms, often called *S. pyogenes*-like, as their microbiologic and clinical features tend to mimic those of group A streptococcus. Despite their different Lancefield antigens, the group C and G streptococci are nearly identical genetically and are placed within the *S. dysgalactiae, equisimilis* subspecies. Their genome sequences are approximately equidistant between *S. pyogenes* and animal pathogens that bear the group C antigen, which are classified as *S. dysgalactiae* subspecies *dysgalactiae*. It is likely that *S. dysgalactiae* will be split into distinct species in the future, when their sequence-based grouping will reflect their propensity to cause human (represented by subspecies *equisimilis*) and animal (represented by subspecies *dysgalactiae*) infections.

The groups C and G streptococci share a number of virulence factors with *S. pyogenes*, including the production of streptolysin O, M protein, streptococcal pyrogenic exotoxin B, and hyaluronidase. The M protein is similar to that of *S. pyogenes* and may account for postinfectious glomerulonephritis that is occasionally seen after infection with these organisms. A toxic-shock–like syndrome associated with groups C and G streptococcal infection has been related to production of a pyrogenic exotoxin by *S. dysgalactiae* subsp. *equisimilis*.

Groups C and G streptococci are common habitants of the pharynx, being detected in up to 5% of asymptomatic children. Other potential sites of colonization include the skin and gastrointestinal tract. Colonization of the vagina is reported and may be the source of occasional *S. dysgalactiae* subsp. *equisimilis* isolated from the umbilicus of healthy neonates.

Clinical manifestations of disease caused by groups C and G streptococci overlap those of *S. pyogenes*. In children, these organisms are implicated most commonly in pharyngitis. The true role of these organisms as a cause of pharyngitis is difficult to determine because asymptomatic colonization is common. Nevertheless, several epidemics of group C and group G streptococcal pharyngitis have been reported, including foodborne outbreaks. It is possible that primary infection with groups C and G streptococci has the same potential to
Clindamycin and macrolides have poor bactericidal activity against these organisms, particularly against group G streptococci. Resistance to quinolones is reported, and up to 70% of group C streptococci are resistant to tetracycline.

Bibliography is available at Expert Consult.
Bibliography

Enterococcus, long recognized as a pathogen in select populations, has become a common and particularly troublesome cause of hospital-acquired infection over the past 2 decades. Enterococci were formerly classified with *Streptococcus bovis* and *Streptococcus equinus* as Lancefield group D streptococci but are now placed in a separate genus and are notorious for their frequent resistance to antibiotics.

**ETIOLOGY**
Enterococci are Gram-positive, catalase-negative facultative anaerobes that grow in pairs or short chains. Most are nonhemolytic (also called γ-hemolytic) on sheep blood agar, although some isolates have α- or β-hemolytic activity. Enterococci are distinguished from most Lancefield groupable streptococci by their ability to grow in bile and hydrolyze esculin. Enterococci are able to grow in 6.5% NaCl and hydrolyze L-pyrrolidonyl-β-naphthylamide, features used by clinical laboratories to distinguish enterococci from group D streptococci. Identification at the species level is enabled by differing patterns of carbohydrate fermentation.

**EPIDEMIOLOGY**
Enterococci are normal inhabitants of the gastrointestinal tract of humans, and organisms throughout the animal kingdom, suggesting
they are highly evolved to occupy this niche. Oral secretions and dental plaque, the upper respiratory tract, skin, and vagina may also be colonized by Enterococcus. Enterococcus faecalis is the predominant organism, with colonization commonly occurring in the 1st wk of life. By the time of adulthood, E. faecalis colonization is nearly ubiquitous. Enterococcus faecium colonization is less consistent, although approximately 25% of adults harbor this organism. Disruption of the normal intestinal microbiota by antibiotic exposure or hematopoietic stem cell transplantation markedly enriches for fecal enterococcal abundance and dramatically increases the risk of subsequent bloodstream infection.

E. faecalis accounts for approximately 80% of enterococcal infections, with almost all of the remaining infections caused by E. faecium. Only rarely are other species, such as Enterococcus gallinarum and Enterococcus casseliflavus, associated with invasive infection, but these organisms are notable for their intrinsic low-level vancomycin resistance. Whole-genome sequencing suggests that the patient’s indigenous flora is the source of enterococcal infection in most cases. However, direct spread from person to person or from contaminated medical devices may occur, particularly within newborn nurseries and intensive care units where nosocomial spread has resulted in hospital outbreaks.

**PATHOGENESIS**

Enterococci are not aggressively invasive organisms, usually causing disease only in children with damaged mucosal surfaces or impaired immune response. Their dramatic emergence as a cause of nosocomial infection is predominately a result of their resistance to antibiotics commonly used in the hospital setting. Hospital-associated enterococci generally lack CRISPR (clustered regularly interspaced short palindromic repeats) elements. Their diverse antimicrobial resistance repertoire is likely related to deficient CRISPR-mediated defense against phage-mediated horizontal gene transfer. Secreted and cell-surface molecules are implicated in pathogenesis. Adhesion-promoting factors such as the surface protein Eps likely account for the propensity of these organisms to cause endocarditis and urinary tract infections (UTIs). The ability to form biofilms likely facilitates the colonization of urinary and vascular catheters. Other proposed virulence factors include cytolysin, aggregation substance, gelatinase, and extracellular superoxide.

**Antimicrobial Resistance**

Enterococci are highly resistant to cephalosporins and semisynthetic penicillins such as nafcillin, oxacillin, and methicillin. They are moderately resistant to extended-spectrum penicillins such as ticarcillin and carbenicillin. Ampicillin, imipenem, and penicillin are the most active β-lactams against these organisms. Some strains of E. faecalis and E. faecium demonstrate decreased resistance to β-lactam antibiotics due to mutations in penicillin binding protein 5. In addition, occasional strains of E. faecalis produce a plasmid-encoded β-lactamase similar to that found in Staphylococcus. These isolates are completely resistant to penicillin, necessitating the combination of a penicillin plus a β-lactamase inhibitor or the use of imipenem or vancomycin. Any active drug may be insufficient if used alone for serious infections wherein high bactericidal activity is desired (Tables 186-1 and 186-2).

All enterococci have intrinsic low-level resistance to aminoglycosides because these antibiotics are poorly transported across the Enterococcus cell wall. Concomitant use of a cell wall active agent, such as a β-lactam or glycopeptide antibiotic, improves the permeability of the cell wall for the aminoglycosides, resulting in synergistic killing. However, some isolates demonstrate high-level resistance, defined as mean inhibitory concentration (MIC) >2,000 μg/mL. A result of modification or inactivation of aminoglycoside agents. Strains demonstrating high-level resistance, and even some moderately resistant isolates, are not affected synergistically by aminoglycosides and cell wall-active antibiotics.

Resistance to almost all other antibiotic classes, including tetracyclines, macrolides, and chloramphenicol, has been described among the enterococci, necessitating individual susceptibility testing for these antibiotics when their use is considered. Despite apparent susceptibility in vitro, trimethoprim-sulfamethoxazole has poor activity in vivo and should not be used as the primary agent against Enterococcus infections.

Vancomycin has traditionally been effective against Enterococcus isolates, but resistance to vancomycin, defined as MIC >32 μg/mL, and other glycopeptides, including teicoplanin, is increasingly common. The emergence of vancomycin-resistant Enterococcus (VRE) has become a major challenge in the care of hospitalized patients. In particular, mortality in patients with VRE bloodstream infections is considerable, and treatment is complicated by frequent resistance of VRE to most other antibiotic classes. Both high- and moderate-level resistance are described in E. faecalis and E. faecium. High-level resistance (MIC 264 μg/mL) can be transferred by way of conjugation and usually results from plasmid-mediated transfer of the vanA gene. High-level resistance is most common among E. faecium, but is increasingly seen among E. faecalis isolates. Moderate-level resistance (MIC 8-256 μg/mL) results from a chromosomal homolog of vanA, known as vanB. Isolates that harbor the vanB gene are only moderately resistant to vancomycin and initially demonstrate susceptibility to teicoplanin, although resistance can emerge during therapy. Resistance to newer agents, including linezolid and daptomycin, is rare thus far. Linezolid resistance is a result of mutations in the 26S ribosomal subunit, whereas daptomycin resistance is associated with mutations in genes required for membrane synthesis and repair.

**CLINICAL MANIFESTATIONS**

Enterococcus infections traditionally occurred predominantly in newborn infants; infection in older children is increasingly common. Most Enterococcus infections occur in patients with breakdown of normal physical barriers such as the gastrointestinal tract, skin, or urinary tract. Other risk factors for Enterococcus infection include
prolonged hospitalization, indwelling vascular catheters, prior use of antibiotics, and compromised immunity.

**Neonatal Infections**

*Enterococcus* accounts for up to 15% of all neonatal bacteremia and septicemia. Like group B streptococcus infections, *Enterococcus* infections are seen in 2 distinct settings in neonatal patients. Early-onset infection (<7 days of age) may mimic early-onset group B streptococcus septicemia, but tends to be milder. Early-onset *Enterococcus* sepsis most often occurs in full-term infants who are otherwise healthy. Late-onset infection (≥7 days of age) is associated with risk factors such as extreme prematurity, presence of an intravascular catheter, or necrotizing enterocolitis, or if follows an intraabdominal surgical procedure. Symptoms in late-onset disease are more severe than those in early-onset disease and include apnea, bradycardia, and deteriorating respiratory function. Focal infections such as scalp abscess and catheter infection are commonly associated. Mortality rates range from 6% in early-onset sepsis to 15% in late-onset infections associated with necrotizing enterocolitis.

Enterococci are an occasional cause of meningitis. In neonates in particular, meningitis usually occurs as a complication of septicemia. Alternatively, the organism may gain access to the central nervous system by way of contiguous spread, such as through a neural tube defect or in association with an intraventricular shunt. *Enterococcus* meningitis can be associated with minimal abnormality of cerebrospinal fluid.

**Infections in Older Children**

*Enterococcus* rarely causes UTIs in healthy children but accounts for approximately 15% of cases of nosocomially acquired UTIs in both children and adults. Presence of an indwelling urinary catheter is the major risk factor for nosocomial UTIs. *Enterococcus* is frequently isolated in intraabdominal infections following intestinal perforation or surgery. The significance of enterococci in polymicrobial infections has been questioned, although reported mortality rates are higher when intraabdominal infections include enterococci. *Enterococcus* is increasingly common as a cause of nosocomial bacteremia; these organisms accounted for approximately 10% of nosocomial bloodstream infection in children, ranking second only to coagulase-negative staphylococci. Predisposing factors for enterococcal bacteremia and endocarditis include an indwelling central venous catheter, gastrointestinal surgery, immunodeficiency, and cardiovascular abnormalities. Risk factors for vancomycin-resistant enterococcal bacteremia include prolonged mechanical ventilation, immunosuppression, and recent vancomycin exposure.

**TREATMENT**

Treatment of invasive *Enterococcus* infections must recognize that these organisms are resistant to antimicrobial agents frequently used as empirical therapy. In particular, cephalosporins should not be relied upon in situations where *Enterococcus* is known or suspected to be involved. In general, in the immunocompetent host, minor localized infections caused by susceptible *Enterococcus* can be treated with ampicillin alone. Antibiotics containing β-lactamase inhibitors (clavulanate or sulbactam) provide advantage only for the few organisms whose resistance is owing to production of β-lactamase. In uncomplicated UTIs, nitrofurantoin is efficacious when the organism is known to be sensitive to this antibiotic.

Invasive infections, such as sepsis, meningitis, and endocarditis, are usually treated with a combination of penicillin or ampicillin and an aminoglycoside when the isolate is susceptible. Vancomycin can be substituted for the penicillins in allergic patients, but should be used with an aminoglycoside, because vancomycin alone is not bactericidal. Endocarditis from strains possessing high-level aminoglycoside resistance may relapse even after prolonged therapy. High-dose or continuous infusion penicillin has been proposed for treatment of these infections in adults, yet ultimately valve replacement may be necessary. In patients with catheter-associated enterococcal bacteremia, the catheter should be removed promptly in most cases, although salvage of infected lines has occurred with the combined use of ampicillin or vancomycin with an aminoglycoside.

**Treatment of Vancomycin-Resistant Enterococci**

The treatment of serious infections caused by multiresistant, vancomycin-resistant strains is particularly challenging. Linezolid, an oxazolidinone antibiotic that inhibits protein synthesis, is bacteriostatic against most *E. faecium* and *E. faecalis*, including vancomycin-resistant isolates. Response rates are generally over 90%, including cases of bacteremia and sepsis, and this antibiotic has become the preferred agent in treatment of VRE infections in many institutions. Anecdotal reports reveal the success of linezolid in treating meningitis caused by vancomycin-resistant enterococci. Unfortunately, as seen with other antibiotics, linezolid resistance is documented and nosocomial spread of these organisms can occur. Linezolid frequently causes reversible bone marrow suppression after prolonged use and is associated with rare occurrences of lactic acidosis and irreversible peripheral neuropathy. Serotonin syndrome may be seen in patients taking concomitant selective serotonin uptake inhibitors and antidepressants. Oxazolidinones in development include tedizolid, which has better in vitro activity against enterococci and appears to have favorable pharmacokinetic and toxicity profiles when compared to linezolid.

Quinupristin/dalfopristin is a combined streptogramin antibiotic that inhibits bacterial protein synthesis at 2 different stages. It has activity against most *E. faecium* strains, including those with high-level vancomycin resistance. Approximately 90% of *E. faecium* strains are susceptible to quinupristin/dalfopristin in vitro. Notably, it is inactive against *E. faecalis* and therefore should not be used as the sole agent against Gram-positive organisms until culture results exclude the presence of *E. faecalis*. Studies in children suggest that this antibiotic is effective and generally well tolerated, though episodes of arthralgia and myalgia during therapy are reported. Emergence of resistance to quinupristin/dalfopristin is rare but has been demonstrated.

Newer antibiotics with reliable activity against VRE include daptomycin and tigecycline. Daptomycin is a cyclic lipopeptide that is rapidly bactericidal against a broad range of Gram-positive organisms. The antibiotic inserts into the bacterial cell wall, causing membrane depolarization and cell death. It has been approved for the treatment of adults with serious skin and soft tissue infections, right-sided endocarditis, and bacteremia due to susceptible organisms. Most strains of VRE (both *E. faecium* and *E. faecalis*) are susceptible to daptomycin in vitro, and its efficacy in adult patients with VRE appears to be similar to that of linezolid. Experience with daptomycin in children is limited, particularly in the setting of *Enterococcus* infections. However, based on the experience with adult patients, daptomycin may be an alternative to linezolid when resistance or side-effects limit utility of that antibiotic. Daptomycin dosages may need to be higher in children when compared to adults because of more rapid renal clearance. The antibiotic has unreliable activity in the lung and therefore should not be used as a sole agent to treat pneumonia. Resistance of both *Staphylococcus aureus* and *Enterococcus* to daptomycin has rarely been described, sometimes arising during therapy. Cefaroline, a fifth-generation cephalosporin with activity against methicillin-resistant *S. aureus*, has activity against many *E. faecalis* strains and may be highly synergistic with daptomycin against daptomycin-nonsusceptible strains.

Tigecycline is the first clinically available glycylcycline antibiotic, an expended-spectrum derivative of the tetracycline family. The agent inhibits protein synthesis by binding to the 30S ribosome and is bacteriostatic against susceptible organisms. Tigecycline has broad activity against Gram-positive, Gram-negative, and anaerobic organisms, including methicillin-resistant *S. aureus* and VRE, and is approved for the treatment of adults with skin and soft-tissue infections and intraabdominal infections caused by susceptible organisms. Its efficacy in VRE infections has not yet been demonstrated in clinical trials and there is little published experience with the use of tigecycline in children thus
far. Like other tetracycline antibiotics, tigecycline use may cause discoloration of the teeth, and its use in children younger than 8 yr of age should generally be avoided. Gastrointestinal side effects are common and may be intolerable.

**Prevention**

Strategies for preventing enterococcal infections include timely removal of urinary and intravenous catheters and debridement of necrotic tissue. Infection control strategies, including surveillance cultures, patient and staff cohorting, and strict gown and glove isolation are effective at decreasing colonization rates with vancomycin-resistant enterococci. Unfortunately, these organisms may persist on inanimate objects such as stethoscopes, complicating efforts to limit their nosocomial spread. In order to prevent the emergence and spread of vancomycin resistant organisms, the Centers for Disease Control and Prevention has developed a series of guidelines for prudent vancomycin use. Antibiotics with broad activity against anaerobic organisms are also thought to contribute to colonization with VRE, suggesting that prudent use of such antibiotics may also help limit spread of VRE. Decolonization strategies have been attempted but are generally ineffective in eradicating skin or gastrointestinal carriage of VRE. In particular, antimicrobial therapy is not indicated for this purpose. The role of probiotic agents in eliminating VRE colonization is currently unclear, but may be a useful adjunct to prudent antimicrobial usage and other infection control interventions in limiting nosocomial spread of VRE.

*Bibliography is available at Expert Consult.*
**Bibliography**
Diphtheria is an acute toxic infection caused by Corynebacterium species, typically Corynebacterium diphtheriae and, rarely, toxigenic strains of Corynebacterium ulcerans. Although diphtheria was reduced from a major cause of childhood death to a medical rarity in the Western hemisphere in the early 20th century, recurring reminders of the fragility of this success emphasize the necessity to continue vigorous promotion of those same control principles across the global community.

ETIOLOGY
Corynebacteria are aerobic, nonencapsulated, non–spore-forming, mostly nonmotile, pleomorphic, Gram-positive bacilli. C. diphtheriae is by far the most commonly isolated agent of diphtheria. C. ulcerans is more commonly isolated from animal sources and can cause similar human disease. As Corynebacteria are not fastidious in growth requirements, their isolation is enhanced by use of a selective medium (e.g., cystine-tellurite blood agar or Tinsdale agar) that inhibits growth of competing organisms and, when reduced by C. diphtheriae, renders colonies gray-black. Differentiation of C. diphtheriae from C. ulcerans is based on urease activity, because C. ulcerans is urease-positive. Four C. diphtheriae biotypes (mitis, intermedius, belfanti, gravis) are capable of causing diphtheria and are differentiated by colonial morphology, hemolysis, and fermentation reactions. The ability to produce diphtheritic toxin results from acquisition of a lysogenic Corynebacterium diphtheriae

riophage by either C. diphtheriae or C. ulcerans, which encodes the diphtheritic toxin gene and confers diphtheria-producing potential on these strains. Thus, indigenous nontoxigenic C. diphtheriae can be rendered toxigenic and disease-producing after importation of a toxigenic C. diphtheriae. Demonstration of diphtheritic toxin production or potential for toxin production by an isolate is necessary to confirm disease. The former is done in vitro using the agar immunoprecipitin technique (Elek test) or in vivo with the toxin neutralization test in guinea pigs, and the latter by polymerase chain reaction testing for carriage of the toxin gene. Toxigenic and nontoxigenic strains are indistinguishable by colony type, microscopic features, or biochemical test results.

EPIDEMIOLOGY
Unlike other diphtheroids (coryneform bacteria), which are ubiquitous in nature, C. diphtheriae is an exclusive inhabitant of human mucous membranes and skin. Spread is primarily by airborne respiratory droplets, direct contact with respiratory secretions of symptomatic individuals, or exudate from infected skin lesions. Asymptomatic respiratory tract carriage is important in transmission. Where diphtheria is endemic, 3-5% of healthy individuals can carry toxigenic organisms, but carriage is exceedingly rare if diphtheria is rare. Skin infection and skin carriage are silent reservoirs of C. diphtheriae, and organisms can remain viable in dust or on fomites for up to 6 mo. Transmission through contaminated milk and through an infected food handler has been proven or suspected.

In the 1920s, more than 125,000 diphtheria cases, with 10,000 deaths, were reported annually in the United States, with the highest fatality rates among the very young and the elderly. The incidence then began to decrease and, with widespread use of diphtheria toxoid in the United States after World War II, declined steadily through the late 1970s. Since then, ≤55 cases have occurred annually in the United States, with no epidemics of respiratory tract diphtheria. Similar decreases occurred in Europe. Despite the worldwide decrease in disease incidence, diphtheria remains endemic in many developing countries with poor immunization rates against diphtheria.

When diphtheria was endemic, it primarily affected children younger than 15 yr of age. Since the introduction of toxoid immunization, the disease has shifted to adults who lack natural exposure to toxigenic C. diphtheriae in the vaccine era and have low rates of booster immunization. In the 27 sporadic cases of respiratory tract diphtheria reported in the United States in the 1980s, 70% occurred among persons older than 25 yr of age. The largest outbreak of diphtheria in the developed world since the 1960s occurred from 1990-1996 in the newly independent countries of the former Soviet Union, involving more than 150,000 cases in 14 countries. Of these, more than 60% of cases occurred in individuals older than 14 yr of age. Case fatality rates ranged from 3-23% by country. Factors contributing to the epidemic included a large population of underimmunized adults, decreased childhood immunization rates, population migration, crowding, and failure to respond aggressively during early phases of the epidemic. Cases of diphtheria among travelers from these endemic areas were transported to many countries in Europe.

Most proven cases of respiratory tract diphtheria in the United States in the 1990s were associated with importation of toxigenic C. diphtheriae, although clonally related toxigenic C. diphtheriae has persisted in this country and Canada for at least 25 yr.

Cutaneous diphtheria, a curiosity when diphtheria was common, accounted for more than 50% of reported C. diphtheriae isolates in the United States by 1975. This indolent local infection, compared with mucosal infection, is associated with more prolonged bacterial shedding, greater contamination of the environment, and increased transmission to the pharynx and skin of close contacts. Outbreaks are associated with homelessness, crowding, poverty, alcoholism, poor hygiene, contaminated fomites, underlying dermatosis, and introduction of new strains from exogenous sources. It is no longer a tropical or subtropical disease; 1,100 C. diphtheriae infections were documented in a neighborhood in Seattle (site of the last major U.S.
outbreak), from 1971–1982; 86% were cutaneous, and 40% involved toxigenic strains. Cutaneous diphtheria is an important source for toxigenic C. diphtheriae in the United States, and its importation is frequently the source for subsequent sporadic cases of respiratory tract diphtheria.

**PATHOGENESIS**

Both toxigenic and nontoxigenic C. diphtheriae cause skin and mucosal infection and can rarely cause focal infection after bacteremia. The organism usually remains in the superficial layers of skin lesions or respiratory tract mucosa, inducing local inflammatory reaction. The major virulence of the organism lies in its ability to produce the potent 62-kDa polypeptide exotoxin, which inhibits protein synthesis and causes local tissue necrosis. Within the 1st few days of respiratory tract infection (usually in the pharynx), a dense necrotic coagulum of organisms, epithelial cells, fibrin, leukocytes, and erythrocytes forms, advances, and becomes a gray-brown, leather-like adherent pseudomembrane (Diphthera is Greek for leather). Removal is difficult and reveals a bleeding edematous submucosa. Paralysis of the palate and hypopharynx is an early local effect of diphtheritic toxin. Toxin absorption can lead to systemic manifestations: kidney tubule necrosis, thrombocytopenia, cardiomyopathy, and/or demyelination of nerves. Because the latter complications can occur 2-10 wk after mucocutaneous infection, the pathophysiology in some cases is suspected to be immunologically mediated.

**CLINICAL MANIFESTATIONS**

The manifestations of C. diphtheriae infection are influenced by the anatomic site of infection, the immune status of the host, and the production and systemic distribution of toxin.

**Respiratory Tract Diphtheria**

In a classic description of 1,400 cases of diphtheria in California (1954), the primary focus of infection was the tonsils or pharynx (94%), with the nose and larynx the next 2 most common sites. After an average incubation period of 2-4 days, local signs and symptoms of inflammation develop. Infection of the anterior nares is more common among infants and causes serosanguineous, purulent, erosive rhinitis with membrane formation. Shallow ulceration of the external nares and upper lip is characteristic. In tonsillar and pharyngeal diphtheria, sore throat is the universal early symptom. Only half of patients have fever, and fewer have dysphagia, hoarseness, malaise, or headache. Mild pharyngeal injection is followed by unilateral or bilateral tonsillar membrane formation, which can extend to involve the uvula (which may cause toxin-mediated paralysis), soft palate, posterior oropharynx, hypopharynx, or glottic areas (Fig. 187-1). Underlying soft-tissue edema and enlarged lymph nodes can cause a bull-neck appearance. The degree of local extension correlates directly with profound prostration, bull-neck appearance, and fatality due to airway compromise or toxin-mediated complications (Fig. 187-2).

The characteristic adherent membrane, extension beyond the faucal area, dysphagia, and relative lack of fever help differentiate diphtheria from exudative pharyngitis caused by Streptococcus pyogenes or Epstein-Barr virus. Vincent angina, infective phlebitis with thrombosis of the jugular veins (Lemierre disease), and mucositis in patients undergoing cancer chemotherapy are usually differentiated by the clinical setting. Infection of the larynx, trachea, and bronchi can be primary or a secondary extension from the pharyngeal infection. Hoarseness, stridor, dyspnea, and croupy cough are clues. Differentiation from bacterial epiglottitis, severe viral laryngotracheobronchitis, and staphylococcal or streptococcal tracheitis hinges partially on the relative paucity of other signs and symptoms in patients with diphtheria and primarily on visualizaton of the adherent pseudomembrane at the time of laryngoscopy and intubation.

Patients with laryngeal diphtheria are at significant risk for suffocation because of local soft-tissue edema and airway obstruction by the diphtheritic membrane, a dense cast of respiratory epithelium, and necrotic coagulum. Establishment of an artificial airway and resection of the pseudomembrane can be lifesaving, but further obstructive complications are common, and systemic toxic complications are inevitable.

**Cutaneous Diphtheria**

Classic cutaneous diphtheria is an indolent, nonprogressive infection characterized by a superficial, eczema-like, nonhealing ulcer with a gray-brown membrane. Diphtheritic skin infections cannot always be differentiated from streptococcal or staphylococcal impetigo, and these conditions frequently coexist. In most cases, a primary process, such as dermatitis, laceration, burns, bite, or impetigo, becomes secondarily infected with C. diphtheriae. Extremities are more often affected than the trunk or head. Pain, tenderness, erythema, and exudate are typical. Local hyperesthesia or hypesthesia is unusual. Respiratory tract colonization or symptomatic infection with toxic complications occurs in the minority of patients with cutaneous diphtheria. Among infected adults in the Seattle outbreak, 3% with cutaneous infections and 21%...
with symptomatic nasopharyngeal infection, with or without skin involvement, demonstrated toxic myocarditis, neuropathy, or obstructive respiratory tract complications. All had received at least 20,000 units of equine antitoxin at the time of hospitalization.

**Infection at Other Sites**

*C. diphtheriae* occasionally causes mucocutaneous infections at other sites, such as the ear (otitis externa), the eye (purulent and ulcerative conjunctivitis), and the genital tract (purulent and ulcerative vulvovaginitis). The clinical setting, ulceration, membrane formation, and submucosal bleeding help differentiate diphtheria from other bacterial and viral causes. Rare cases of septicaemia are described and are universally fatal. Sporadic cases of endocarditis occur, and clusters among intravenous drug users have been reported in several countries; skin was the probable portal of entry, and almost all strains were nonotoxigenic. Sporadic cases of pyogenic arthritis, mainly from nontoxicogenic strains, have been reported in adults and children. Diphtheroids isolated from sterile body sites should not be routinely dismissed as contaminants without careful consideration of the clinical setting.

**DIAGNOSIS**

Specimens for culture should be obtained from the nose and throat and any other mucocutaneous lesion. A portion of membrane should be removed and submitted for culture along with underlying exudate. The laboratory must be notified to use selective medium. *C. diphtheriae* survives drying. If obtained in a remote area, a swab specimen can be placed in a silica gel pack and sent to the laboratory. Evaluation of a direct smear using Gram stain or specific fluorescent antibody is unreliable. Culture isolates of coryneform organisms should be identified to the species level, and toxigenicity and antimicrobial susceptibility tests should be performed for *C. diphtheriae* isolates.

**COMPLICATIONS**

Respiratory tract obstruction by pseudomembranes may require bronchoscopy or intubation and mechanical ventilation. Two other tissues usually remote from sites of *C. diphtheriae* infection can be significantly affected by diphtheritic toxin: the heart and the nervous system.

**Toxic Cardiomyopathy**

Toxic cardiomyopathy occurs in 10-25% of patients with respiratory diphtheria and is responsible for 50-60% of deaths. Subtle signs of myocarditis can be detected in most patients, especially the elderly, but the risk for significant complications correlates directly with the extent and severity of exudative local oropharyngeal disease as well as delay in administration of antitoxin. The first evidence of cardiac toxicity characteristically occurs during the 2nd and 3rd wk of illness as the liability. Culture isolates of coryneform organisms should be identified to the species level, and toxigenicity and antimicrobial susceptibility tests should be performed for *C. diphtheriae* isolates.

**Toxic Neuropathy**

Neurologic complications parallel the severity of primary infection and are multiphasic in onset. Acutely or 2-3 wk after onset of oropharyngeal inflammation, it is common for hypesthesia and local paralysis of the soft palate to occur. Weakness of the posterior pharyngeal, laryngeal, and facial nerves may follow, causing a nasal quality in the voice, difficulty in swallowing, and risk for aspiration. Cranial neuropathies characteristically occur in the 5th wk, leading to oculomotor and ciliary paralysis, which can cause strabismus, blurred vision, or difficulty with accommodation. Symmetric polyneuropathy has its onset 10 days to 3 mo after oropharyngeal infection and causes principally motor deficits with diminished deep tendon reflexes. Distal muscle weakness in the extremities with proximal progression is more commonly described than proximal muscle weakness with distal progression. Clinical and cerebrospinal fluid findings in the former are indistinguishable from those of Guillain-Barré syndrome. Paralysis of the diaphragm may ensue. Complete neurologic recovery is likely, but rarely vasomotor center dysfunction 2-3 wk after onset of illness can cause hypotension or cardiac failure.

Recovery from the myocarditis and neuritis is often slow but usually complete. Corticosteroids do not diminish these complications and are not recommended.

**TREATMENT**

Specific antitoxin is the mainstay of therapy and should be administered on the basis of clinical diagnosis. Because it neutralizes only free toxin, antitoxin efficacy diminishes with elapsed time after the onset of mucocutaneous symptoms. Equine diphtheria antitoxin is available in the United States only from the Centers for Disease Control and Prevention (CDC). Physicians treating a case of suspected diphtheria should contact the CDC diphtheria duty officer (770-488-7100 at all times). Antitoxin is administered as a single empirical dose of 20,000-100,000 units based on the degree of toxicity, site and size of the membrane, and duration of illness. Antitoxin is probably of no value for local manifestations of cutaneous diphtheria, but its use is prudent because toxic sequelae can occur. Commercially available intravenous immunoglobulin preparations contain low titers of antibodies to diphtheria toxin; their use for therapy of diphtheria is not proven or approved. Antitoxin is not recommended for asymptomatic carriers.

The role of antimicrobial therapy is to halt toxin production, treat localized infection, and prevent transmission of the organism to contacts. *C. diphtheriae* is usually susceptible to various agents in vitro, including penicillins, erythromycin, clindamycin, rifampin, and tetracycline. Resistance to erythromycin is common in populations if the drug has been used broadly. Only erythromycin or penicillin is recommended; erythromycin is marginally superior to penicillin for eradication of nasopharyngeal carriage. Appropriate therapy is erythromycin (40-50 mg/kg/day divided every 6 hr by mouth [PO] or intravenously [IV]; maximum 2 g/day), aqueous crystalline penicillin G (100,000-150,000 units/kg/day divided every 6 hr IV or intramuscularly [IM]), or daily procaine penicillin (300,000 units/day IM for those <10 kg in weight; 600,000 units/day IM for those >10 kg in weight) for 14 days. Antibiotic therapy is not a substitute for antitoxin therapy. Some patients with cutaneous diphtheria have been treated for 7-10 days. Elimination of the organism should be documented by negative results of at least 2 successive cultures of specimens from the nose and throat (or skin) obtained 24 hr apart after completion of therapy. Treatment with erythromycin is repeated if either culture yields *C. diphtheriae*.

**SUPPORTIVE CARE**

Droplet precautions are instituted for patients with pharyngeal diphtheria; for patients with cutaneous diphtheria, contact precautions are observed until the results of cultures of specimens taken after cessation of therapy are negative. Cutaneous wounds are cleaned thoroughly with soap and water. Bed rest is essential during the acute phase of disease, usually for ≥2 wk until the risk for symptomatic cardiac damage has passed, with a return to physical activity guided by the degree of toxicity and cardiac involvement.

**PROGNOSIS**

The prognosis for patients with diphtheria depends on the virulence of the organism (subspecies gravis has the highest fatality rate), patient age, immunization status, site of infection, and speed of administration
of the antitoxin. Mechanical obstruction from laryngeal diphtheria or bull-neck diphtheria and the complications of myocarditis account for most diphtheria-related deaths. The case fatality rate of almost 10% for respiratory tract diphtheria has not changed in 50 yr; the rate was 8% in a Vietnamese series described in 2004. At recovery, administration of diphtheria toxoid is indicated to complete the primary series or booster doses of immunization, because not all patients develop antibodies to diphtheritic toxin after infection.

**PREVENTION**

Protection against serious disease caused by imported or indigenously acquired *C. diphtheriae* depends on immunization. In the absence of a precisely determined minimum protective level for diphtheria antitoxin, the presumed minimum is 0.01-0.10 IU/mL. In outbreaks, 90% of individuals with clinical disease have had antibody values <0.01 IU/mL, and 92% of asymptomatic carriers have had values >0.1 IU/mL. In serosurveys in the United States and Western Europe, where almost universal immunization during childhood has been achieved, 25% to >60% of adults lack protective antitoxin levels, with very low levels common in the elderly.

All suspected diphtheria cases should be reported to local and state health departments. Investigation is aimed at preventing secondary cases in exposed individuals and at determining the source and carriers to halt spread to unexposed individuals. Reported rates of carriage in household contacts of case patients are 0-25%. The risk for development of diphtheria after household exposure to a case is approximately 2%, and the risk is 0.3% after similar exposure to a carrier.

**Asymptomatic Case Contacts**

All household contacts and people who have had intimate respiratory or habitual physical contact with a patient are closely monitored for illness through the 7-day incubation period. Cultures of the nose, throat, and any cutaneous lesions are performed. Antimicrobial prophylaxis is presumed effective and is administered regardless of immunization status, using a single injection of benzathine penicillin G (600,000 units IM for patients younger than 6 yr of age, or 1,200,000 units IM for patients older than 6 yr of age) or erythromycin (40-50 mg/kg/day divided qid PO for 10 days; maximum: 2 g/day). Diphtheria toxoid vaccine, in age-appropriate form, is given to immunized individuals who have not received a booster dose within 5 yr. Children who have not received their 4th dose should be vaccinated. Those who have received fewer than 3 doses of diphtheria toxoid or who have uncertain immunization status are immunized with an age-appropriate preparation on a primary schedule.

**Asymptomatic Carriers**

When an asymptomatic carrier is identified, antimicrobial prophylaxis is given for 10-14 days and an age-appropriate preparation of diphtheria toxoid is administered immediately if a booster has not been given within 1 yr. Droplet precautions (respiratory tract colonization) or contact precautions (cutaneous colonization only) are observed until at least 2 subsequent cultures obtained 24 hr apart after cessation of therapy have negative results.

Repeat cultures are performed about 2 wk after completion of therapy for cases and carriers; if results are positive, an additional 10-day course of oral erythromycin should be given and follow-up cultures performed. Susceptibility testing of isolates should be performed, as erythromycin resistance is reported. Neither antimicrobial agent eradicates carriage in 100% of individuals. In one report, a single course of therapy failed in 21% of carriers. Transmission of diphtheria in modern hospitals is rare. Only those who have an unusual contact with respiratory or oral secretions should be managed as contacts. Investigation of the casual contacts of patients and carriers or persons in the community without known exposure has yielded extremely low carriage rates and is not routinely recommended.

**Vaccine**

Universal immunization with diphtheria toxoid throughout life, to provide constant protective antitoxin levels and to reduce severity of *C. diphtheriae* disease, is the only effective control measure. Although immunization does not preclude subsequent respiratory or cutaneous carriage of toxigenic *C. diphtheriae*, it decreases local tissue spread, prevents toxic complications, diminishes transmission of the organism, and provides herd immunity when at least 70-80% of a population is immunized.

Diphtheria toxoid is prepared by formaldehyde treatment of toxin, standardized for potency, and adsorbed to aluminum salts, enhancing immunogenicity. Two preparations of diphtheria toxoids are formulated according to the limit of flocculation (Lf) content, a measure of the quantity of toxoid. The pediatric (6 mo-6yr) preparations (i.e., DTaP [diphtheria and tetanus toxoids with acellular pertussis vaccine], DT [diphtheria and tetanus toxoids vaccine]) contain 6.7-25.0 Lf units of diphtheria toxoid per 0.5 mL dose; the adult preparation (dT; 10% of pediatric diphtheria toxoid dose, Tdap [diphtheria and tetanus toxoids with acellular pertussis vaccine]) contain no more than 2 Lf units of toxoid per 0.5 mL dose. The higher-potency (D) formulation of toxoid is used for primary series and booster doses for children through 6 yr of age because of superior immunogenicity and minimal reactogenicity. For individuals 7 yr of age or older, DT is recommended for the primary series and booster doses because the lower concentration of diphtheria toxoid is adequately immunogenic and increasing the content of diphtheria toxoid heightens reactogenicity with increasing age.

For children 6 wk to 6 yr of age, five 0.5 mL doses of diphtheria-containing (D) vaccine (DTaP preferred) are given in the primary series, including 3 doses at 2, 4, and 6 mo of age, and a 4th dose, an integral part of the primary series, 15-18 mo after the 3rd dose. A booster dose is given at 4-6 yr of age (unless the 4th primary dose was administered at age 4 yr or older). For persons 7 yr of age and older, three 0.5 mL doses of lower-level diphtheria-containing (D) vaccine are given in a primary series of 2 doses 4-8 wk apart and a 3rd dose 6-12 mo after the 2nd dose. The 1st dose should be Td, and subsequent doses should be Td. The only contraindication to tetanus and diphtheria toxoid is a history of neurologic or severe hypersensitivity reaction after a prior dose. For children younger than 7 yr of age in whom pertussis immunization is contraindicated, DT is used. Those whose immunization is begun with DTaP or DT before 1 yr of age should have a total of five 0.5 mL doses of diphtheria-containing (D) vaccines by 6 yr of age. For those whose immunization is begun at around 1 yr of age, the primary series is three 0.5 mL doses of diphtheria-containing (D) vaccine, with a booster given at 4-6 yr, unless the 3rd dose was given after the 4th birthday.

A booster dose, consisting of the adult preparation of Tdap, is recommended at 11-12 yr of age. Adolescents 13-18 yr of age who missed the Td or Tdap booster dose at 11-12 yr or in whom it has been 5 or more years since the Td booster dose also should receive a single dose of Tdap if they have completed the DTP/DTaP series.

There is no association of DT or dT with convulsions. Local adverse effects alone do not preclude continued use. The patient who experiences an Arthus-type hypersensitivity reaction or a temperature >39.4°C (103°F) after a dose of dT, which is rare, usually has high serum tetanus antitoxin levels and should not be given dT more frequently than every 10 yr, even if the patient sustains a significant tetanus-prone injury. The DT or dT preparation can be given concurrently with other vaccines. *Haemophilus influenzae* conjugate vaccines containing diphtheria toxoid (PRP-D) or the variant of diphtheria toxin, CRM197 protein (HbO2), are not substitutes for diphtheria toxoid immunization and do not affect reactogenicity.

*Bibliography is available at Expert Consult.*
Bibliography
Listeriosis in humans is caused principally by *Listeria monocytogenes*, 1 of 6 species of the genus *Listeria* that are widely distributed in the environment and throughout the food chain. Human infections can usually be traced to an animal reservoir. Infection occurs commonly at the extremes of age. In the pediatric population, perinatal infections predominate and usually occur secondary to maternal infection or colonization. Outside the newborn period, disease is most commonly encountered in immunosuppressed (T-cell deficiencies) children and adults and in the elderly. For most people the major risk for infection with *Listeria* is foodborne transmission. In the United States, foodborne outbreaks are caused by improperly processed dairy products and contaminated vegetables and principally affect the same individuals at risk for sporadic disease.

**Etiology**

Members of the genus *Listeria* are facultatively anaerobic, non–spore-forming, motile, Gram-positive bacilli that are catalase positive. In the laboratory *Listeria* can be distinguished from other Gram-positive bacilli by their characteristic tumbling motility and growth at cold temperature (4-10°C [39.2-50°F]). The 6 *Listeria* species are divided into 2 genomically distinct groups based on the basis of DNA-DNA hybridization studies. One group contains the species *Listeria grayi*, considered nonpathogenic. The second group contains 5 species: the nonhemolytic species *Listeria innocua* and *Listeria welshimeri* and the hemolytic species *L. monocytogenes, Listeria seeligeri*, and *Listeria ivanovii*. *L. ivanovii* is pathogenic primarily in animals, and the vast majority of both human and animal disease is caused by *L. monocytogenes*.

Subtyping of *L. monocytogenes* isolates for epidemiologic purposes has been attempted with the use of heat-stable somatic O and heat-labile flagellar H antigens, phage typing, pulsed-field gel electrophoresis, ribotyping, and multilocus enzyme electrophoresis. Electrophoretic typing demonstrates the clonal structure of populations of *L. monocytogenes* as well as the sharing of populations between human and animal sources. Subtyping is an important component of determining whether cases are connected or sporadic but usually requires collaboration with a specialized laboratory.

Selected biochemical tests together with the demonstration of tumbling motility, umbrella-type formation below the surface in semisolid media, hemolysis, and a typical cyclic adenosine monophosphate test are usually sufficient to establish a presumptive identification of *L. monocytogenes*.

**Epidemiology**

*L. monocytogenes* is widespread in nature, has been isolated throughout the environment, and is associated with epizootic disease and zoonotic carriage in more than 42 species of wild and domestic animals and 22 avian species. Epizootic disease in large animals such as sheep and cattle is associated with abortion and “circling disease,” a form of basilar meningitis. *L. monocytogenes* is isolated from sewage, silage, and soil, where it survives for longer than 295 days. Human-to-human transmission rarely occurs except in maternal-fetal transmission. The annual incidence of listeriosis decreased by 36% between 1996 and 2004 and has remained level since then. However, outbreaks continue to occur. In 2002, an outbreak that resulted in 54 illnesses, 8 deaths, and 3 fetal deaths in 9 states was traced to consumption of contaminated turkey meat. In 2011, an outbreak with 84 cases and 15 deaths in 19 states was traced to cantaloupes from a single source. The cases were connected by use of pulsed-field gel electrophoresis, which showed that 4 different strains traced to the same source. The rate of listeria infections varies among states. Epidemic human listeriosis has been associated with foodborne transmission in several large outbreaks, especially in association with aged soft cheeses; improperly pasteurized milk and milk products; contaminated raw and ready-to-eat beef, pork, and poultry, and packaged meats; and vegetables grown on farms where the ground is contaminated with the feces of colonized animals. The incidence of *Listeria* infections in the United States in 2008 was 0.29 cases per 100,000 population, being highest in children younger than 4 yr of age and next highest in adults older than 60 yr of age. The ability of *L. monocytogenes* to grow at temperatures as low as 4°C (39.2°F) increases the risk for transmission from aged soft cheeses and stored contaminated food. Small clusters of nosocomial person-to-person transmission have occurred in hospital nurseries and obstetric suites. Sporadic endemic listeriosis is less well characterized. Likely routes include foodborne infection and zoonotic spread. Zoonotic transmission with cutaneous infections occurs in veterinarians and farmers who handle sick animals.

Reported cases of listeriosis are clustered at the extremes of age. Some studies show higher rates in males and a seasonal predominance in the late summer and fall in the Northern hemisphere. Outside the newborn period and during pregnancy, disease is usually reported in patients with underlying immunosuppression, with a 100-300 times increased risk in HIV-infected persons and in the elderly (Table 188-1). In a recent surveillance study from England, malignancies accounted for one-third of cases, with special risk associated with cancer in the elderly.

The incubation period, which is defined only for common-source foodborne disease, is 21-30 days but in some cases may be longer. Asymptomatic carriage and fecal excretion are reported in 1-5% of healthy persons and 5% of abattoir workers, but duration of excretion, when studied, is short (<1 mo).

**Pathology**

One of the major concepts of *Listeria* pathology and pathogenesis is its ability to survive as an intracellular pathogen. *Listeria* incites a mononuclear response and elaboration of cytokines, producing multisystem disease, particularly pyogenic meningitis. Granulomatous reactions and microabscess formation develop in many organs, including liver, lungs, adrenals, kidneys, central nervous system (CNS), and, notably, the placenta. Animal models demonstrate translocation, the transfer of infection from contaminated food product to the human host.
of intraluminal organisms across intact intestinal mucosa. Histologic examination of tissues including the placenta shows granulomatous inflammation and microabscess formation. Intracellular organisms can often be demonstrated with special stains.

**PATHOGENESIS**

*Listeria* organisms usually enter the host through the gastrointestinal tract. Gastric acidity provides some protection, and drugs that raise gastric pH may promote infection. Studies of intracellular and intercellular spread of *L. monocytogenes* have revealed a complex pathogenesis. Four pathogenic steps are described: internalization by phagocytosis, escape from the phagocytic vacuole, nucleation of actin filaments, and cell-to-cell spread. Listeriolysin, a hemolysin and the best-characterized virulence factor, probably mediates lysis of vacuoles and is responsible for the zone of hemolysis around colonies on blood-containing solid media. In cell-to-cell spread, locomotion proceeds via cytoplasmic-sensitive polymerization of actin filaments, which extrude the bacteria in pseudopods, which, in turn, are phagocytosed by adjacent cells, necessitating escape from a double-membrane vacuole. This mechanism protects intracellular bacteria from the humoral arm of immunity and is responsible for the well-known requirement of T-cell–mediated activation of monocytes by lymphokines for clearance of infection and establishment of immunity. It appears that secretion of cyclic-di-adenosine monophosphate by the bacteria induces the host to produce interferon, which activates the immune system to fight the organism. The significant risk for listeriosis in patients with depressed T-cell immunity speaks for the role of this arm of the immune system. The role of opsonizing antibody in protecting against infection is unclear. The significant risk for listeriosis in patients with depressed T-cell immunity speaks for the role of this arm of the immune system. The role of opsonizing antibody in protecting against infection is unclear.

**CLINICAL MANIFESTATIONS**

The clinical presentation of listeriosis is highly dependent on the age of the patient and the circumstances of the infection.

**Listeriosis in Pregnancy**

Pregnant women have increased susceptibility to *Listeria* infection (approximately 20 times higher than nonpregnant women), probably owing to a relative impairment in cell-mediated immunity. *L. monocytogenes* has been grown from placental and fetal cultures of pregnancies ending in spontaneous abortion. The usual presentation in the 2nd and 3rd trimesters is a flu-like illness that may result in seeding of the uterine contents by bacteremia. Rarely is maternal listeriosis severe, but meningitis in pregnancy has been reported. Recognition and treatment at this stage are associated with normal pregnancy outcomes, but the fetus may not be infected even if listeriosis in the mother is not treated. In other instances, placental listeriosis develops with infection of the fetus that may be associated with stillbirth or premature delivery. Delivery of an infected premature fetus is associated with very high infant mortality. Disseminated disease is apparent at birth, often with a diffuse purpuric rash. Infection in the mother usually resolves without specific therapy after delivery, but postpartum fever and infected lochia may occur.

**Neonatal Listeriosis**

Two clinical presentations are recognized for neonatal listeriosis: early-onset neonatal disease (<5 days, usually within 1-2 days of birth), which is a predominantly septicemic form, and late-onset neonatal disease (>5 days, mean 14 days of life), which is a predominantly meningitic form (Table 188-2). The principal characteristics of the 2 presentations resemble the clinical syndromes described for group B streptococci (see Chapter 184).

Early-onset disease occurs via milder transplacental or ascending infections from the female genital tract. There is a strong association with recovery of *L. monocytogenes* from the maternal genital tract, obstetric complications, prematurity, and neonatal sepsis with multiorgan involvement without CNS localization. The mortality rate is approximately 20-30%.

### Table 188-2

<table>
<thead>
<tr>
<th>Characteristic Features of Early- and Late-Onset Neonatal Listeriosis</th>
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<tbody>
<tr>
<td><strong>EARLY ONSET (&lt;5 DAYS)</strong></td>
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<tr>
<td>Positive result of maternal <em>Listeria</em> culture</td>
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<tr>
<td>Obstetric complications</td>
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<tr>
<td>Premature delivery</td>
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<tr>
<td>Low birthweight</td>
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<tr>
<td>Neonatal sepsis</td>
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<tr>
<td>Mean age at onset 1.5 days</td>
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<tr>
<td>Mortality rate &gt;30%</td>
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</tbody>
</table>

The epidemiology of late-onset disease is poorly understood. Onset is usually after 5 days but before 30 days of age. Affected infants frequently are full-term, and the mothers are culture negative and asymptomatic. The presenting syndrome is usually purulent meningitis, which, if adequately treated, has a mortality rate of <20%.

**Postneonatal Infections**

Listeriosis beyond the newborn period may rarely occur in otherwise healthy children but is most often encountered in association with underlying malignancies or immunosuppression. When associated with foodborne outbreaks, disease may cause gastrointestinal symptoms or any of the *Listeria* syndromes. The clinical presentation is usually meningitis, less commonly sepsis, and rarely other CNS involvement, such as cerebritis, meningoencephalitis, brain abscess, spinal cord abscess, or a focus outside the CNS, such as suppurative arthritis, osteomyelitis, endocarditis, peritonitis (associated with peritoneal dialysis), or liver abscess. It is not known whether the frequent gastrointestinal signs and symptoms result from enteric infection, because the mode of acquisition is often unknown.

**DIAGNOSIS**

Listeriosis should be included in the differential diagnosis of infections in pregnancy, of neonatal sepsis and meningitis, and of sepsis or meningitis in older children who have underlying malignancies, are receiving immunosuppressive therapy, or have undergone transplantation. The diagnosis is established by culture of *L. monocytogenes* from blood or cerebrospinal fluid (CSF). Cultures from the maternal cervix, vagina, lochia, and placenta, if possible, should be obtained when intrauterine infections lead to premature delivery or early-onset neonatal sepsis. Cultures from closed-space infections may also be useful. It is helpful to alert the laboratory to suspected cases so that *Listeria* isolates are not discarded as contaminating diphtheroids.

Histologic examination of the placenta is also useful. Polymerase chain reaction assays detect *L. monocytogenes*, but commercial assays are available only as research use only, not for diagnostic purposes. Serodiagnostic tests have not proved useful.

**Differential Diagnosis**

Listeriosis is indistinguishable clinically from neonatal sepsis and meningitis due to other organisms. The presence of increased peripheral blood monocytes suggests the possibility of listeriosis. Monocytosis or lymphocytosis may be modest or striking. Beyond the neonatal period, *L. monocytogenes* CNS infection is associated with fever, headache, seizures, and signs of meningeal irritation. The brainstem may be characteristically affected. The white blood cell concentration may vary from normal to slightly elevated, and the CSF laboratory findings are variable and less striking than in the more common causes of bacterial meningitis. Polymorphonuclear leukocytes or mononuclear cells may predominate, with shifts from polymorphonuclear to mononuclear...
cells in sequential lumbar puncture specimens. The CSF glucose concentration may be normal but a low level mirrors the severity of disease. The CSF protein concentration is moderately elevated. \textit{L. monocytogenes} is isolated from the blood in 40–75\% of cases of meningitis due to the organism. Deep focal infections caused by \textit{L. monocytogenes}, such as endocarditis, osteomyelitis, and liver abscess, are also indistinguishable clinically from such infections caused by more common organisms. Cutaneous infections should be suspected in patients with a history of contact with animals, especially products of conception.

**TREATMENT**
The emergence of multiple-antibiotic resistance mandates routine susceptibility testing of all isolates. The recommended therapy is ampicillin (100–200 mg/kg/day divided every 6 hr IV; 200–400 mg/kg/day divided every 6 hr IV if meningitis is present) alone or in combination with an aminoglycoside (5.0–7.5 mg/kg/day divided every 8 hr IV). The aminoglycoside enhances the bactericidal activity and is generally recommended in cases of endocarditis and meningitis. The adult dose is ampicillin 4–6 g/day divided every 6 hr plus an aminoglycoside. The ampicillin dose is doubled if meningitis is present. Special attention to dosing is required for neonates, who require longer dosing intervals because of the longer half-lives of the antibiotics in their bodies. \textit{L. monocytogenes} is not susceptible to the cephalosporins, including third-generation cephalosporins. If these agents are used for empirical therapy for neonatal sepsis or meningitis in a newborn, ampicillin must be added for the possibility of \textit{L. monocytogenes} infection. Vancomycin, vancomycin plus an aminoglycoside, trimethoprim-sulfamethoxazole, and erythromycin are alternatives. The duration of therapy is usually 2–3 wk, with 3 wk recommended for immunocompromised persons and patients with meningitis. A longer course is needed for endocarditis, brain abscess, and osteomyelitis. Antibiotic treatment is unnecessary for gastroenteritis without invasive disease.

**PREVENTION**
Listeria can be prevented by pasteurization and thorough cooking of foods. Irradiation of meat products may also be beneficial. Consumption of unpasteurized or improperly processed dairy products, especially aged soft cheeses, uncooked and precooked meat products that have been stored at 4°C (39.2°F) for extended periods, and unwashed vegetables should be avoided (Table 188-3). This avoidance is particularly important during pregnancy and for immunocompromised persons. Infected domestic animals should be avoided when possible. Education regarding risk reduction is aimed particularly at pregnant women and people being treated for cancers. Careful handwashing is essential to prevent nosocomial spread within obstetric and neonatal units. Immunocompromised patients given prophylaxis with trimethoprim-sulfamethoxazole are protected from \textit{Listeria} infections. Cases and especially outbreaks should be reported immediately to public health authorities so that timely investigation can be initiated in order to interrupt transmission from the contaminated source.

*Bibliography is available at Expert Consult.*

### Table 188-3  Prevention of Food-Borne Listeriosis

<table>
<thead>
<tr>
<th>General recommendations to prevent an infection with \textit{Listeria}:</th>
<th>FDA recommendations for washing and handling food.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rinse raw produce, such as fruits and vegetables, thoroughly under running tap water before eating, cutting, or cooking. Even if the produce will be peeled, it should still be washed first.</td>
<td></td>
</tr>
<tr>
<td>Scrub firm produce, such as melons and cucumbers, with a clean produce brush.</td>
<td></td>
</tr>
<tr>
<td>Dry the produce with a clean cloth or paper towel.</td>
<td></td>
</tr>
<tr>
<td>Separate uncooked meats and poultry from vegetables, cooked foods, and ready-to-eat foods. Keep your kitchen and environment cleaner and safer.</td>
<td></td>
</tr>
<tr>
<td>Wash hands, knives, countertops, and cutting boards after handling and preparing uncooked foods.</td>
<td></td>
</tr>
<tr>
<td>Be aware that \textit{Listeria monocytogenes} can grow in foods in the refrigerator. Use an appliance thermometer, such as a refrigerator thermometer, to check the temperature inside your refrigerator. The refrigerator should be 4.5°C (40°F) or lower and the freezer –17.8°C (0°F) or lower.</td>
<td></td>
</tr>
<tr>
<td>Clean up all spills in your refrigerator right away—especially juices from hot dog and lunch meat packages, raw meat, and raw poultry.</td>
<td></td>
</tr>
<tr>
<td>Clean the inside walls and shelves of your refrigerator with hot water and liquid soap, then rinse. Cook meat and poultry thoroughly.</td>
<td></td>
</tr>
<tr>
<td>Thoroughly cook raw food from animal sources, such as beef, pork, or poultry to a safe internal temperature. For a list of recommended temperatures for meat and poultry, visit the safe minimum cooking temperatures chart at <a href="http://www.FoodSafety.gov">http://www.FoodSafety.gov</a>.</td>
<td></td>
</tr>
<tr>
<td>Store foods safely.</td>
<td></td>
</tr>
<tr>
<td>Use precooked or ready-to-eat food as soon as you can. Do not store the product in the refrigerator beyond the use-by date; follow USDA refrigerator storage time guidelines:</td>
<td></td>
</tr>
<tr>
<td>Hot dogs–store opened package no longer than 1 wk and unopened package no longer than 2 wk in the refrigerator.</td>
<td></td>
</tr>
<tr>
<td>Luncheon and deli meat–store factory-sealed, unopened package no longer than 2 wk. Store-opened packages and meat sliced at a local deli no longer than 3-5 days in the refrigerator.</td>
<td></td>
</tr>
<tr>
<td>Divide leftovers into shallow containers to promote rapid, even cooling. Cover with airtight lids or enclose in plastic wrap or aluminum foil. Use leftovers within 3-4 days. Choose safer foods.</td>
<td></td>
</tr>
<tr>
<td>Do not drink raw (unpasteurized) milk, and do not eat foods that have unpasteurized milk in them.</td>
<td></td>
</tr>
</tbody>
</table>
### Table 188-3  Prevention of Food-Borne Listeriosis—cont’d

<table>
<thead>
<tr>
<th>Recommendations for persons at higher risk, such as pregnant women, persons with weakened immune systems, and older adults in addition to the recommendations listed above, include:</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Meats</strong></td>
</tr>
<tr>
<td>• Do not eat hot dogs, luncheon meats, cold cuts, other deli meats (e.g., bologna), or fermented or dry sausages unless they are heated to an internal temperature of 73.9°F (165°F) or until steaming hot just before serving.</td>
</tr>
<tr>
<td>• Avoid getting fluid from hot dog and lunch meat packages on other foods, utensils, and food preparation surfaces, and wash hands after handling hot dogs, luncheon meats, and deli meats.</td>
</tr>
<tr>
<td>• Pay attention to labels. Do not eat refrigerated pâté or meat spreads from a deli or meat counter or from the refrigerated section of a store. Foods that do not need refrigeration, like canned or shelf-stable pâté and meat spreads, are safe to eat. Refrigerate after opening.</td>
</tr>
<tr>
<td><strong>Cheeses</strong></td>
</tr>
<tr>
<td>• Do not eat soft cheese such as feta, queso blanco, queso fresco, brie, Camembert, blue-veined, or panela (queso panela) unless it is labeled as made with pasteurized milk. Make sure the label says, “MADE WITH PASTEURIZED MILK.”</td>
</tr>
<tr>
<td><strong>Seafood</strong></td>
</tr>
<tr>
<td>• Do not eat refrigerated smoked seafood, unless it is contained in a cooked dish, such as a casserole, or unless it is a canned or shelf-stable product.</td>
</tr>
<tr>
<td>• Refrigerated smoked seafood, such as salmon, trout, whitefish, cod, tuna, and mackerel, is most often labeled as “nova-style,” “lox,” “kippered,” “smoked,” or “jerky.”</td>
</tr>
<tr>
<td>• These fish are typically found in the refrigerator section or sold at seafood and deli counters of grocery stores and delicatessens.</td>
</tr>
<tr>
<td>• Canned and shelf stable tuna, salmon, and other fish products are safe to eat. Follow this general FDA advice for melon safety:</td>
</tr>
<tr>
<td>• Consumers and food preparers should wash their hands with warm water and soap for at least 20 sec before and after handling any whole melon, such as cantaloupe, watermelon, or honeydew.</td>
</tr>
<tr>
<td>• Scrub the surface of melons, such as cantaloupes, with a clean produce brush under running water and dry them with a clean cloth or paper towel before cutting. Be sure that your scrub brush is sanitized after each use, to avoid transferring bacteria between melons.</td>
</tr>
<tr>
<td>• Promptly consume cut melon or refrigerate promptly. Keep your cut melon refrigerated at, or less than 4.5°F (40°F) (0-1.1°C [32-34°F] is best), for no more than 7 days.</td>
</tr>
<tr>
<td>• Discard cut melons left at room temperature for more than 4 hr.</td>
</tr>
</tbody>
</table>

Adapted from the Centers for Disease Control and Prevention: Listeria (Listeriosis): prevention. Available at: [http://www.cdc.gov/listeria/prevention.html](http://www.cdc.gov/listeria/prevention.html)
Bibliography
Actinomyces organisms are anaerobic, nonsporulating, Gram-positive bacteria that are part of the endogenous oral flora in humans and have a filamentous and branching structure. Infection caused by these bacteria is termed actinomycosis, which is a chronic, granulomatous, suppurative disease characterized by direct extension to contiguous tissue across natural anatomic barriers with the formation of numerous draining fistulas and sinus tracts. These infections usually involve the cervicofacial, thoracic, abdominal, or pelvic regions.

**ETIOLOGY**

At least 21 species of *Actinomyces* causing human infection have been identified using 16S rRNA sequencing. *Actinomyces israelii* is the predominant species causing human actinomycosis. Other implicated species include: *Propionibacterium propionicum, Actinomyces odontolyticus, Actinomyces meyeri, Actinomyces naeslundii, Actinomyces gerencseriae, and Actinomyces viscosus.*

*Actinomyces* organisms are part of the endogenous flora of mucous membranes and are often found in clinical specimens such as sputum, bronchial washes, purulent exudates, and tissues obtained surgically or at necropsy. Staining of crushed tissue specimens rinsed with sterile saline or purulent exudate stained with Gram or acid-fast procedures may reveal organisms within the classic sulfur granules, which are characteristically associated with pulmonary disease caused by *A. israelii* or *A. meyeri.* Cultures on brain-heart infusion agar incubated at 37°C (98.6°F) anaerobically (95% nitrogen and 5% carbon dioxide) and a separate set incubated aerobically reveal organisms within the lines of streak at 24-48 hr. *A. israelii* colonies appear as loose masses of delicate, branching filaments with a characteristic spider-like growth. Colonies of *A. naeslundii, A. viscosus,* and *P. propionicum* may have similar growth characteristics. Biochemical testing is frequently used for speciation but is limited by the complexity within this group. Newer speciation methods are based on 16S recombinant RNA sequence analysis.

**EPIDEMILOGY**

Actinomycosis occurs worldwide among people of all ages, with higher incidence among males, possibly related to increased trauma or poorer dental hygiene. There is no relationship to race, season, or occupation. In a review of 85 cases of actinomycosis, 27% were in persons younger than 20 yr of age, with 7% among children younger than 10 yr of age. The youngest patient in this series was 28 days old. The source of human infection is almost always endogenous flora. The incidence has declined as a result of improved oral hygiene and early antibiotic treatment of oral infections. Risk factors in children include trauma, dental caries, debilitation, and poorly controlled diabetes mellitus. Although actinomycosis is not a common opportunistic infection, disease has been associated with corticosteroid use, leukemia, renal failure, congenital immunodeficiency diseases, and HIV infection. In one study, antecedent disease and surgery predisposed 81 of 181 subjects to infection.

**PATHOGENESIS**

The 3 significant sites of *Actinomyces* infection are, in order of frequency, cervicofacial, abdominal and pelvic, and pulmonary, although infection may involve any organ in the body. Infection typically follows introduction of the organism into tissues after trauma or surgery. The hallmark of actinomycosis is spread that fails to respect tissue or fascial...
planes. The use of intrauterine devices may predispose to development of pelvic actinomycosis. Pulmonary actinomycosis occurs after inhalation or aspiration of organisms, introduction of a colonized foreign body, or spread from an existing cervicofacial or abdominal actinomycotic infection.

Infection spreads contiguously and, rarely, hematogenously. Actinomycosis is a chronic, suppurative, scarring inflammatory process. Sites of infection show dense cellular infiltrates and suppuration that form many interconnecting abscesses and sinus tracts. These abscesses and sinus tracts may be followed by cicatricial healing from which the organism spreads by burrowing along fascial planes, causing deep, communicating scarred sinus tracts. Sulfur granules are characteristic of actinomycosis. On hematoxylin-and-eosin staining, they appear as an adherent mass of polymorphonuclear neutrophils attached to the radially arranged eosinophilic clubs of the granule, which is the host immune response. They may be microscopic or macroscopic and are typically yellow, accounting for their name, but may be white, gray, or brown.

Actinomycosis, even in closed infections, is usually, if not always, polymicrobial in nature, involving mixed bacteria. In a large study of more than 650 cases, infection with *Actinomyces* was identified in pure culture in only 1 case and in others was usually identified with other oral flora, most notably members of the HACEK group, which includes *Haemophilus aphrophilus*, *Aggregatibacter* (formerly *Actinobacillus*) *actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella kingae*. *A. actinomycetemcomitans* is a fastidious, Gram-negative bacillus that is part of the oral flora and has been implicated as a pathogen in periodontal disease. Other bacterial species frequently isolated concomitantly in human actinomycosis include *Fusobacterium*, *Capnocytophaga*, *Staphylococcus*, aerobic and anaerobic streptococci, and *Enterobacteriaceae*.

**CLINICAL MANIFESTATIONS**

The 3 major forms of actinomycosis—cervicofacial, abdominal and pelvic, and pulmonary—arise by different routes but may progress to other forms of the disease. Actinomycosis in children suggests an underlying immunodeficiency, especially chronic granulomatous disease (see Chapter 130).

**Cervicofacial Actinomycosis**

In the patient with cervicofacial actinomycosis, there is often a history of oral trauma, oral surgery, dental procedures, or caries, facilitating entry of organisms into cervicofacial tissues. Cervicofacial actinomycosis usually manifests as a painless, slow-growing, hard mass and can produce cutaneous fistulas, a condition commonly known as lumpy jaw (Fig. 189-1). Less frequently, cervicofacial actinomycosis manifests clinically as an acute pyogenic infection with a tender, fluctuant mass with trismus, firm swelling, and fistulas with drainage containing the characteristic sulfur granules. Bone is not involved early in the disease, but periostitis, mandibular osteomyelitis, or perimandibular abscess may develop. Infection may spread by way of sinus tracts to the cranial bones, possibly giving rise to meningitis. The ability of *Actinomyces* to burrow through tissue planes and even bone is a key difference between actinomycosis and nocardiosis. The cervicofacial form of actinomycosis has the best prognosis and is usually cured with surgical debridement and excision combined with antibiotic therapy.

**Abdominal and Pelvic Actinomycosis**

In abdominal and pelvic actinomycosis, characteristically there is some disruption of the mucosa of the gastrointestinal tract, usually as a result of an acute gastrointestinal perforation or abdominal trauma. Patients often present with a history of gastrointestinal surgery, diverticulitis, or appendicitis. Of all the forms of actinomycosis, delayed diagnosis is most typical for abdominal and pelvic infection. Gastrointestinal disease clinically develops as appendicitis in 25% of cases but can be manifested as various ulcerative diseases. Infection classically appears after appendectomy as a firm, irregular mass in the iliopectineal area that softens and then drains externally through a fistula. Hepatic involvement occurs in approximately 15% of cases of abdominal actinomy- cosis, with solitary or multiple liver abscesses or in a miliary pattern. The clinical course is indolent, with chills, fever, night sweats, and weight loss, and the presentation is similar to that of tuberculous peritonitis. Infection usually spreads by direct extension or, rarely, hematogeneously, possibly involving any tissue or organ, including muscle, spleen, kidneys, fallopian tubes, ovaries, uterus, testes, bladder, and rectum.

Women using intrauterine devices are at risk for development of pelvic actinomycosis, which classically manifests as vaginal discharge, pelvic pain, abdominal pain, menorrhagia, fever, pelvic mass, and a history of pelvic inflammatory disease. The risk is higher if the intrauterine device has been in place for longer than 2-3 yr.

**Pulmonary Actinomycosis**

Undetected aspiration in a predisposed host is the typical mechanism for thoracic actinomycosis. Neither the clinical nor the radiographic presentation of pulmonary actinomycosis is specific. Pulmonary actinomycosis may manifest as an endobronchial infection, a tumor-like lesion, diffuse pneumonia, or a pleural effusion. Principal symptoms include fever, productive cough, chest pain, and weight loss. Infection frequently dissects along tissue planes and may extend through the chest wall or diaphragm, characteristically producing numerous sinus tracts that contain small abscesses and purulent drainage. Other complications include bony destruction of adjacent ribs, sternum, and vertebral bodies. Multiple lobe involvement of the lungs is occasionally found. Predisposing conditions include dental caries, aspiration, thermal or chemical inhalation injury, introduction of a colonized foreign body, and preexisting cervicofacial or abdominal disease. The classic radiographic triad of thoracic actinomycosis is chronic lower lobe pulmonary consolidation, empyema, and wavy periostitis of the ribs. Accurate diagnosis is difficult because of the propensity of Actinomyces to infect preexisting pulmonary cavities. Diagnosis can be confirmed by examination of purulent sinus tract drainage for sulfur granules, and with appropriate cultures. The significance of the presence of Actinomyces in sputum or bronchoscopy specimens is limited because these organisms are normal oral flora.

**Other Forms**

Laryngeal actinomycosis rarely has been reported in older teenagers. Oropharyngeal colonization with *Actinomyces* may be involved in the development of obstructive tonsillar hypertrophy. *Actinomyces pyogenes* has only rarely been implicated as a cause of human infection, although there are reported cases of septiciemia, endocarditis, meningitis, arthritis, empyema, pneumonia, otitis media, cystitis, mastoiditis, appendicitis, and cutaneous infection.

Severe forms of periodontitis, particularly localized juvenile periodontitis, are associated with *Actinomyces*, especially in children 10-19 yr of age. *Actinomyces* has a propensity for infecting heart valves, a process that results in an insidious presentation of endocarditis, with fever present in less than half of cases.

![Figure 189-1](image-url) A 2 yr old boy with HIV infection who has cervicofacial actinomycosis and a chronic draining fistula.
DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

Microscopic examination with appropriate stains and culture of purulent drainage from fistulas, abscesses, draining sinus tracts, bronchoalveolar lavage, and sputum can reveal *Actinomyces*. Except for *A. meyeri*, which is nonbranching, *Actinomyces* organisms appear as branching, filamentous rods. Inoculation of anaerobic and aerobic cultures enhances the yield of cultures. Gram, Gomori methenamine silver, or Giemsa stains of purulent material or tissue reveal diagnostic filamentous, branching bacteria at the periphery of sulfur granules. *Nocardia* is indistinguishable from *Actinomyces* on Gram stain, but unlike *Actinomyces*, *Nocardia* stains with the modified acid-fast stain.

Cranial CT or MRI is important to evaluate the possibility of cerebral actinomycosis in patients with cervicofacial disease or neurologic findings. Infection that invades across tissue planes and ignores anatomic boundaries is highly suggestive of actinomycosis. Abdominal CT may be helpful in identifying the presence of a contrast-enhancing, multicystic lesion, which could be approached by CT-guided needle biopsy for culture.

The mass-like lesion of actinomycosis may manifest as a tumor, necessitating invasive approaches for diagnosis. Actinomycosis must be differentiated from other chronic inflammatory infections, including tuberculosis, nocardiosis, polymicrobial bacterial infections, and fungal infections. Actinomycosis may mimic appendicitis, pseudoappendicitis caused by *Yersinia enterocolitica*, amebiasis, hepatic abscess, lung abscess, and osteomyelitis.

TREATMENT

The mainstay of treatment for actinomycosis is an appropriate surgical approach to sinus tracts and abscesses, prolonged antibiotic therapy, and management of complications such as hemoptysis. Large abscesses usually require complete surgical excision. Bone disease may require multiple debridements. Prompt initiation of antibiotics results in a high cure rate. Actinomycosis is treated with penicillin G (250,000 units/kg/day IV divided every 4-6 hr; maximum: 18-24 million units/day). Other appropriate antibiotics may include tetracycline, clindamycin, and carbapenems. Although controversy still exists about the optimal dosage and duration of therapy, appropriate therapy usually includes parenteral antibiotics for 2-6 wk followed by oral antibiotics for 3-12 mo. The oral antibiotic of choice is penicillin V (100 mg/kg/day divided every 6 hr PO). Hepatic abscesses or other deep tissue infections should be treated for 6-12 mo. Although most *A. israelii* strains are sensitive to penicillin with minimum inhibitory concentrations of 0.03-0.5 µg/mL, some resistant strains have been identified. Antibiotic susceptibility testing should be performed on all isolates from patients who have significant disease or are immunocompromised.

*A. actinomycetemcomitans* is a copathogen in at least 30% of actinomycotic infections. It is important to consider also treating this organism empirically, especially in the critically ill patient. Failure to recognize this organism and treat it adequately has resulted in clinical relapse and deterioration in patients with actinomycosis. *A. actinomycetemcomitans* is susceptible to cephalosporins, amoxicillin-clavulanate, rifampin, trimethoprim-sulfamethoxazole, aminoglycosides, ciprofloxacin, tetracycline, and azithromycin. It is susceptible to penicillin and ampicillin in vitro, but test results do not correlate necessarily with clinical outcome. In some patients with periodontitis associated with *A. actinomycetemcomitans*, mechanical periodontal treatment combined with metronidazole plus amoxicillin is effective for subgingival suppression.

PROGNOSIS

The prognosis is excellent with early diagnosis, adequate surgical debridement, and antimicrobial therapy. Removal of chronically infected tonsils and treatment of periodontitis or caries may eliminate sources of possible reinfection.

Bibliography is available at Expert Consult.
Bibliography
Nocardia organisms cause localized and disseminated disease in children and adults. These organisms are primarily opportunistic pathogens infecting immunocompromised persons. Infection caused by these bacteria is termed nocardiosis, which consists of acute, subacute, or chronic suppurative infections with a tendency for remissions and exacerbations.

**ETIOLOGY**

There are more than 80 species to date in the Nocardia genus. Nocardia are Gram-positive filamentous bacteria. These organisms are environmental saprophytes that are ubiquitous in soil and decaying vegetable matter. They are obligate aerobes and grow on ordinary culture media. Growth is achieved best at 37°C (98.6°F) with 10% carbon dioxide, although many isolates of Nocardia are thermophilic and grow at temperatures up to 50°C (122°F). Colonies appear within 1-2 wk on brain–heart infusion agar, Lowenstein-Jensen media, and simple blood agar, usually as waxy, folded, or heaped colonies at the edges. With modified Kinyoun acid-fast staining of biopsy specimens or body fluids, Nocardia demonstrates fragmented bacilli with stain concentrated in a beaded pattern along portions of the branching filaments.

Ongoing identification of new species continues to challenge microbiology laboratories. Speciation and antimicrobial susceptibility testing is critical for optimal clinical outcomes, especially in severe disease in immunocompromised patients. The most common clinical isolates of Nocardia asteroides have now been classified into complex groups I-VI. Valid taxonomic clusters by gene sequencing and antimicrobial susceptibility testing have led to new information to guide clinicians. The term N. asteroides complex I-VI now refers to a cluster of similar strains. Non-N. asteroides complex organisms are usually Nocardia brasiliensis or Nocardia otitidiscaviarum.

N. asteroides complex includes the most common agents of systemic nocardiosis in the United States. N. brasiliensis is the principal cause of localized nocardial cellulitis and lymphadenitis in immunocompetent children and can also cause pulmonary and systemic disease, especially in immunocompromised persons. N. brasiliensis is found more commonly in the southern United States, Central America, South America, and Asia.

**EPIDEMIOLOGY**

Once thought to be a rare human disease, nocardiosis is being recognized more frequently and has been diagnosed in persons from 4 wk to 82 yr of age. Almost all patients have compromised cellular immunity from an underlying disease such as organ transplantation, malignancy, corticosteroids, diabetes, HIV infection, or primary immunodeficiency, especially chronic granulomatous disease (see Chapter 130). Nocardia infections among stem cell transplant recipients are associated with a high rate of concomitant invasive fungal infection and a notable lack of protection with trimethoprim-sulfamethoxazole prophylaxis. An evaluation of opportunistic infections in 547 organ transplant recipients receiving alemtuzumab (humanized monoclonal CD52 antibody) revealed that 62 opportunistic infections developed in 56 patients (10%), including Nocardia in 4 patients.

**PATHOGENESIS**

Soil is the natural habitat of Nocardia, which has been isolated worldwide. The organism is inhaled in aerosolized dust and causes pulmonary infection, with widespread dissemination in susceptible hosts. It can be transmitted by direct cutaneous inoculation, including after
arthropod and cat bites. Although human-to-human transmission is rare, a description of *Nocardia farcinica* sternal wound infections among patients undergoing open heart surgery raises concern about *Nocardia* as a nosocomial pathogen.

**CLINICAL MANIFESTATIONS**

Pulmonary nocardiosis accounts for 75% of cases of infection, almost all of which occur among immunocompromised patients or patients with underlying pulmonary disease. Demonstration of tissue invasion is important for identifying active pulmonary infection because the organism occasionally exists as a respiratory saprophyte. Clinical manifestations include pneumonia and necrotizing pneumonia with single or multiple abscesses.

Single or multiple metastatic lesions may occur anywhere in the body. The brain is the most common secondary site and is involved in 15-40% of cases of pulmonary nocardiosis. Brain abscess is the most common presentation, and meningitis is the second most common presentation, manifested by pleocytosis (with a lymphocytic or neutrophilic predominance), elevated cerebrospinal fluid protein, and hypoglycorrhachia. Persistent neutrophilic meningitis with sterile culture results is classic for central nervous system (CNS) infection. The onset may be gradual or sudden and includes manifestations varying from headache to coma.

The skin is the third most commonly involved organ, manifested by sporotrichoid nocardiosis or superficial ulcers (Fig. 190-1). Mycetoma is a chronic, progressive infection developing days to months after inoculation, usually on a distal location on the limbs. Renal nocardiosis, the fourth most common type of disease, typically manifests as dysuria, hematuria, or pyuria. Lesions may extend from the cortex into the medulla. Gastrointestinal involvement may also be associated with nausea, vomiting, diarrhea, abdominal distention, and melena. Infection may spread to skin, pericardium, myocardium, spleen, liver, or adrenal glands. Bone involvement is rare. Almost all of the involved organs have several abscesses. In contrast to actinomycosis, granules are rarely found in nocardiosis.

**DIAGNOSIS**

Laboratory diagnosis of nocardiosis requires direct examination of clinical material for characteristic Gram-positive, acid-fast organisms and isolation by culture methods. Smears of clinical material are stained with Gram stain or the modified Kinyoun acid-fast stain. *N. asteroides* complex and *N. brasiliensis* appear as delicately branched, Gram-positive, coccoid to bacillary bacteria that tend to fragment. In properly stained and decolorized acid-fast smears, the organisms may appear as fragmented bacilli with the stain concentrated in a beaded pattern along the portions of the filaments. Gene sequence analysis (16S rRNA; multilocus sequence analysis) is required for definitive identification. Clinical laboratory susceptibility testing is now standardized with breakpoints.

Diagnosis of pulmonary nocardiosis is established in 30% of cases in adults by sputum analysis and culture. Bronchoalveolar lavage or lung biopsy may be required to establish the diagnosis in the remaining 60% of adults and in children.

Cranial CT or MRI is recommended for all immunocompromised patients with pulmonary nocardiosis, even if asymptomatic, because of the high frequency of CNS involvement, and should also be considered for immunocompetent patients.

**TREATMENT**

Surgical drainage of abscesses is important. The choice, dose, and duration of antimicrobial treatment depend on the site and extent of infection, host immune status, initial clinical response, and species and susceptibility testing of the *Nocardia* isolate. The initial selection of antimicrobial therapy must be empiric. Sulfonamides have been the cornerstone of therapy for the treatment of nocardiosis since the 1940s, but increasing reports of resistance have led to the use of other regimens. Trimethoprim-sulfamethoxazole (TMP-SMX) is the formulation that is recommended, although sulfadiazine and sulfisoxazole have been used. TMP-SMX resistance ranges from 20% for *N. brasiliensis* to 80% for *N. farcinica*. A susceptibility study of 78 clinical isolates of the *N. asteroides* complex from the United States found that 95% of strains exhibited 1 of 6 antibiotic resistance patterns. The most common pattern, occurring in 35% of isolates, showed resistance to ampicillin and erythromycin, but susceptibility to cefotaxime, ceftriaxone, and carbapenems. Approximately 20% of isolates, which were subsequently identified as *N. farcinica*, were resistant to cefotaxime and ceftriaxone. Based on analysis of all strains tested to date, resistance was lowest for amikacin (5%), imipenem (30%), and ceftriaxone (52%). *N. farcinica* is typically always resistant to ertapenem. Imipenem resistance *Nocardia cyriacigeorgica* infection in a child with chronic granulomatous disease has been reported. The most active oral agents were sulfonamides (100%) and minocycline (100%). Additional antimicrobial agents with oral bioavailability are desirable because of the increasing reports of sulfonamide resistance and the adverse effects reported among patients with HIV infection. In vitro studies show susceptibility of all strains to linezolid, which appears to be an effective alternative treatment, but potential toxicity with long-term oral therapy with this agent must be kept in mind.

Combination therapy involving a carbapenem or a third-generation cephalosporin with or without amikacin is usually recommended for severely ill patients and patients with CNS involvement. The mortality rate approaches 50% when a sulfonamide is used alone for treatment. On the basis of in vitro susceptibility testing for specific *N. asteroides* complex isolates, alternative drug combinations may include erythromycin and newer macrolides (azithromycin and clarithromycin), carbapenems, streptomycin, minocycline, quinolones, third-generation cephalosporins, and linezolid. The issues to be considered for use of linezolid include the limited data of use in children and the adverse effects of long-term use. Clinical trials show that ampicillin and amoxicillin-clavulanate are effective in *N. brasiliensis* infections.

Susceptibility testing of *Nocardia* should be performed by a reference laboratory for isolates from deep-seated or disseminated infections.

![Figure 190-1](image-url)
infections of strains such as *N. farcinica* and *Nocardia otitidiscaviarum* that are commonly resistant to cephalosporins, if nonsulfonamide treatment regimens are being considered, for poor response to initial therapy, and for relapse.

Superficial cutaneous infection is treated for at least 6-12 wk. Mycetoma or pulmonary or systemic nocardiosis in immunocompetent persons is treated for 6-12 mo. CNS infection is treated for at least 12 mo, using at least 2-3 antibiotics with proven susceptibility for at least the 1st 4-12 wk, until some evidence of clinical and radiographic improvement. Relapses of systemic *Nocardia* infection that had been treated for <3 mo have occurred.

**PROGNOSIS**

Despite appropriate therapy, the overall mortality rate for nocardiosis is >50%. This high rate may be secondary to delay in diagnosis or to the debilitated state of patients with severely compromised host defenses.

*Bibliography is available at Expert Consult.*
Bibliography


Neisseria meningitidis (the meningococcus) is a commensal of the human nasopharynx in approximately 10% of the population and rarely enters the bloodstream to cause devastating invasive disease such as meningitis and meningococcal septicemia (meningococcaemia). Although a rare endemic disease in most countries, the epidemiology varies widely over time and in different geographic regions with both hyperendemic and epidemic disease patterns occurring. Onset of disease in susceptible individuals may be very rapid, within hours, and the case fatality rate is high, especially among those presenting with septic shock, despite access to modern critical care. Individual susceptibility is now known to involve a complex relationship between environmental, host, and bacterial factors, and prevention of disease through behavior modification (such as avoiding tobacco smoke) and vaccination offers the best prospect for control.

ETIOLOGY

N. meningitidis was first described by Weichselbaum who observed the organism, which he called Diplococcus intracellularis meningitidis, in specimens from 6 patients who died of meningitis in 1887. N. meningitidis is a Gram-negative, fastidious, encapsulated, oxidase-positive, aerobic diplococcus. Differences in the chemistry of the polysaccharide capsule allow definition of 13 serologically distinct meningococcal capsular groups, of which 6, designated A, B, C, W (previously designated W135), X, and Y, are responsible for almost all cases of disease. Meningoococcal strains may be subclassified on the basis of antigenic variation in 2 porin proteins found in the outer membrane, PorB (serotype) and PorA (serosubtype), and lipopolysaccharide (immunotype), using serology. Serologic typing is being replaced by molecular typing methods, which target genes under immune selection to provide antigen sequence typing (based on amino acid variation in various surface proteins, including PorA and FetA). Sequencing of antigen genes (such as PorA, fHbp, NadA, and NHBA) is set to be an important means of monitoring pressure on meningococcal populations by protein-based vaccines. Because meningococci readily exchange genetic material, typing based on a few antigens cannot provide an accurate picture of relatedness of strains, an important goal in monitoring epidemiology. Multilocus sequence typing, which types meningococci using variation in 7 housekeeping genes, is now widely used to map the distribution of genetic lineages of meningococci (http://pubmlst.org/neisseria/) and provides a clearer picture of the genetic and epidemiologic relatedness of strains. To provide still better definition of genetic variation, in some countries, including the United Kingdom, whole-genome sequencing is now being used to type meningococci and appears set to replace both antigen sequencing and multilocus sequence typing as costs continue to fall. The application of molecular approaches to epidemiology has established that (1) endemic meningococcal disease is caused by genetically heterogeneous strains, although only a small number of genetic lineages are associated with the majority of cases of invasive disease; and (2) outbreaks are usually clonal, caused by single strains.

EPIDEMIOLOGY

Meningococci are transmitted during close contact via aerosol droplets or exposure to respiratory secretions, such as through kissing. The organism does not survive for long periods in the environment. Enhanced rates of mucosal colonization and increased disease risk are associated with activities that increase the likelihood of exposure to a new strain or increase proximity to a carrier, thus facilitating transmission including kissing, bar patronage, binge drinking, attendance at nightclubs, and living in freshman college dormitories. Factors that damage the nasopharyngeal mucosa such as smoking and respiratory viral infection (notably influenza) are also associated with increased rates of carriage and disease, perhaps by driving upregulation of host adhesion molecules that are receptors for meningococci. Carriage is unusual in early childhood and peaks during adolescence and young adulthood.

Meningococcal disease is a global problem, but disease rates vary by a factor of 10-100-fold in different geographic locations at one point in time and in the same location at different times. Most cases of meningococcal disease are sporadic, but small outbreaks (usually in schools or colleges, representing <3% of U.S. cases), hyperendemic disease (increased rates of disease persisting for a decade or more as a result of a single clone), and epidemic disease are all recognized patterns. However, over the last decade, rates of meningococcal disease have declined in most industrialized countries partly through introduction of immunization programs, possibly aided by widespread legislation against smoking in public places. In the United States, the disease rate was 1.1 cases per 100,000 population in 1999 but had fallen to 0.2 cases per 100,000 population by 2011 (Fig. 191-1). By contrast, the rate of disease in Ireland in 1999 was >12 per 100,000 population and rates of 1,000 per 100,000 population have been described during epidemic disease in sub-Saharan Africa. Disease caused by dominant hyperendemic clones has been recognized in the last decade in Oregon, United States, across New Zealand, and in Normandy, France. Laboratory data underreport meningococcal disease incidence rates as up to 50% of cases are not culture confirmed. In the United Kingdom, polymerase chain reaction (PCR) methods are used routinely for diagnosis of suspected cases, doubling the number of confirmed cases.

The highest rate of meningococcal disease occurs in infants younger than 1 yr old, probably as a result of immunologic inexperience (antibody that recognizes meningococcal antigens is naturally acquired during later childhood), immaturity of the alternative and lectin complement pathways, and perhaps the poor responses made by infants to bacterial polysaccharides. In the absence of immunization, incidence
Colonization of the nasopharynx by *N. meningitidis* is the first step in either carriage or invasive disease. Disease usually occurs 1-14 days after acquisition of the pathogen. Initial contact of meningococci with host epithelial cells is mediated by pili, which may interact with the host CD46 molecule or an integrin. Close adhesion is then mediated by Opa and Opc binding to carinoembryonic antigen cell adhesion molecule receptors and integrins, respectively. Subsequent internalization of meningococci by epithelial cells is followed by transcytosis through to the basolateral tissues and dissemination into the bloodstream. Immunoglobulin A, protease secreted by invasive bacteria degrades secretory immunoglobulin A on the mucosal surface, circumventing this first-line host defense mechanism.

Once in the bloodstream, meningococci multiply rapidly to high levels to cause septicemia. Patients with a higher bacterial load have a more rapid clinical deterioration and longer period of hospitalization, as well as a higher risk of death and permanent sequelae. Resistance to complement-mediated lysis and phagocytosis is largely mediated by the polysaccharide capsule and lipopolysaccharide (LPS). Outer membrane vesicle blebs released from the surface of the organism contain LPS, outer membrane proteins, periplasmic proteins, and phospholipid, and play a major role in the inflammatory cascade that leads to severe disease.

Much of the tissue damage is caused by host immune mechanisms activated by meningococcal components, in particular LPS. During invasive disease LPS is bound to a circulating plasma protein, known as LPS binding protein. The host receptor complex for LPS consists of toll-like receptor 4, CD14, and myeloid differentiation protein 2. Binding of LPS to toll-like receptor 4, which is upregulated on circulating leukocytes during septicemia, results in activation of a number of different cell types. An intense inflammatory reaction ensues due to the secretion of pro-inflammatory cytokines such as tumor necrosis factor-α, interleukin (IL)-1β, IL-6, IL-8, and granulocyte macrophage colony-stimulating factor, levels of which are closely associated with plasma levels of LPS. The major antiinflammatory cytokines IL-1Ra, IL-2, IL-4, and IL-12, and transforming growth factor-β are present at very low levels. Both high and low levels have been observed for IL-10 and interferon-γ.

The pathophysiologic events that occur during meningococcal septicemia are largely related to microvascular injury. This leads to increased vascular permeability and the capillary leak syndrome, pathologic vasoconstriction and vasodilation, disseminated intravascular coagulation, and profound myocardial dysfunction. Increased vascular permeability can lead to dramatic fluid loss and severe hypovolemia. Capillary leak syndrome with or without aggressive fluid resuscitation (which is essential in severe cases) leads to pulmonary edema and respiratory failure. Initial vasoconstriction is a compensatory mechanism in response to hypovolemia and results in the clinical features of pallor and cold extremities. Following resuscitation, some patients experience “warm shock,” that is, intense vasodilation with bounding pulses and warm extremities, despite persistent hypotension and metabolic acidosis. Virtually all antithrombotic mechanisms appear to be dysfunctional during meningococcal sepsis, leading to a procoagulant state and disseminated intravascular coagulation. All of these factors contribute to depressed myocardial function, but there is also a direct negative cytokine effect on myocardial contractility, thought to be largely mediated via IL-6. Hypoxia, acidosis, hypoglycemia, hypokalemia, hypocalcemia, and hypophosphatemia are all common in severe septicemia and further depress cardiac function. Some patients become unresponsive to the positive inotropic effects of catecholamines and require high levels of inotropic support during intensive care management. These processes result in impairment of microvascular blood flow throughout the body and ultimately lead to multiorgan failure, which is responsible for much of the mortality.

Following invasion of the circulation, meningococci may also penetrate the blood–brain barrier and enter the cerebrospinal fluid (CSF), facilitated by pili and possibly Opc. Once there, bacteria continue to proliferate and LPS and other outer membrane products can stimulate a proinflammatory cascade similar to that observed in the blood. This leads to upregulation of specific adhesion molecules and recruitment of leukocytes into the CSF. Central nervous system damage occurs directly by meningeal inflammation and indirectly by circulatory collapse and causes a high rate of neurologic sequelae in affected patients. Death can occur from cerebral edema, which leads to raised intracranial pressure and cerebral or cerebellar herniation.
Immunity
There is an inverse correlation between the incidence of disease and the prevalence of complement-dependent serum bactericidal antibody (SBA). The level of SBA is highest at birth and among adults and lowest in children between 6 mo and 2 yr of age when the highest incidence of disease occurs. Such antibodies are naturally elicited by asymptomatic carriage of pathogenic and nonpathogenic meningococci as well as by carriage of antigenically related species such as Neisseria lactamica. A similar relationship was described for serogroups A, B, and C. Vaccine trials support these earlier findings. For the meningococcal serogroup C conjugate vaccine, an SBA titer of $\geq 1:8$ correlated strongly with postlicensure vaccine effectiveness. For serogroup B disease the data are less certain, but the proportions of serogroup B vaccine recipients with 24-fold rises in SBA following vaccination or SBA titers $\geq 1:4$ have been correlated with clinical efficacy in trials of outer membrane vesicle vaccines. These cutoffs are, therefore, currently used for regulatory approval of new meningococcal vaccines.

There has been increasing evidence that mechanisms other than complement-dependent bactericidal antibodies are important in determining protection against meningococcal disease. The relationship between incidence of disease and prevalence of SBA was not observed in more recent studies in the United Kingdom and Canada, where a decline in disease incidence throughout childhood was not associated with a change in the seroprevalence of SBA. In the UK study, the second peak of disease in teenagers coincided with a paradoxical increase in the proportion with an SBA titer $\geq 1:4$ and adults had a low risk of disease despite a much lower prevalence of SBA activity. In addition, disease in individuals with complement deficiency has a different age distribution with less severe clinical features and often involves unusual serogroups. In particular, complement deficiency does not appear strongly related to an increased risk of serogroup B disease. Alternative surrogate markers of protection include the opsonophagocytic assay and antibody avidity, but there are no studies that have attempted to link these laboratory tests with vaccine efficacy or even population protection, as has been found with SBA.

Host Factors
Host susceptibility is strongly related to age as described above, indicating that immunologic responsiveness and/or naïvety in infancy and early childhood are key determinants of risk. Complement is a key factor in protection against meningococcal disease. Individuals with inherited deficiencies of properdin, factor D, or terminal complement components have up to a 1,000-fold higher risk for development of meningococcal disease than complement-sufficient people. The risk of meningococcal disease is also increased in patients with acquired complement deficiencies associated with diseases such as nephrotic syndrome, systemic lupus erythematosus, and hepatic failure.

Among those with complement deficiencies, meningococcal disease is more prevalent during late childhood and adolescence, when carriage rates are higher than in children younger than age 10 yr; meningococcal infections may be recurrent. Although meningococcal disease can occasionally be overwhelming in patients with late complement component deficiency, cases are more typically described as being less severe than in complement-sufficient persons (properdin deficiency being the exception), perhaps reflecting the fact that these cases are often caused by unusual capsular serogroups. In 1 study, one-third of individuals with meningococcal disease caused by serogroups X, Y, and W had a complement deficiency. Although protective against early infection, extensive complement activation and bacteriolysis may contribute to the pathogenesis of severe disease once bacterial invasion has occurred.

The sibling risk ratio for meningococcal disease is similar to that for other diseases where susceptibility shows polygenic inheritance, and there are a number of host genetic factors that have now been identified to affect either susceptibility to meningococcal disease or severity of disease. The difficulties of these studies are the requirement for large numbers of cases and controls, and the need to confirm any potential associations in more than 1 population. The molecules implicated involved polymorphisms in genes expressed at epithelial surfaces, the complement cascade, pattern recognition receptors, clotting factors, or inflammatory mediators. Deficiencies in the complement pathways are consistently associated with an increased risk of meningococcal disease, with specific polymorphisms in mannan-binding lectin, and factor H found to be associated with disease susceptibility. A genome-wide association study of 7,522 individuals in Europe identified single-nucleotide polymorphisms within genes encoding complement factor H (CFH) and CFH-related protein 3 (CFHR3), which were associated with host susceptibility to meningococcal disease. Complement-mediated bacteriolysis is known to be extremely important in protection against meningococcal disease, giving these associations biologic plausibility. In particular, factor H attaches to various binding proteins expressed on the bacterial surface, downregulating complement activation and allowing the organism to evade host responses.

In terms of disease severity, a meta-analysis performed to collate data from smaller studies found that single-nucleotide polymorphisms in genes encoding plasminogen activator inhibitor 1 (SERPINE1), IL-1 receptor antagonist (IL1RN) and IL-1β (IL1B) are associated with increased mortality from meningococcal disease, which, again, is predictable from the known pathophysologic changes that occur during invasive disease. Given that any single specific single-nucleotide polymorphism is likely to have only a small impact on disease susceptibility or severity, further large genome-wide association study in genetically different populations are required.

CLINICAL MANIFESTATIONS
The most common clinical manifestation of meningococcal infection is asymptomatic carriage of the organism in the nasopharynx. In the rare cases where invasive disease occurs, the clinical spectrum of meningococcal disease varies widely, but the highest proportion of cases present with meningococcal meningitis (30-50% of cases). Other recognized presentations include bacteremia without sepsis, meningococcal septicemia with or without meningitis, pneumonia, chronic bacteremia, and occult bacteremia. Focal infections in various sites (e.g., myocardium, joints, periarticular, bone, eye, peritoneum, sinuses, and middle ear) are well recognized, and all may progress to disseminated disease. Urethritis, cervicitis, vulvovaginitis, orchitis, and proctitis may also occur.

Acute meningococcal septicemia cannot be distinguished from other viral or bacterial infections early after onset of symptoms (Table 191-1). Typical nonspecific early symptoms include fever, irritability, lethargy, respiratory symptoms, refusal to drink, and vomiting. Less commonly, diarrhea, sore throat, and chills/shivering are reported. A fine maculopapular rash, which is indistinguishable from rashes seen after viral infections, is evident in approximately 7% of cases early in the course of infection. Limb pain, myalgia, or refusal to walk may occur as the primary complaint in 7% of otherwise clinically unsuspected cases. As disease progresses, cold hands or feet and abnormal skin color may be important signs, capillary refill time becomes prolonged, and a nonblanching petechial rash will develop in more than 80% of cases. In fulminant meningococcal septicemia, the disease progresses rapidly over several hours from fever with nonspecific signs to septic shock characterized by prominent petechiae and purpura (purpura fulminans) with poor peripheral perfusion, tachycardia (to compensate for reduced blood volume resulting from capillary leak), increased respiratory rate (to compensate for pulmonary edema), hypotension (a late sign of shock in young children), confusion, and coma (resulting from decreased cerebral perfusion). Coagulopathy, electrolyte disturbance (especially hypokalemia), acidosis, adrenal hemorrhage, renal failure, and myocardial failure, may all develop (Fig. 191-2). Meningitis may be present.

Meningococcal meningitis is indistinguishable from meningitis caused by other bacteria. Nonspecific symptoms and signs (see Table 191-1), including fever and headache, predominate, especially in the young and early in the illness. Children younger than 5 yr of age rarely report headache. More specific symptoms of photophobia, nuchal rigidity, bulging of the fontanel, and clinical signs of meningeal irritation may develop but are unusual in infants. Seizures and focal neurologic signs occur less frequently than in patients with meningitis
Table 191-1: Prevalence of Symptoms and Signs in Children and Young People with Meningococcal Septicemia, Meningococcal Disease and Bacterial Meningitis

<table>
<thead>
<tr>
<th>SYMPTOM OR SIGN</th>
<th>BACTERIAL MENINGITIS</th>
<th>MENINGOCOCCAL DISEASE</th>
<th>MENINGOCOCCAL SEPTICEMIA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>66-97% (10)</td>
<td>58-97% (7)</td>
<td>98% (1)</td>
</tr>
<tr>
<td>Vomiting or nausea</td>
<td>18-70% (10)</td>
<td>44-76% (6)</td>
<td>64% (1)</td>
</tr>
<tr>
<td>Rash</td>
<td>9-62% (6)</td>
<td>59-100% (9)</td>
<td>70% (1)</td>
</tr>
<tr>
<td>Headache</td>
<td>3-59% (7)</td>
<td>16-49% (5)</td>
<td>40% (1)</td>
</tr>
<tr>
<td>Lethargy</td>
<td>13-87% (6)</td>
<td>36-65% (3)</td>
<td>59% (1)</td>
</tr>
<tr>
<td>Coughing</td>
<td>N/A (0)</td>
<td>15-27% (2)</td>
<td>33% (1)</td>
</tr>
<tr>
<td>Irritable or unsettled</td>
<td>21-79% (8)</td>
<td>36-67% (3)</td>
<td>32% (1)</td>
</tr>
<tr>
<td>Runny nose</td>
<td>N/A (0)</td>
<td>24% (1)</td>
<td>31% (1)</td>
</tr>
<tr>
<td>Muscle ache or joint pain</td>
<td>23% (1)</td>
<td>7-65% (3)</td>
<td>30% (1)</td>
</tr>
<tr>
<td>Refusing food or drink</td>
<td>26-76% (4)</td>
<td>13-60% (3)</td>
<td>27% (1)</td>
</tr>
<tr>
<td>Altered mental state*</td>
<td>26-93% (6)</td>
<td>45-81% (3)</td>
<td>N/A (0)</td>
</tr>
<tr>
<td>Stiff neck</td>
<td>13-74% (13)</td>
<td>5-71% (6)</td>
<td>N/A (0)</td>
</tr>
<tr>
<td>Impaired consciousness</td>
<td>60-87% (4)</td>
<td>10-72% (2)</td>
<td>N/A (0)</td>
</tr>
<tr>
<td>Unconsciousness</td>
<td>4-18% (4)</td>
<td>N/A (0)</td>
<td>N/A (0)</td>
</tr>
<tr>
<td>Chills or shivering</td>
<td>N/A (0)</td>
<td>39% (1)</td>
<td>N/A (0)</td>
</tr>
<tr>
<td>Photophobia</td>
<td>5-16% (2)</td>
<td>2-31% (5)</td>
<td>N/A (0)</td>
</tr>
<tr>
<td>Respiratory symptoms</td>
<td>25-49% (4)</td>
<td>16-23% (2)</td>
<td>N/A (0)</td>
</tr>
<tr>
<td>Breathing difficulty</td>
<td>13-34% (4)</td>
<td>11% (1)</td>
<td>N/A (0)</td>
</tr>
<tr>
<td>Cold hands or feet</td>
<td>N/A (0)</td>
<td>43% (1)</td>
<td>N/A (0)</td>
</tr>
<tr>
<td>Shock</td>
<td>8-16% (2)</td>
<td>27-29% (2)</td>
<td>N/A (0)</td>
</tr>
<tr>
<td>Seizures</td>
<td>14-38% (12)</td>
<td>7-17% (3)</td>
<td>N/A (0)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>21-29% (2)</td>
<td>7-9% (2)</td>
<td>N/A (0)</td>
</tr>
<tr>
<td>Abdominal pain or distention</td>
<td>17% (1)</td>
<td>4% (1)</td>
<td>N/A (0)</td>
</tr>
<tr>
<td>Leg pain</td>
<td>N/A (0)</td>
<td>11-37% (2)</td>
<td>N/A (0)</td>
</tr>
<tr>
<td>Thirst</td>
<td>N/A (0)</td>
<td>8% (1)</td>
<td>N/A (0)</td>
</tr>
<tr>
<td>Sore throat, coryza or throat infection</td>
<td>18% (1)</td>
<td>24% (1)</td>
<td>N/A (0)</td>
</tr>
<tr>
<td>Ill appearance</td>
<td>N/A (0)</td>
<td>79% (1)</td>
<td>N/A (0)</td>
</tr>
<tr>
<td>Capillary refill time &gt;2 sec</td>
<td>N/A (0)</td>
<td>83% (1)</td>
<td>N/A (0)</td>
</tr>
<tr>
<td>Hypotension</td>
<td>N/A (0)</td>
<td>28% (1)</td>
<td>N/A (0)</td>
</tr>
<tr>
<td>Abnormal skin color</td>
<td>N/A (0)</td>
<td>19% (1)</td>
<td>N/A (0)</td>
</tr>
<tr>
<td>Bulging fontanelle†</td>
<td>13-45% (4)</td>
<td>N/A (0)</td>
<td>N/A (0)</td>
</tr>
<tr>
<td>Ear infection or ear, nose and throat infections ‡</td>
<td>18-49% (5)</td>
<td>N/A (0)</td>
<td>N/A (0)</td>
</tr>
<tr>
<td>Chest infection</td>
<td>14% (1)</td>
<td>N/A (0)</td>
<td>N/A (0)</td>
</tr>
<tr>
<td>Brudzinski sign</td>
<td>11-66% (2)</td>
<td>N/A (0)</td>
<td>N/A (0)</td>
</tr>
<tr>
<td>Kernig sign</td>
<td>10-53% (3)</td>
<td>N/A (0)</td>
<td>N/A (0)</td>
</tr>
<tr>
<td>Abnormal pupils</td>
<td>10% (1)</td>
<td>N/A (0)</td>
<td>N/A (0)</td>
</tr>
<tr>
<td>Cranial nerve pair involvement</td>
<td>4% (1)</td>
<td>N/A (0)</td>
<td>N/A (0)</td>
</tr>
<tr>
<td>Toxic or moribund state</td>
<td>3-49% (2)</td>
<td>N/A (0)</td>
<td>N/A (0)</td>
</tr>
<tr>
<td>Back rigidity</td>
<td>46% (1)</td>
<td>N/A (0)</td>
<td>N/A (0)</td>
</tr>
<tr>
<td>Paresis</td>
<td>6% (1)</td>
<td>N/A (0)</td>
<td>N/A (0)</td>
</tr>
<tr>
<td>Focal neurological deficit</td>
<td>6-47% (3)</td>
<td>N/A (0)</td>
<td>N/A (0)</td>
</tr>
</tbody>
</table>

Classification of conditions presented in the table reflects the terminology used in the evidence.

*This includes confusion, delirium, and drowsiness.
†The age ranges in the 4 studies are 0-14 yr, 0-2 yr, 0-12 mo, and 0-13 wk.
‡One study reported the number of children and young people with ear, nose, and throat infections; the 4 other studies reported the number of ear infections only.
N/A, not applicable.

caused by Streptococcus pneumoniae or Haemophilus influenzae type b. A meningococcal meningitis-like picture can occur that is associated with rapidly progressive cerebral edema and death from raised intracranial pressure, which may be more common with serogroup A infection.

Occult meningococcal bacteremia manifests as fever with or without associated symptoms that suggest a minor viral infection. Resolution of bacteremia may occur without antibiotics, but sustained bacteremia leads to meningitis in approximately 60% of cases and to distant infection of other tissues.

Chronic meningococcemia, which occurs rarely, is characterized by fever, nontoxic appearance, arthralgia, headache, splenomegaly, and a maculopapular or petechial rash. Symptoms are intermittent, with a mean duration of illness of 6-8 wk. Blood culture results are usually positive, but cultures may initially be sterile. Chronic meningococcemia may spontaneously resolve, but meningitis may develop in untreated cases. Some cases have been associated with complement deficiency and others with sulfonamide therapy. One report indicates that up to 47% of isolates from patients with chronic meningococcemia (compared with less than 10% in acute cases) have a mutation in the lpxl 1 gene, leading to a reduced inflammatory response and the milder course of infection.

**DIAGNOSIS**

The initial diagnosis of meningococcal disease should be made on clinical assessment to avoid delay in implementation of appropriate therapy. Laboratory findings are variable but may include leukocytopenia or leukocytosis, often with increased percentages of neutrophils and band forms, an anemia, thrombocytopenia, proteinuria, and hematuria. Elevations of erythrocyte sedimentation rate and C-reactive protein may occur, but in patients with rapid onset of disease, these values may be within normal limits at presentation. Conversely, a raised C-reactive protein in the presence of fever and petechiae makes the diagnosis likely. Hypoaalbuminemia, hypocalcemia, hypokalemia, hypomagnesemia, hypophosphatemia, hypoglycemia, and metabolic acidosis, often with increased lactate levels, are common in patients with meningococcal septicemia. Patients with coagulopathy have decreased serum concentrations of prothrombin and fibrinogen and prolonged coagulation times.

A confirmed diagnosis of meningococcal disease is established by isolation of *N. meningitidis* from a normally sterile body fluid such as blood, CSF, or synovial fluid. Meningococci may be identified in a Gram stain preparation and/or culture of petechial or purpuric skin lesions, although this procedure is rarely undertaken, and occasionally are seen on Gram stain of the buffy coat layer of a centrifuged blood sample. Although blood culture may be positive in more than two-thirds of cases prior to antibiotic use, culture results often are negative if the patient has been treated with antibiotics prior to collection of the culture specimen; data suggest that less than 50% are culture-positive. Isolation of the organism from the nasopharynx is not diagnostic of invasive disease because the organism is a common commensal.

PCR using primers specific for meningococcal genes (e.g., *ctrA*), has high sensitivity and specificity for detection of meningococci using whole blood samples and has increased confirmation of suspected cases by more than 40% in the United Kingdom.

Lumbar puncture should be undertaken to establish a diagnosis of meningococcal meningitis in those patients without contraindications (including presence of septic shock, coagulopathy, thrombocytopenia, respiratory distress, seizures, raised intracranial pressure, or local infection). In patients with meningococcal meningitis, the cellular and chemical characteristics of the CSF are those of acute bacterial meningitis, showing Gram-negative diplococci on Gram stain in up to 75% of cases. CSF culture results may be positive in patients with meningococcal meningitis in the absence of CSF pleocytosis or clinical evidence of meningitis; conversely, positive CSF specimens that are positive for Gram stain are sometimes culture negative. Over-decolorized pneumococci in Gram stain preparations can be mistaken for meningococci, and, therefore, empirical therapy should not be narrowed to *N. meningitidis* infection on the basis of Gram stain findings alone.

Detection of capsular polysaccharide antigens using rapid latex agglutination tests on CSF can support the diagnosis in cases clinically consistent with meningococcal disease, but the tests have not performed adequately in clinical practice (poor sensitivity and cross-reactivity of the serogroup B test with *Escherichia coli* K1 antigen) and have been replaced by molecular diagnostic methods. Urine antigen testing is insensitive and should not be used. PCR-based assays for detection of meningococci in blood and CSF have been developed, and multiplex PCR assays that detect several bacterial species associated with meningitis, including the meningococcus, are used in some laboratories.

**DIFFERENTIAL DIAGNOSIS**

Meningococcal disease can appear similar to sepsis or meningitis caused by many other Gram-negative bacteria, *S. pneumoniae, Staphylococcus aureus*, or group A streptococcus; to Rocky Mountain spotted fever, ehrlichiosis, or epidemic typhus; and to bacterial endocarditis. Viral and other infectious etiologies of meningoencephalitis should be considered in some cases.

Petechial rashes are common in viral infections (enteroviruses, influenza and other respiratory viruses, measles, Epstein Barr virus, cytomegalovirus, parvovirus) and may be confused with meningococcal disease. Petechial or purpuric rashes are also associated with protein C or S deficiency, platelet disorders (including idiopathic thrombocytopenic purpura), Henoch-Schönlein purpura, connective tissue disorders, drug eruptions, and trauma, including nonaccidental injury. The nonpetechial, blanching maculopapular rash observed in some cases by more than 40% in the United Kingdom.

**TREATMENT**

**Antibiotics**

Empirical antimicrobial therapy should be initiated immediately after the diagnosis of invasive meningococcal infection is suspected and cultures are obtained, using a third-generation cephalosporin to cover the most likely bacterial pathogens until the diagnosis is confirmed. In regions with a high rate of β-lactam resistant *S. pneumoniae*, empiric addition of intravenous (IV) vancomycin is recommended (see Chapter 603.1) while awaiting the outcome of bacterial identification and sensitivity, but this is unnecessary in other settings where cephalosporin...
resistance of pneumococci is very rare (in these settings a risk assessment of each case should be made). Once the diagnosis of β-lactam sensitive meningococcal disease is confirmed in the laboratory, some authorities recommend a switch to penicillin; however, even though there is no evidence that survival outcomes are different, there is limited evidence from 1 study that, in meningococcal purpura, necrotic skin lesions are less common among children treated with ceftriaxone than with penicillin. Furthermore, there may be cost-saving by using a once-daily dose of ceftriaxone for therapy in younger children, and this is now recommended practice in the United Kingdom (Table 191-2). No adequate studies have investigated the optimal duration of therapy for children, but the course is generally continued for 5-7 days.

Early treatment of meningococcal infections may prevent serious sequelae, but timely early diagnosis is often difficult in the absence of petechial or purpuric skin findings. Among children presenting with petechial rashes, 1-10% may have underlying meningococcal disease and protocols have been established to ensure that these patients are identified without exposing the more than 90% of cases without meningococcal disease to unnecessary parenteral antibiotic therapy (Fig. 191-3). Isolates of N. meningitidis with decreased susceptibility to penicillin (minimal inhibitory concentration of penicillin of 0.1-1.0 mg/mL) have been reported from Europe, Africa, Canada, and the United States (4% of isolates in 2006). Decreased susceptibility is caused, at least in part, by altered penicillin-binding protein 2 and does not appear to adversely affect the response to therapy, and is irrelevant if third-generation cephalosporins are being used for therapy.

Supportive Care
Most children with meningococcal disease can be managed with antibiotics and simple supportive care and will improve rapidly. However, with an overall 10% case-fatality rate, the priority in initiating management of children presenting with meningococcal disease is identification of the life-threatening features of the disease: shock and raised intracranial pressure. Delayed initiation of supportive therapy is associated with poor outcome, and protocols have therefore been established to aid clinicians in a step-by-step approach (http://www.meningitis.org). In all children presenting with meningococcal disease, assessment of the airway should be made, as the airway could be compromised as a result of a depressed level of consciousness (raised intracranial pressure in meningitis or poor cerebral perfusion in shock). In patients with meningococcal septicemia supplementary oxygen should be used to treat hypoxia, which is caused by pulmonary edema (from capillary leak), and some patients will require endotracheal intubation. Hypovolemia requires both volume replacement and inotropic support to maintain cardiac output. Because ongoing fluid resuscitation may lead to pulmonary edema, endotracheal intubation and ventilation should be initiated in a patient who remains in compensated shock after 40 mL/kg of fluid resuscitation to improve oxygenation and reduce work of breathing. Biochemical and hematologic abnormalities are common in meningococcal septicemia, and protocols recommend anticipation, assessment, and correction of glucose, potassium, calcium, magnesium, phosphate, clotting factors, and blood.

Children with meningococcal meningitis should be cautiously managed with maintenance fluids (fluid restriction is not recommended and may be harmful), and those with raised intracranial pressure should be managed with close attention to maneuvers to maintain normal cerebral perfusion. If there is shock in the presence of raised intracranial pressure, the shock should be carefully corrected to ensure that cerebral perfusion pressure is maintained.

Many adjunctive therapies have been attempted in patients with severe meningococcal septicemia, but few have been subjected to randomized controlled trials. There are insufficient data to recommend use of anticoagulant or fibrinolytic agents, extracorporeal membrane oxygenation, plasmapheresis, or hyperbaric oxygen. In well-designed clinical trials, an antibody directed against endotoxin (HA1A) did not confer any benefit in children with meningococcal disease, and, although initially promising in adult sepsis, activated protein C was not useful in pediatric sepsis and was associated with an increased risk of bleeding. Recombinant bactericidal permeability increasing protein was studied in an underpowered (survival end point) trial and showed some potentially beneficial effects against secondary end points (amputations, transfusions, functional outcome) and requires further investigation.

Although the benefits of steroids for adjunctive therapy in pediatric bacterial meningitis caused by H. influenzae type b (Hib) are accepted, there are no pediatric data specifically demonstrating benefit in meningococcal meningitis. However, some authorities extrapolate from animal data, from experience with Hib, and from compelling data from adult meningitis and recommend use of steroids as adjunctive therapy in meningococcal meningitis given with or soon after the 1st dose of antibiotics. Therapeutic doses of steroids should not be used routinely in meningococcal septicemia. Some intensivists recommend use of replacement doses of steroids in patients with severe septic shock, since severe sepsis caused by meningococcus is associated with adrenal insufficiency caused by adrenal necrosis/hemorrhage (Waterhouse-Friderichsen syndrome).

### Table 191-2 Treatment of Neisseria meningitidis Invasive Infections

<table>
<thead>
<tr>
<th>DRUG</th>
<th>ROUTE OF ADMINISTRATION</th>
<th>DOSE</th>
<th>DOSING INTERVAL (hr)</th>
<th>MAXIMUM DAILY DOSE</th>
<th>NOTES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillin G</td>
<td>IM or IV</td>
<td>300,000 units/kg/day</td>
<td>4-6</td>
<td>12-24 million units</td>
<td>Does not clear carriage and “prophylaxis” is required at the end of treatment</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>IM or IV</td>
<td>200-400 mg/kg/day</td>
<td>6</td>
<td>6-12 g</td>
<td>Does not clear carriage and “prophylaxis” is required at the end of treatment</td>
</tr>
<tr>
<td>Cefotaxime</td>
<td>IM or IV</td>
<td>200-300 mg/kg/day</td>
<td>6</td>
<td>8-12 g</td>
<td>Recommended in the neonate</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>IM or IV</td>
<td>100 mg/kg/day</td>
<td>12-24</td>
<td>2-4 g</td>
<td>Preferred treatment as only once or twice daily and may reduce skin complications</td>
</tr>
</tbody>
</table>

**ALTERNATIVE THERAPY IN THE FACE OF LIFE-THREATENING β-LACTAM ALLERGY**

<table>
<thead>
<tr>
<th>DRUG</th>
<th>ROUTE OF ADMINISTRATION</th>
<th>DOSE</th>
<th>MAXIMUM DAILY DOSE</th>
<th>NOTES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chloramphenicol*</td>
<td>IV</td>
<td>50-100 mg/kg/day</td>
<td>6</td>
<td>2.4 g</td>
</tr>
<tr>
<td>Ciprofloxacin†</td>
<td>IV</td>
<td>30-40 mg/kg/day</td>
<td>12</td>
<td>1-1.5 g</td>
</tr>
<tr>
<td>Meropenem‡</td>
<td>IV</td>
<td>60-120 mg/kg/day</td>
<td>8</td>
<td>1.5-6 g</td>
</tr>
</tbody>
</table>

*Monitor blood levels to avoid toxicity.
†Licensed for individuals older than age 18 yr.
‡Rate of crossreactivity in penicillin-allergic adults is 2-3%.
IM, intramuscular; IV, intravenous.

**Chapter 191  Neisseria meningitidis (Meningococcus) 1361**
**COMPPLICATIONS**

Adrenal hemorrhage, endophthalmitis, arthritis, endocarditis, pericarditis, myocarditis, pneumonia, lung abscess, peritonitis, and renal infarcts can occur during acute infection. Renal insufficiency requiring dialysis may result from prerenal failure. Reactivation of latent herpes simplex virus infections is common during meningococcal infection.

A self-limiting immune complex vasculitis may occur, usually in the 1st 10 days after onset of the disease, resulting in various manifestations, including fever, rash, arthritis, and, rarely, iritis, pericarditis, or carditis. The arthritis is monoarticular or oligoarticular, involves large joints, and is associated with sterile effusions that respond to nonsteroidal antiinflammatory agents. Because most patients with meningococcal meningitis become afebrile by the 7th hospital day, persistence or recrudescence of fever after 5 days of antibiotics warrants evaluation for immune complex–mediated complications.

The most common complication of acute severe meningococcal septicemia is focal skin infarction, which most commonly affects the lower limbs and can lead to substantial scarring and require skin grafting. Distal tissue necrosis in purpura fulminans may require amputation (which should be delayed to allow demarcation) in approximately 2% of survivors. Avascular necrosis of epiphyses and epiphyseal–metaphyseal defects can result from the generalized disseminated intravascular coagulation and may lead to growth disturbance and late skeletal deformities.

Deafness is the most frequent neurologic sequela of meningitis, occurring in 5-10% of children. Cerebral arterial or venous thrombosis with resultant cerebral infarction can occur in severe cases. Meningococcal meningitis is rarely complicated by subdural effusion or empyema or by brain abscess. Other rare neurologic sequelae include ataxia, seizures, blindness, cranial nerve palsies, hemiparesis or quadripareis, and obstructive hydrocephalus (manifests 3-4 wk after onset
of illness). Finally, behavioral and psychosocial complications of the disease are frequently reported.

**PROGNOSIS**

The case-fatality rate for invasive meningococcal disease is 5-10%, with clear differences related to age of the patient and meningococcal genotype. Most deaths occur within 48 hr of hospitalization in children with meningococcemia. Poor prognostic factors on presentation include hypothermia or extreme hyperpyrexia, hypotension or shock, purpura fulminans, seizures, leukopenia, thrombocytopenia (including disseminated intravascular coagulation), acidosis, and high circulating levels of endotoxin and tumor necrosis factor-α. The presence of petechiae for <12 hr before admission, absence of meningitis, and low or normal erythrocyte sedimentation rate indicate rapid, fulminating progression and poorer prognosis.

Because complement deficiency is rare following capsular group B infection, screening is unlikely to be useful in detecting cases caused by this group. However, with one-third or more of cases of disease caused by groups X, Y, and W apparently associated with complement deficiency, it is appropriate to screen after infection with non-B serogroups.

**PREVENTION**

**Secondary Prevention**

Close contacts of patients with meningococcal disease are at increased risk of infection because such individuals are likely to be colonized with the index's (hyperinvasive) strain. Antibiotic prophylaxis should be offered as soon as possible to individuals who have been exposed directly to a patient's oral secretions, for whom risk may be 1,000 times the background rate in the population. This includes household, kissing, and close family contacts of cases, as well as childcare and recent preschool contacts in the United States. Up to 30% of cases occur in the 1st wk, but risk persists for up to a year after presentation of the index case. Although prophylaxis is effective in preventing secondary cases, coprimary cases may occur in the days after presentation of the index case and contacts should be carefully evaluated if they develop symptoms. Advice on management of non–close contacts, such as those in daycare, nursery settings, or school and other institutions, varies in different countries because the risk of a secondary case in this situation is low and opinion on risk assessment varies. Ceftriaxone and ciprofloxacin are the most effective agents for prophylaxis, the latter being the drug of choice in some countries. Rifampin is most widely used but fails to eradicate colonization in 15% of cases (Table 191-3). Prophylaxis is not routinely recommended for medical personnel except those with exposure to aerosols of respiratory secretions, such as through mouth–to-mouth resuscitation, intubation, or suctioning before or in the 24 hr after antibiotic therapy is initiated in the index case.

Neither penicillin nor ampicillin treatment eradicates nasopharyngeal carriage and should not be routinely used for prophylaxis. Patients with meningococcal infection treated solely with penicillin or ampicillin are therefore at risk of relapse or transmission to a close contact and should receive antimicrobial prophylaxis with one of the agents listed in Table 191-3 prior to hospital discharge. As discussed above, our preference is to use ceftriaxone for treatment of the index case, in which case further prophylaxis is not required. Droplet precautions should be observed for hospitalized patients for 24 hr after initiation of effective therapy. All confirmed or probable cases of meningococcal infection must be reported to the local public health department according to national or regional regulations.

Close contacts of cases could also be immunized to further reduce the risk of secondary infection as is described below.

**Vaccination**

Meningococcal plain polysaccharide vaccines containing capsular polysaccharides from serogroups A + C or serogroups A, C, W, Y have been available since the 1960s and have been used in the control of outbreaks and epidemics and for high-risk groups. However, these vaccines are poorly immunogenic in infants, do not induce immunologic memory, and are associated with immunologic hyporesponsiveness (reduced response to future doses of polysaccharide). Plain polysaccharide vaccines have been superseded by meningococcal protein-polysaccharide conjugate vaccines, which are generally more immunogenic than plain polysaccharides, are immunogenic from early infancy, induce immunologic memory, and are not associated with hyporesponsiveness. The conjugate vaccines contain meningococcal polysaccharides that are chemically conjugated to a carrier protein. Three carrier proteins are used in various meningococcal conjugate vaccines: tetanus, diphtheria, and the mutant diphtheria toxin, CRM197. However, although plain polysaccharides vaccines should now be considered redundant in most industrialized countries where the new-generation conjugates are available, they may still have a role in some regions where conjugates are not yet available.

The first meningococcal conjugate vaccine to be used was a monovalent serogroup C meningococcal conjugate vaccine (MenC), which was introduced in the United Kingdom in 1999 and was administered to all children and young people under the age of 19 yr in a mass catch-up campaign before establishment in the routine infant immunization schedule. The MenC vaccine has proved highly (>95%) effective in controlling disease through both direct protection of the vaccinated population and induction of herd immunity, protecting the wider population. Herd immunity is induced through the impact of conjugate vaccines on colonization, reducing carriage and blocking transmission of meningococci among adolescents and young adults. Monovalent MenC vaccines are now used widely in the industrialized countries of Western Europe, Canada, and Australia, where disease caused by serogroup C meningococci has virtually disappeared. However, serologic surveys show that antibody levels wane, especially after infant immunization, and booster doses are now recommended during adolescence to sustain individual and population immunity.

Quadrivalent meningococcal A, C, Y, W conjugate vaccines (MenACWY) have been available since 2005 and are now routinely used for adolescents in the United States and as a single adolescent “booster” dose in some countries that had established MenC infant

<table>
<thead>
<tr>
<th>Table 191-3</th>
<th>Antibiotic Prophylaxis to Prevent Neisseria meningitidis Infection</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DRUG</strong></td>
<td><strong>DOSE</strong></td>
</tr>
<tr>
<td>Rifampin†</td>
<td>Infants &lt;1 mo</td>
</tr>
<tr>
<td></td>
<td>Children ≥1 mo</td>
</tr>
<tr>
<td></td>
<td>Adults</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>Children &lt;15 yr</td>
</tr>
<tr>
<td></td>
<td>Children ≥15 yr</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>Children ≥1 mo‡</td>
</tr>
</tbody>
</table>

*Recommended for household and kissing contacts. In the United States, chemoprophylaxis is recommended for:
  - Household contact, especially children younger than 2 yr of age
  - Childcare or preschool contact at any time during 7 days before onset of illness
  - Direct exposure to index patient's secretions through kissing, sharing toothbrushes or eating utensils at any time during 7 days before onset of illness
  - Mouth-to-mouth resuscitation, unprotected contact during endotracheal intubation during 7 days before onset of illness
  - Frequently slept in same dwelling as index patient during 7 days before onset of illness
  - Passengers seated directly next to the index case during airline flights lasting more than 8 hr

†Not recommended for pregnant women.
‡Not recommended routinely for people younger than 18 yr of age; use only if fluoroquinolone-resistant strains of N. meningitidis have not been identified in the community.
IM, intramuscular; PO, by mouth.
programs more than a decade ago. MenACWY was initially introduced as a single dose at 11 yr of age in the United States, but concerns about waning immunity led to the adoption of a 2nd dose. The initial reports on effectiveness (>80%) of MenACWY in the U.S. program indicates that these vaccines are likely to provide control of disease caused by serogroups C, W, and Y (serogroup A being unimportant currently), although the program has taken some time to become fully established. As the population of immunized adolescents and young adults in the U.S. grows, it is likely that the effects of these vaccines on carriage of meningococci will reduce disease among other segments of the population through herd immunity, assuming that the transmission dynamics of Y and W meningococci are the same as for serogroup C. While MenACWY vaccines are not currently recommended in the United States for routine use in younger age groups in view of the low rate of disease caused by these serogroups in infancy, they may provide broader protection in countries that are already using MenC vaccines in infant programs. Other combination vaccines containing various conjugates, including Hib-MenC (used in the United Kingdom as a 12 mo booster) and Hib-MenCY, may have a role in broadening protection beyond MenC, in early life. Table 191-4 outlines the current U.S. programmatic recommendations.

Individuals at high risk of meningococcal disease, such as those with complement deficiency and travelers to regions where there is a risk of epidemic meningococcal disease caused by A or W, should receive MenACWY (Table 191-4 lists recommendations for use in the United States). The risk of disease among close contacts of cases of disease caused by vaccine serogroups may be further reduced if they are offered MenACWY in addition to antimicrobial prophylaxis. A possible association between MenACWY-diphtheria and Guillain-Barré syndrome, which caused concern early after the vaccine was first used in the United States, has not been substantiated.

A serogroup A meningococcal conjugate vaccine, MenA, has been developed for use in the sub-Saharan African meningitis belt, and implementation in 2010 through mass vaccination appears already to have interrupted disease caused by this serogroup. More than 100 million people had been vaccinated by the end of 2012.

As discussed above, the majority of disease in infants and in most industrialized countries is caused by serogroup B polysaccharide-bearing meningococci. This polysaccharide capsule has chemical identity with glycosylated protein antigens in the human fetus and, as a self-antigen, is therefore not immunogenic in humans and leads to the theoretical risk of induction of autoimmunity. Vaccine development has therefore focused on subcapsular protein antigens. Several countries (including Cuba, Norway, and New Zealand) successfully controlled serogroup B epidemics by immunizing with tailor-made outer membrane vesicle vaccines prepared from blebs of outer membrane harvested from the respective epidemic strains. The principal limitation of outer membrane vesicle vaccines is that the bactericidal antibody responses induced by immunization are limited to the vaccine strain, because the response is largely directed against the homologous PorA (serosubtype) protein, and they are therefore not considered for use in endemic settings, including the United States or most other industrialized countries.

Promising approaches for prevention of serogroup B disease have been developed over the past decade. One vaccine that was developed for adolescent immunization was licensed in the United States in 2014 and contains two variants of factor H-binding protein; it appears highly immunogenic in the target population. Recommendations for its use are awaited. Factor H-binding protein appears to be an important virulence determinant, aiding survival of meningococci in blood, and is expressed by virtually all strains.

Another 4-component meningococcal vaccine, 4CMenB, which has been licensed by the European Medicines Agency (2013) for use from infancy, is also available in various other regions and is expected to be licensed in the United States in 2015. This vaccine contains an outer membrane vesicle (derived from the New Zealand outbreak strain) and

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Table 191-4  Recommendations for Meningococcal Vaccination

<table>
<thead>
<tr>
<th>GENERAL POPULATION</th>
<th>2-10 YR</th>
<th>11-21 YR</th>
<th>22-55 YR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not recommended</td>
<td>Not recommended</td>
<td>A single dose of MenACWY-D or MenACWY-CRM at age 11-12 yr or at 13-18 yr if not previously vaccinated. Age 19-21 yr: not routinely recommended but may be given as catch-up for those who have not received a dose after their 16th birthday. A booster dose 5 yr later (see text)*</td>
<td>Not recommended</td>
</tr>
</tbody>
</table>

**SPECIAL POPULATIONS AT INCREASED RISK OF MENINGOCOCCAL DISEASE†**

<table>
<thead>
<tr>
<th>RISK FACTOR</th>
<th>2-18 MONTHS</th>
<th>9-23 MONTHS</th>
<th>2-55 YR‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Persistent complement deficiencies, functional or anatomic asplenia</td>
<td>4 doses of Hib-MenCY-TT at 2, 4, 6, and 12-15 months</td>
<td>2 doses of MenACWY-D 12 wk apart†</td>
<td>2 doses of MenACWY 8-12 wk apart†</td>
</tr>
<tr>
<td>At risk during a community outbreak with a vaccine serogroup</td>
<td>4 doses of Hib-MenCY-TT at 2, 4, 6, and 12-15 months</td>
<td>2 doses of MenACWY-D 12 wk apart</td>
<td>1 dose of MenACWY</td>
</tr>
<tr>
<td>Travel to or resident of countries where meningococcal disease is hyperendemic or epidemic§</td>
<td>Should receive a quadrivalent meningococcal vaccination licensed for children aged ≥9 mo prior to travel</td>
<td>2 doses of MenACWY-D 12 wk apart**</td>
<td>1 dose of MenACWY</td>
</tr>
<tr>
<td>Have HIV, if another indication for vaccination exists</td>
<td>—</td>
<td>2 doses of MenACWY-D 12 wk apart</td>
<td>2 doses of MenACWY 8-12 wk apart†</td>
</tr>
<tr>
<td>Other risk factors</td>
<td>—</td>
<td>—</td>
<td>1 dose MenACWY</td>
</tr>
</tbody>
</table>

*Otherwise healthy adolescents who received a 1st dose at age 11-12 yr should receive a booster dose of a meningococcal conjugate vaccine at 16 yr of age. For those given a 1st dose at age 13-15 yr, and who have not yet reached their 21st birthday, the booster dose should be given 5 yr after the 1st dose.
†Assuming not previously vaccinated.
‡Persons previously vaccinated at 7 yr of age or older who are at prolonged increased risk should be revaccinated 5 yr after their previous meningococcal vaccine and every 5 yr thereafter. Persons previously vaccinated at ages 2 mo-6 yr who are at prolonged increased risk should be revaccinated 3 yr after their previous meningococcal vaccination and every 5 yr thereafter.
§Because of high risk for invasive pneumococcal disease, children with functional or anatomic asplenia should not be immunized with MenACWY-D before age 2 yr to avoid interference with the immune response to the pneumococcal conjugate vaccine (PCV).
¶If MenACWY-D is used, it should be administered at least 4 wk after completion of all PCV doses.
**For example, visitors to the "meningitis belt" of sub-Saharan Africa. Vaccination also is required by the government of Saudi Arabia for all travelers to Mecca during the annual Hajj.
††If receiving the vaccine prior to travel, 2 doses may be administered as early as 8 wk apart.
3 recombinant proteins: a single variant of factor H-binding protein, neisserial adhesin A, and neisserial heparin binding antigen. 4CMenB vaccine induced bactericidal antibodies against strains containing the vaccine antigens in infants, toddlers, and adolescents in clinical trials. The vaccine appears to have a generally favorable safety profile, although induction of fever in infants and pain at the injection site in other age groups are common. This vaccine has been used to control outbreaks of capsular group B meningococcal disease at two universities in the United States and hyperendemic disease in Canada. It was recommended for routine use in the infant immunization program in the United Kingdom in 2014 if a cost-effective price could be negotiated with the manufacturer.

Bibliography is available at Expert Consult.
Bibliography


Neisseria gonorrhoeae produces several forms of gonorrhea, an infection of the genitourinary tract mucous membranes and rarely of the mucosa of the rectum, oropharynx, and conjunctiva. Gonorrhea transmitted by sexual contact or perinatally is second only to chlamydial infections in the number of cases reported to the Centers for Disease Control and Prevention (CDC) in the United States. This high prevalence and the development of antibiotic-resistant strains have produced significant morbidity in adolescents.

ETIOLOGY

*N. gonorrhoeae* is a nonmotile, aerobic, non–spore-forming, Gram-negative intracellular diplococcus with flattened adjacent surfaces. Optimal growth occurs at 35-37°C (95-98.6°F) and at pH 7.2-7.6 in an atmosphere of 3-5% carbon dioxide. The specimen should be inoculated immediately onto fresh, moist, modified Thayer-Martin or special transport media, because gonococci do not tolerate drying. Thayer-Martin medium contains antimicrobial agents that inhibit harder normal flora present in clinical specimens that may otherwise overgrow gonococci. Presumptive identification may be based on colony appearance, Gram stain appearance, and production of cytochrome oxidase. Gonococci are differentiated from other *Neisseria* species by the fermentation of glucose but not maltose, sucrose, or lactose. Gram-negative diplococci are seen in infected material, often within polymorphonuclear leukocytes.

Like all Gram-negative bacteria, *N. gonorrhoeae* possesses a cell envelope composed of an inner cytoplasmic membrane, a middle layer of peptidoglycan, and an outer membrane. The outer membrane contains lipooligosaccharides (endotoxin), phospholipid, and a variety of proteins that contribute to cell adherence, tissue invasion, and resistance to host defenses. The 2 systems primarily used to characterize gonococcal strains are auxotyping and serotyping. Auxotyping is based on genetically stable requirements of strains for specific nutrients or cofactors as defined by an isolate’s ability to grow on chemically defined specialized transport media. The most widely used serotyping system is based on a porin called PorI, a trimeric outer membrane protein that makes up a substantial part of the gonococcal envelope structure.

EPIDEMIOLOGY

*N. gonorrhoeae* infection occurs only in humans. The organism is shed in the exudate and secretions of infected mucosal surfaces and is transmitted through intimate contact, such as sexual contact or parturition, and, rarely, by contact with fomites. Gonococcal infections in the newborn period are generally acquired during delivery. Gonorrhea is the most common sexually transmitted infection found in sexually abused children. Rarely, *N. gonorrhoeae* may be spread by sexual play among children, but the index patient is likely to be a victim of sexual abuse. Gonococcal infections in children are acquired rarely through household exposure to infected caretakers. In such cases, the possibility of sexual abuse should be seriously considered.

The number of reported cases of gonorrhea increased steadily in the United States from 1964 to 1977, fluctuated through the early 1980s, and increased until 1987, when reported rates were 323 per 100,000 population. After implementation of the national gonorrhea control program, rates decreased or were stable annually from 1987 to 2004. In 2005, the national rate (116 per 100,000 population) increased for the first time since 1999. In 2009, rates were 98.1 per 100,000 population, which is the lowest since recording of gonorrhea rates began. The rate increased slightly in 2010 to 100.2 per 100,000 population and increased again in 2011 to 104.2 per 100,000 population. The report of increasing minimum inhibitory concentrations for cephalosporin antibiotics in 2011 raises alarms for a threat of untreatable gonorrhea and need for intensive surveillance. The incidence of gonorrhea is highest in high-density urban areas among persons younger than 24 yr of age who have multiple sex partners and engage in unprotected sexual intercourse. Increases in gonorrhea prevalence have been noted among men who have sex with men. Risk factors include nonwhite race, homosexuality, increased number of sexual partners, prostitution, presence of other sexually transmitted infections, unmarried status, poverty, and failure to use condoms. Auxotyping and serotyping techniques and molecular typing methods are used to analyze the spread of individual strains of *N. gonorrhoeae* within a community.

Maintenance and subsequent spread of gonococcal infections in a community require a hyperendemic, high-risk core group such as prostitutes or adolescents with multiple sexual partners. This observation reflects the fact that most persons who have gonorrhea cease sexual activity and seek care, unless economic need or other factors (e.g., drug addiction) drive persistent sexual activity. Thus, many core transmitters belong to a subset of infected persons who lack or ignore symptoms and continue to be sexually active, underscoring the importance of seeking out and treating the sexual contacts of infected persons who present for treatment.

Gonococcal infection of neonates usually results from peripartum exposure to infected exudate from the cervix of the mother. An acute infection begins 2-5 days after birth. The incidence of neonatal infection depends on the prevalence of gonococcal infection among pregnant women, prenatal screening for gonorrhea, and neonatal ophthalmic prophylaxis.

PATHOGENESIS AND PATHOLOGY

*N. gonorrhoeae* infects primarily columnar epithelium, because stratified squamous epithelium is relatively resistant to invasion. Mucosal invasion by gonococci results in a local inflammatory response that produces a purulent exudate consisting of polymorphonuclear leukocytes, serum, and desquamated epithelium. The gonococcal lipooligosaccharide (endotoxin) exhibits direct cytotoxicity, causing ciliostasis and sloughing of ciliated epithelial cells. Once the gonococcus traverses the mucosal barrier, the lipooligosaccharide binds bacterial immunoglobulin (Ig) M antibody and serum complement, causing an acute inflammatory response in the subepithelial space. Tumor necrosis factor and other cytokines are thought to mediate the cytotoxicity of gonococcal infections.

Gonococci may ascend the urogenital tract, causing urethritis or PID in postpubertal females. Dissemination from the fallopian tubes through the peritoneum to the liver capsule results in...
perihepatitis (Fitz–Hugh–Curtis syndrome). Gonococci that invade the lymphatics and blood vessels may cause inguinal lymphadenopathy; perineal, perianal, ischiorectal, and periprostatic abscesses; and disseminated gonococcal infection (DGI).

A number of gonococcal virulence and host immune factors are involved in the penetration of the mucosal barrier and subsequent manifestations of local and systemic infection. Selective pressure from different mucosal environments probably leads to changes in the outer membrane of the organism, including expression of variants of pili, opacity or Opa proteins (formerly protein II), and lipooligosaccharides. These changes may enhance gonococcal attachment, invasion, replication, and evasion of the host’s immune response.

For infection to occur, the gonococcus must first attach to host cells. A gonococcal IgA protease inactivates IgA; by cleaving the molecule in the hinge region and may be an important factor in colonization or invasion of host mucosal surfaces. Gonococci adhere to the microvilli of noncililiated epithelial cells by hair-like protein structures (pili) that extend from the cell wall. Pili are thought to protect the gonococcus from phagocytosis and complement-mediated killing. Pili undergo high-frequency antigenic variation that may aid in the organism’s escape from the host immune response and may provide specific ligands for different cell receptors. Opacity proteins, most of which confer an opaque appearance to colonies, are also thought to function as ligands to facilitate binding to human cells. Gonococci that express certain Opa proteins adhere to and are phagocytosed by human neutrophils in the absence of serum.

Other phenotypic changes that occur in response to environmental stresses allow gonococci to establish infection. Examples include iron-repressible proteins for binding transferrin or lactoferrin, anaerobically expressed proteins, and proteins that are synthesized in response to contact with epithelial cells. Gonococci may grow in vivo under anaerobic conditions or in an environment with a relative lack of iron.

Approximately 24 hr after attachment, the epithelial cell surface invaginates and surrounds the gonococcus in a phagocytic vacuole. This phenomenon is thought to be mediated by the insertion of gonococcal outer membrane protein I into the host cell, causing alterations in membrane permeability. Subsequently, phagocytic vacuoles begin releasing gonococci into the subepithelial space by means of exocytosis. Viable organisms may then cause local disease (i.e., salpingitis) or disseminate through the bloodstream or lymphatics.

Serum IgG and IgM directed against gonococcal proteins and lipooligosaccharides lead to complement-mediated bacterial lysis. Stable serum resistance to this bactericidal antibody probably results from a particular type of porin protein expressed in gonococci (most contain PorLA), predisposing to disseminated disease. N. gonorrhoeae differentially subverts the effectiveness of complement and alters the inflammatory responses elicited in human infection. Isolates from cases of DGI typically resist killing by normal serum (i.e., are serum resistant), inactivate more C3b, generate less C5a, and result in less inflammation at local sites. PID isolates are serum sensitive, inactivate less C3b, generate more C5a, and result in more inflammation at local sites. IgG antibody directed against gonococcal reduction-modifiable protein (Rmp) blocks complement-mediated killing of N. gonorrhoeae. Anti-Rmp blocking antibodies may harbor specificity for outer membrane protein sequences shared with other neisserial species or Enterobacteriaceae, may be directed against unique Rmp upstream of cysteine loop–specific sequences, or both. Preexisting antibodies directed against Rmp facilitate transmission of gonococcal infection to exposed women; Rmp is highly conserved in N. gonorrhoeae, and the blocking of mucosal defenses may be one of its functions. Gonococcal adaptation also appears to be important in the evasion of killing by neutrophils. Examples include sialylation of lipooligosaccharides, increases in catalase production, and changes in the expression of surface proteins.

Host factors may influence the incidence and manifestations of gonococcal infection. Prepubertal girls are susceptible to vulvovaginitis and, rarely, experience salpingitis. N. gonorrhoeae infects noncornified epithelium, and the thin noncornified vaginal epithelium and alkaline pH of the vaginal mucin predispose this age group to infection of the lower genital tract. Estrogen-induced cornification of the vaginal epithelium in neonates and mature females resists infection. Postpubertal females are more susceptible to salpingitis, especially during menses, when diminished bactericidal activity of the cervical mucus and reflux of blood from the uterine cavity into the fallopian tubes facilitate passage of gonococci into the upper reproductive tract.

Populations at risk for DGI include asymptomatic carriers; neonates; menstruating, pregnant, and postpartum women; homosexuals; and immunocompromised hosts. The asymptomatic carrier state implies failure of the host immune system to recognize the gonococcus as a pathogen, the capacity of the gonococcus to avoid being killed, or both. Pharyngeal colonization has been proposed as a risk factor for DGI. The high rate of asymptomatic infection in pharyngeal gonorrhea may account for this phenomenon. Women are at greater risk for development of DGI during menstruation, pregnancy, and the postpartum period, presumably because of the maximal endocervical shedding and decreased peroxidase bactericidal activity of the cervical mucus during these periods. A lack of neonatal bactericidal IgM antibody is thought to account for the increased susceptibility of neonates to DGI. Persons with terminal complement component deficiencies (C5–C9) are at considerable risk for development of recurrent episodes of DGI.

**CLINICAL MANIFESTATIONS**

Gonorrhea is manifested by a spectrum of clinical presentations from asymptomatic carriage, to the characteristic localized urogenital infections, to disseminated systemic infection (see Chapter 120).

**Asymptomatic Gonorrhea**

The incidence of asymptomatic gonorrhea in children has not been ascertained. Gonococci have been isolated from the oropharynx of young children who have been abused sexually by male contacts; oropharyngeal symptoms are usually absent. Most genital tract infections produce symptoms in children. However, as many as 80% of sexually mature females with urogenital gonorrhea infections are asymptomatic in settings in which most infections are detected through screening or other case-finding efforts. This situation is in contrast to that in men, who are asymptomatic only 10% of the time. Asymptomatic rectal carriage of N. gonorrhoeae has been documented in 40-60% of females with urogenital infection. Most persons with positive rectal culture results are asymptomatic. Most pharyngeal gonococcal infections are asymptomatic. The importance of documenting pharyngeal infection is debated. Most cases resolve spontaneously, transmission from the pharynx to other patients is uncommon, and the pharynx is rarely the only site of infection. Nevertheless, asymptomatic pharyngeal infection may lead to systemic infection and is occasionally the source of transmission to sexual partners.

**Uncomplicated Gonorrhea**

Genital gonorrhea has an incubation period of 2-5 days in men and 5-10 days in women. Primary infection develops in the urethra of males, the vulva and vagina of prepubertal females, and the cervix of postpubertal females. Neonatal ophthalmitis (ophthalmia neonatorum) occurs in both sexes.

**Urethritis** is usually characterized by a purulent discharge and by dysuria without urgency or frequency. Untreated urethritis in males resolves spontaneously in several weeks or may be complicated by epididymitis, penile edema, lymphangitis, prostatitis, or seminal vesiculitis. Gram-negative intracellular diplococci are found in the discharge.

In prepubertal females, vulvovaginitis is usually characterized by a purulent vaginal discharge with a swollen, erythematous, tender, and excoriated vulva. Dysuria may occur. In postpubertal females, symptomatic gonococcal cervicitis and urethritis are characterized by purulent discharge, suprapubic pain, dysuria, intermenstrual bleeding, and dyspareunia. The cervix may be inflamed and tender. In urogenital gonorrhea limited to the lower genital tract, pain is not enhanced by moving the cervix, and the adnexa are not tender to palpation. Purulent material may be expressed from the urethra or ducts of the Bartholin gland. Rectal gonorrhea is often asymptomatic but may cause...
proctitis with symptoms of anal discharge, pruritus, bleeding, pain, tenesmus, and constipation. Asymptomatic rectal gonorrhea may not be from anal intercourse but may represent colonization from vaginal infection.

Gonococcal ophthalmitis may be unilateral or bilateral and may occur in any age group after inoculation of the eye with infected secretions. Ophthalmia neonatorum caused by *N. gonorrhoeae* usually appears from 1-4 days after birth (see Chapter 626). Ocular infection in older patients results from inoculation or autoinoculation from a genital site. The infection begins with mild inflammation and a serous-purulent discharge. Within 24 hr, the discharge becomes thick and purulent, and tense edema of the eyelids with marked chemosis occurs. If the disease is not treated promptly, corneal ulceration, rupture, and blindness may follow.

**Disseminated Gonococcal Infection**

Hematogenous dissemination occurs in 1-3% of all gonococcal infections, more frequently after asymptomatic primary infections than symptomatic infections. Women account for the majority of cases, with symptoms beginning 7-30 days after infection and within 7 days of menstruation. The most common manifestations are asymmetric arthralgia, petechial or purpuric acral skin lesions, tenosynovitis, suppurative arthritis, and, rarely, carditis, meningitis, and osteomyelitis. The most common initial symptom is acute onset of polyarthritis with fever. Only 25% of patients complain of skin lesions. Most deny genitourinary symptoms; however, primary mucosal infection is documented by genitourinary cultures. Results of approximately 80-90% of cervical cultures are positive in women with DGI. In males, urethral culture results are positive in 50-60%, pharyngeal culture results are positive in 10-20%, and rectal culture results are positive in 15% of cases.

DGI is classified into 2 clinical syndromes that have some overlapping features. The 1st and more common is the tenosynovitis-dermatitis syndrome, which is characterized by fever, chills, skin lesions, and polyarthralgia predominantly involving the wrists, hands, and fingers. Blood culture results are positive in approximately 30-40% of cases, and results of synovial fluid cultures are almost uniformly negative. The 2nd syndrome is the suppurative arthritis syndrome, in which systemic symptoms and signs are less prominent and monoarticular arthritis, often involving the knee, is more common. A polyarthralgia phase may precede the monoarticular infection. In cases of monoarticular involvement, synovial fluid culture results are positive in approximately 45-55%, and synovial fluid findings are consistent with septic arthritis. Blood culture results are usually negative. DGI in neonates usually occurs as a polyarticular suppurative arthritis.

Dermatologic lesions usually begin as painful, discrete, 1-20 mm pink or red macules that progress to maculopapular, vesicular, bullous, purpuric, or petechial lesions. The typical necrotic pustule on an erythematous base is distributed unevenly over the extremities, including the palm and plantar surfaces, usually sparing the face and scalp. The lesions number between 5 and 40, and 20-30% may contain gonococci. Although immune complexes may be present in DGI, complement levels are normal, and the role of the immune complexes in pathogenesis is uncertain.

Acute endocarditis is an uncommon (1-2%) but often fatal manifestation of DGI that usually leads to rapid destruction of the aortic valve. Acute pericarditis is a rarely described entity in patients with disseminated gonorrhea. Meningitis with *N. gonorrhoeae* has been documented, and signs and symptoms are similar to those of any acute bacterial meningitis.

**DIAGNOSIS**

It is not possible to distinguish gonococcal from nongonococcal urethritis on the basis of symptoms and signs alone. Gonococcal urethritis and vulvovaginitis must be distinguished from other infections that produce a purulent discharge, including β-hemolytic streptococci, *Chlamydia trachomatis*, *Mycoplasma hominis*, *Trichomonas vaginalis*, and *Candida albicans*. Rarely, infection with human herpes simplex virus type 2 may produce symptoms similar to those of gonorrhea.

In males with symptomatic urethritis, a presumptive diagnosis of gonorrhea can be made by identification of Gram-negative intracellular diplococci (within leukocytes) in the urethral discharge. A similar finding in females is not sufficient because *Mima polymorpha* and *Moraxella*, which are normal vaginal flora, have a similar appearance. The sensitivity of the Gram stain for diagnosing gonococcal cervicitis and asymptomatic infections is also low. The presence of commensal *Neisseria* species in the oropharynx prevents the use of the Gram stain for diagnosis of pharyngeal gonorrhea. Nonpathogenic *Neisseria* organisms are not found intracellularly.

Specific testing for *N. gonorrhoeae* is recommended because a specific diagnosis might enhance partner notification. Highly sensitive and specific testing methods are available. Culture, nucleic acid hybridization tests, and nucleic acid amplification tests (NAATs) are available for the detection of genitourinary infection. Disadvantages of culture include its lower sensitivity than DNA amplification techniques and a 48-hr delay in availability of results. Culture can be performed of any site, including nongenital sites. Nucleic acid hybridization tests require female endocervical or male urethral swab specimens and are inferior to NAAT testing in terms of sensitivity. The FDA has approved NAATs for use with endocervical swabs, vaginal swabs, male urethral swabs, and female and male urine. Although urine specimens are acceptable for women, the sensitivity appears to be lower when compared with vaginal swab samples. In contrast, the sensitivity and specificity of urine and urethral swab specimens from men are similar. Product inserts for each NAAT vendor must be carefully examined to assess current indications. Nonculture tests are not FDA cleared for use with specimens from the rectum, pharynx, or conjunctiva. However, some laboratories have established performance specifications for NAAT testing on non-genital samples, facilitating their use for clinical management. Nonculture gonococcal tests (e.g., Gram-stained smear, nucleic acid hybridization tests, and NAATs) should not be used without standard culture in children because of the legal implications of a diagnosis of *N. gonorrhoeae* infection in a child. Nonculture tests cannot provide antimicrobial susceptibility results, so in cases of persistent gonococcal infection after treatment, clinicians should perform both culture and antimicrobial susceptibility testing.

Material for cervical cultures is obtained as follows: After the exocervix is wiped, a swab is placed in the cervical os and rotated gently for several seconds. Male urethral specimens are obtained by placement of a small swab 2-3 cm into the urethra. Rectal swabs are best obtained by passing of a swab 2-4 cm into the anal canal; specimens that are heavily contaminated by feces should be discarded. For optimal culture results, specimens should be obtained with noncotton swabs (e.g., a urethrogenital calcium alginate–tipped swab [Calgiswab, Puritan Medical Products, Guilford, ME]), inoculated directly onto culture plates, and incubated immediately. The choice of anatomic sites to culture depends on the sites exposed and the clinical manifestations. Samples from the urethra should be cultured for heterosexual men, and samples from the endocervix and rectum should be cultured for all females, regardless of a history of anal intercourse. A pharyngeal culture specimen should be obtained from both men and women if symptoms of pharyngitis are present or in the case of oral exposure to a person known to have genital gonorrhea. In a suspected case of child sexual abuse, rectal, pharyngeal, and urethral (males) or vaginal (females) swabs should be cultured. Culture of the endocervix should not be attempted until after puberty.

Specimens from sites that are normally colonized by other organisms (e.g., cervix, rectum, pharynx) should be inoculated on a selective culture medium, such as modified Thayer-Martin medium (fortified with vancomycin, colistin, nystatin, and trimethoprim to inhibit growth of indigenous flora). Specimens from sites that are normally sterile or minimally contaminated (i.e., synovial fluid, blood, cerebrospinal fluid) should be inoculated on a nonselective chocolate agar medium. If DGI is suspected, blood, pharynx, rectum, urethra, cervix, and synovial fluid (if involved) should be cultured. Cultured specimens should be incubated promptly at 35-37°C (95-98.6°F) in 3-5% carbon dioxide. When specimens must be transported to a central laboratory for culture plating, a reduced, nonnutrient holding medium (i.e.,
Amoxicillin (1 g PO as a single dose) or doxycycline (100 mg PO twice daily for 7 days) can be used. The use of azithromycin (2 g PO as a single dose) as a single agent should be limited to patients with severe penicillin allergy who cannot undergo β-lactam desensitization. If a patient with gonorrhea is treated with an alternative oral regimen, the patient should return 1 wk after treatment for a test-of-cure of the infected anatomic site. The test-of-cure should be performed with culture or with a NAAT for N. gonorrhoeae if culture is not readily available. If the NAAT is positive, every effort should be made to perform a culture. All test-of-cure specimens that reveal positive growth should undergo phenotypic antimicrobial susceptibility testing. Patients who experience treatment failure after treatment with alternative regimens should be treated with ceftriaxone (250 mg IM) as a single dose and azithromycin (2 g PO as a single dose) and should receive infectious disease consultation. The case should be reported to CDC through the local or state health department.

Spectinomycin (2 g IM as a single dose) is a safe and effective parenteral alternative for urogenital gonorrhea but is not effective for pharyngeal infection. It is not currently available in the United States.

Pregnant women should not be treated with quinolones or tetracyclines. Those infected with N. gonorrhoeae should be treated with ceftriaxone (250 mg IM) and azithromycin (1 g PO as a single dose). If the patient is allergic to β-lactam antibiotics, desensitization procedures should be employed prior to administration.

The initial management of DGI includes hospitalization and parenteral administration of ceftriaxone (1 g/day). Alternative cephalosporins include cefotaxime (1 g IV q8h) and cefotaxime (1g IV q8h). Patients should also receive azithromycin (1 g PO in a single dose), for dual therapy of gonococcal infections and to cover potential C. trachomatis coinfection. Doxycycline (100 mg PO twice daily for 7 days) is an alternative second agent. Patients should be examined for clinical evidence of endocarditis and meningitis. Ceftriaxone treatment should be continued for at least 7 days, and those with purulent arthritis require antibiotic therapy for 7-14 days, although the dose can be changed following clinical improvement to ceftriaxone (250 mg IM daily). Because of the decreasing susceptibility of N. gonorrhoeae to oral agents, "stepdown" therapy to oral agents to complete therapy, such as cefixime (400 mg PO bid) and cefpodoxime (400 mg PO bid), should only be considered if culture and susceptibility testing of the isolate are available and full susceptibility to the oral agent is documented. Fluoroquinolones may be an alternative treatment option if antimicrobial susceptibility to these agents can be documented by culture. Patients with purulent arthritis should also undergo joint drainage with needle aspiration, arthroscopically, or with an open surgical procedure. Open surgical drainage should be performed in patients who exhibit continued symptoms (leukocytosis, fever, severe joint pain, and effusion) despite aspiration and appropriate antibiotic therapy.

 Gonococcal conjunctivitis should be treated with ceftriaxone (1g IM in a single dose) with lavage of the infected eye with saline. Meningitis is treated with ceftriaxone (1-2 g IV q12h) for 10-14 days. Endocarditis is treated for longer than 4 wk with ceftriaxone (1-2 g IV q12h). Concurrent therapy for treatment of genital Chlamydia infection is important.

Infant and Pediatric Infections
Uncomplicated gonococcal infections in children should be treated with ceftriaxone in a single dose (50 mg/kg IM, not to exceed 125 mg). Children who have bacilceremia or arthritis should be treated with ceftriaxone (50 mg/kg/day; maximum: 1 g/day if weights <45 kg) for a minimum of 7 days. Meningitis should be treated for 10-14 days, and endocarditis for a minimum of 28 days, with ceftriaxone (50 mg/kg dose q12h with maximum of 1-2 g IV q12h). Neonatal gonococcal ophthalmia is treated effectively with a single dose of ceftriaxone (50 mg/kg IM, not to exceed 125 mg); a single dose of cefotaxime (100 mg/kg IM) is an acceptable alternative. The conjunctivae should be irrigated frequently with physiologic saline solution. Infants born
to mothers who have gonococcal infection should also receive a single
dose of ceftriaxone (50 mg/kg IM, not to exceed 125 mg). Neonatal
sepsis should be treated parenterally for a minimum of 7 days, and
meningitis for a minimum of 10 days. Cefotaxime is recommended for
infants with hyperbilirubinemia, because ceftriaxone competes for bili-
rubin binding sites on albumin. Neonates with gonococcal ophthalmitis
must be hospitalized and evaluated for DGI.

**Pelvic Inflammatory Disease**

PID encompasses a spectrum of infectious diseases of the upper genital
tract caused by *N. gonorrhoeae*, *C. trachomatis*, and endogenous flora
(streptococci, anaerobes, Gram-negative bacilli). For women with
more-severe symptoms, parenteral therapy should be initiated in the
hospital. A commonly recommended therapeutic regimen is cefoxitin
(2g IV q6h) or cefotetan (2g IV q12h) plus doxycycline (100 mg PO
or IV q12h). Alternative regimens include clindamycin (900 mg IV
q8h) plus a loading dose of gentamicin (2 mg/kg IV) followed by
maintenance gentamicin (1.5 mg/kg q8h), and ampicillin/subactam
(3 g IV q6h) plus doxycycline (100 mg PO or IV q12h). Clinical experi-
ence should guide transition to oral therapy, which usually can be initi-
ated within 24 hr of improvement. Thereafter, oral doxycycline is given
to complete 14 days of total therapy.

Parenteral therapy and oral therapy appear to be similar in clinical
efficacy for women with PID of mild to moderate severity. Clinical
response to outpatient treatment is similar among younger and older
women. The decision to hospitalize adolescents with acute PID should
be based on clinical criteria used for older women. Those who do not
show response to oral therapy within 72 hr should be reevaluated to
confirm the diagnosis and then should receive parenteral therapy. Rec-
ommended oral regimens are as follows: a single dose of ceftriaxone
(250 mg IM) plus doxycycline (100 mg PO bid) with or without met-
ronidazole (500 mg PO bid) for 14 days; and single doses of cefoxitin
(2 g IM) and probenecid (1 g PO) plus doxycycline (100 mg PO bid)
with or without metronidazole (500 mg PO bid) for 14 days. Sexual
partners should be examined and treated for uncomplicated gonor-
rhea. Follow-up culture (test of cure) after cephalosporin-doxycycline
therapy of gonococcal infection is not recommended owing to the low
treatment failure rate. Patients receiving outpatient therapy should be
carefully evaluated for clinical improvement within 72 hr. A follow-up
examination and culture are recommended in 1-2 mo to evaluate the
possibility of reinfection or, rarely, treatment failure.

**COMPLICATIONS**

Complications of gonorrhea result from the spread of gonococci from
a local site of invasion. The interval between primary infection and
development of a complication is usually days to weeks. In postpuber-
tal females, endometritis may occur, especially during menses, and
may progress to salpingitis and peritonitis (PID). Manifestations of
PID include signs of lower genital tract infection (e.g., vaginal dis-
charge, suprapubic pain, cervical tenderness) and upper genital tract
infection (e.g., fever, leukocytosis, elevated erythrocyte sedimentation
rate, and adnexal tenderness or mass). The differential diagnosis
includes gynecologic diseases (ovarian cyst, ovarian tumor, ectopic
pregnancy) and intraabdominal disorders (appendicitis, urinary tract
infection, inflammatory bowel disease).

Once inside the peritoneum, gonococci may seed the liver capsule,
causing a pericholangitis with right upper quadrant pain (Fitz-Hugh–
Curtis syndrome), with or without signs of salpingitis. Pericholangitis
may also be caused by *C. trachomatis*. Progression to PID occurs in
approximately 20% of cases of gonococcal cervicitis, and *N. gonor-
rhoeae* is isolated in approximately 40% of cases of PID in the United
States. Untreated cases may lead to hydrosalpinx, pyosalpinx, tubo-
ovarian abscess, and eventual sterility. Even with adequate treatment
of PID, the risk for sterility from bilateral tubal occlusion approaches
20% after 1 episode of salpingitis and exceeds 60% after 3 or more
episodes. The risk for ectopic pregnancy is increased approximately
7-fold after 1 or more episodes of salpingitis. Additional sequelae of
PID include chronic pain, dyspareunia, and increased risk for recur-
rent PID.

**PROGNOSIS**

Prompt diagnosis and correct therapy ensure complete recovery from
uncomplicated gonococcal disease. Complications and permanent
sequelae may be associated with delayed treatment, recurrent infec-
tion, metastatic sites of infection (meninges, aortic valve), and delayed
or topical therapy of gonococcal ophthalmia.

**PREVENTION**

Efforts to develop a gonococcal pilus vaccine have been unsuccessful
thus far. The high degree of interstrain and intrastrain antigenic vari-
bility of pil poses a formidable deterrent to the development of a
single effective pilus vaccine. Other gonococcal surface structures, such
as the porin protein, stress proteins, and lipooligosaccharides, may
prove more promising as vaccine candidates. In the absence of a
vaccine, prevention of gonorrhea can be achieved through education,
use of barrier contraceptives (especially condoms and spermicides),
intensive epidemiologic and bacteriologic surveillance (screening
sexual contacts), and early identification and treatment of infected
contacts. Gonococcal ophthalmia neonatorum can be prevented by
instilling erythromycin (0.5%) ophthalmic ointment into the conjunc-
tival sac (see Chapter 626).

*Bibliography is available at Expert Consult.*
Neisseria gonorrhoeae (Gonococcus)

Bibliography

Kingella kingae is being increasingly recognized as the most common etiology of joint and bone infections in young children.

ETIOLOGY

*K. kingae* is a fastidious, facultative anaerobic, β-hemolytic member of the Neisseriaceae family that appears as pairs or short chains of Gram-negative coccobacilli with tapered ends (Fig. 193-1).

EPIDEMIOLOGY

*K. kingae* is asymptomatically carried in the posterior pharynx. Colonization usually starts after the age of 6 mo, reaches a prevalence of 10% between 12 and 24 mo of age, and decreases in older children. Pharyngeal colonization plays a crucial role in the transmission of the organism through intimate contact between siblings and playmates. Colonizing *K. kingae* strains differ in their invasive potential. Whereas certain clones are commonly found as respiratory colonizers but are seldom cultured from sites of disease, other clones are rarely detected in healthy children and, once acquired, readily penetrate into the bloodstream and disseminate to remote sites. Daycare attendance increases the risk for colonization and transmission, and clusters of invasive infection have been reported in childcare facilities.

Invasive *K. kingae* disease is most commonly diagnosed in otherwise healthy children between the ages of 6 mo and 3 yr, coinciding with the peak prevalence of pharyngeal carriage (Fig. 193-2). In contrast, older children and adults with *K. kingae* infections often suffer from underlying chronic diseases, immunosuppressing conditions, malignancy, or cardiac valve pathology. An annual incidence of 9.4 per 100,000 culture-proven invasive infections among Israeli children younger than 5 yr of age has been estimated.
**Clinical Spectrum and Relative Frequency of Kingella kingae Infections**

<table>
<thead>
<tr>
<th>CLINICAL DISEASE</th>
<th>FREQUENCY</th>
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<tbody>
<tr>
<td>Skeletal system</td>
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<td>Septic arthritis</td>
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<tr>
<td>Osteomyelitis</td>
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<tr>
<td>Spondylodiscitis</td>
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<td>Tenosynovitis</td>
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<td>Dactylitis</td>
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<td>Bursitis</td>
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<td>Endophthalmitis</td>
<td>±</td>
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<tr>
<td>Eyelid abscess</td>
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+++ Very common; ++ common; + infrequent; ± exceptional.

**Septic Arthritis**

Although *K. kingae*-driven arthritis especially affects the large weight-bearing joints, involvement of the small metacarpophalangeal, sternoclavicular, and tarsal joints is not unusual (see Chapter 685). The disease has an acute presentation, and children are brought to medical attention after a median of 3 days. The leukocyte count in the synovial fluid shows less than 50,000 white blood cells/μL in almost 25% of the patients, and the Gram stain of synovial fluid is positive in only a small percentage of cases.

**Osteomyelitis**

*K. kingae* osteomyelitis usually involves the long bones of the extremities (see Chapter 685). The calcaneus, talus, sternum, and clavicle are also frequently affected (and are rarely infected by other bacterial pathogens). Onset of *K. kingae* osteomyelitis is insidious, and the disease is diagnosed after 1 wk or more in 70% of patients. The MRI shows mild bone and soft tissue changes. Involvement of the epiphyseal cartilage appears to be specifically associated with the organism. Despite the frequent diagnostic delay, chronic osteomyelitis and functional orthopedic disabilities are unusual.

**Spondylodiscitis**

*K. kingae* is currently the second most common bacterium isolated in children younger than 4 yr of age with spondylodiscitis after *Staphylococcus aureus* (see Chapter 679.7). It is presumed that the organism penetrates into the rich network of blood vessels that traverse the cartilaginous vertebral endplates and enter the annulus in young children during a bacteremic episode. *K. kingae* spondylodiscitis usually involves the lumbar intervertebral spaces and, with decreasing frequency, the thoracolumbar, thoracic, lumbar-sacral, and cervical discs. Involvement of multiple discs is uncommon. Patients present with limping, lumbar pain, back stiffness, refusal to sit or walk, neurologic symptoms, or abdominal complaints. Radiography or MRI studies demonstrate narrowing of the intervertebral space. Patients respond...
well to appropriate antibiotic treatment and recover without complications, although residual narrowing of the intervertebral space may occur.

**Occult Bacteremia**

Patients with *K. kingae* bacteremia and no focal infection (occult bacteremia) commonly present with mild to moderate fever, symptoms suggestive of a viral upper respiratory infection, a mean C-reactive protein level of 2.2 mg/dL, and a mean white blood cell count of 12,700/µL. Children with *K. kingae* bacteremia respond favorably to a short course of antibiotics.

**Endocarditis**

In contrast to other *K. kingae* infections, endocarditis is also diagnosed in school-age children, adolescents, and adult patients. The disease may affect native as well as prosthetic valves. Predisposing factors include congenital cardiac malformations or rheumatic valvular disease, but some patients have previously normal hearts. Typically, the left side of the heart is involved, usually the mitral valve. Fever and acute-phase reactants are more elevated in patients with endocarditis compared with those with uncomplicated bacteremia; no particular cutoff value accurately distinguishes between the 2 conditions. Despite the exquisite susceptibility of *K. kingae* to antibiotics, cardiac failure, septic shock, cerebrovascular accidents, and other life-threatening complications are common, and the mortality rate is high (~16%). Because of the potential severity of *K. kingae* endocarditis, routine echocardiographic evaluation of children with isolated bacteremia is indicated.

**DIAGNOSIS**

The diagnosis of *K. kingae* disease is established by isolation of the bacterium or by a positive nucleic acid amplification assay from a normally sterile site such as blood, synovial fluid, or bone tissue. Although *K. kingae* grows on routine bacteriologic media, its recovery from exudates is frequently unsuccessful. Detection is enhanced by inoculating synovial fluid specimens onto blood-culture vials, suggesting that diluting purulent samples in a large volume of nutrient broth reduces the concentration of detrimental factors, improving the isolation of this fastidious bacterium.

Testing bone and joint specimens by nucleic acid amplification assays that target specific *K. kingae* genes such as cpn or those encoding the bacterium RTX toxin, have further improved detection of the organism and reduced the fraction of “culture-negative septic arthritis” in young children.

**TREATMENT**

*K. kingae* is usually highly susceptible to penicillin and cephalosporins but exhibits decreased susceptibility to oxacillin. Although β-lactamase production is frequently detected in colonizing *K. kingae* strains, its prevalence among invasive organisms is low and shows wide geographic variation. Testing for β-lactamase production should be routinely performed in all isolates derived from normally sterile body sites.

Because of the lack of specific guidelines for treating *K. kingae* disease, patients have been administered a variety of antibiotic regimens according to protocols developed for infections caused by traditional pathogens. The first-line therapy for skeletal infections in young children usually consists of intravenous administration of a second- or third-generation cephalosporin, pending culture results. *K. kingae* is always resistant to glycopeptide antibiotics and 40% of isolates are also resistant to clindamycin, a serious concern in areas where bacterial infections caused by community-associated methicillin-resistant *S. aureus* are common, and vancomycin or clindamycin are initially administered to children with presumptive septic arthritis or osteomyelitis. The initial antibiotic regimen is frequently changed to ampicillin or cephalexin (ceftazidime, ceftriaxone) once *K. kingae* is identified and β-lactamase production is excluded. A favorable clinical response and decreasing C-reactive protein levels to ≤20 µg/mL are used to guide switching to oral antibiotics and defining duration of therapy. Antibiotic treatment has ranged from 2-3 wk for *K. kingae* arthritis,
Bibliography


An effective vaccine to prevent *Haemophilus influenzae* type b disease, introduced in the United States and most other countries, has resulted in a dramatic decrease in the incidence of infections caused by this organism. However, mortality and morbidity from *H. influenzae* type b infection remain a problem worldwide, primarily in developing countries. Occasional cases of invasive disease caused by non–type b organisms continue to occur but are infrequent. Nontypable members of the species are an important cause of otitis media, sinusitis, and chronic bronchitis.

**ETIOLOGY**

*H. influenzae* is a fastidious, Gram-negative, pleomorphic coccobacillus that requires factor X (hematin) and factor V (phosphopyridine nucleotide) for growth. Some *H. influenzae* isolates are surrounded by a polysaccharide capsule and can be serotyped into 6 antigenically and biochemically distinct types designated a, b, c, d, e, and f.

**EPIDEMIOLOGY**

Before the advent of an effective type b conjugate vaccine in 1988, *H. influenzae* type b was a major cause of serious disease among children. There was a striking age distribution of cases, with more than
90% in children younger than 5 yr of age and the majority in children younger than 2 yr of age. The annual attack rate of invasive disease was 64-129 cases per 100,000 children younger than 5 yr of age. Invasive disease caused by other capsular serotypes has been much less frequent but continues to occur. The incidence of invasive disease caused by type b and non–type b serotypes has been estimated at approximately 0.08 and 1.02 cases per 100,000 children younger than 5 yr of age per year, respectively, in the United States. Nonencapsulated (nontypable) \textit{H. influenzae} strains also occasionally cause invasive disease, especially in neonates, immunocompromised children, and children in developing countries. The estimated rate of invasive disease caused by nontypable \textit{H. influenzae} in the United States is 1.88 per 100,000 children younger than 5 yr of age per year. Nontypable isolates are common etiologic agents in otitis media, sinusitis, and chronic bronchitis.

Humans are the only natural hosts for \textit{H. influenzae}, which is part of the normal respiratory flora in 60-90% of healthy children. Most isolates are nontypable. Before the advent of conjugate vaccine immunization, \textit{H. influenzae} type b could be isolated from the pharynx of 2-5% of healthy preschool and school-age children, with lower rates among infants and adults. Asymptomatic colonization with \textit{H. influenzae} type b occurs at a much lower rate in immunized populations.

The continued circulation of the type b organism despite current vaccine coverage levels suggests that elimination of type b disease may be a formidable task. The few cases of type b invasive disease in the United States now occur in both unvaccinated and fully vaccinated children. Approximately 50% of cases occur in young infants who are too young to have received a complete primary vaccine series. Among the cases in patients who are old enough to have received a complete vaccine series, the majority are underimmunized. To highlight this point, during a recent shortage of \textit{H. influenzae} type b vaccine, invasive disease developed in 5 children in Minnesota, all of whom were incompletely immunized. Continued efforts are necessary to provide currently available conjugate vaccines to children in developing countries, where affordability remains an important issue.

In the prevaccine era, certain groups and individuals had an increased incidence of invasive type b disease, including Alaskan Eskimos, Apaches, Navajos, and African-Americans. Persons with certain chronic medical conditions were also known to be at increased risk for invasive disease, including those with sickle cell disease, asplenia, congenital and acquired immunodeficiencies, and malignancies. Unvaccinated infants with invasive \textit{H. influenzae} type b infection are also at increased risk for recurrence, reflecting the fact that they typically do not develop a protective immune response to \textit{H. influenzae}.

Socioeconomic risk factors for invasive \textit{H. influenzae} type b disease include childcare outside the home, the presence of siblings of elementary school age or younger, short duration of breastfeeding, and parental smoking. A history of otitis media is associated with an increased risk for invasive disease. Much less is known about the epidemiology of invasive disease caused by non–type b strains, and it is not clear whether the epidemiologic features of type b disease apply to disease caused by non–type b isolates.

Among age-susceptible household contacts who have been exposed to a case of invasive \textit{H. influenzae} type b disease, there is increased risk for secondary cases of invasive disease in the 1st 30 days, especially in susceptible children younger than 24 mo of age. Whether a similar increased risk occurs for contacts of individuals with non–type b disease is unknown.

The mode of transmission is most commonly direct contact or inhalation of respiratory tract droplets containing \textit{H. influenzae}. The incubation period for invasive disease is variable, and the exact period of communicability is unknown. Most children with invasive \textit{H. influenzae} type b disease are colonized in the nasopharynx before initiation of antimicrobial therapy; 25–40% may remain colonized during the 1st 24 hr of therapy.

With the decline of disease caused by type b organisms, disease caused by other serotypes (a, c-f) and nontypable organisms has been recognized more clearly. There is no evidence that these non–type b infections have increased in frequency. However, clusters of type a and, less often, type f and type e infections have occurred. Data from Israel suggest that nontypable \textit{H. influenzae} is now the most common case of invasive \textit{H. influenzae} disease in that country.

**PATHOGENESIS**

The pathogenesis of disease begins with adherence to respiratory epithelium and colonization of the nasopharynx, which is mediated by pilus and nonpilus adherence factors. The mechanism of entry into the intravascular compartment is unclear but appears to be influenced by cytotoxic factors. Once in the bloodstream, \textit{H. influenzae} type b, and perhaps other encapsulated strains, resist intravascular clearance mechanisms at least in part via the presence of a polysaccharide capsule. In the case of \textit{H. influenzae} type b, the magnitude and duration of bacteremia influence the likelihood of dissemination of bacteria to sites such as the meninges and joints.

Noninvasive \textit{H. influenzae} infections such as otitis media, sinusitis, and bronchitis are usually caused by nontypable strains. These organisms gain access to sites such as the middle ear and sinus cavities by direct extension from the nasopharynx. Factors facilitating spread from the pharynx include eustachian tube dysfunction and antecedent viral infections of the upper respiratory tract.

**Antibiotic Resistance**

Most \textit{H. influenzae} isolates are susceptible to ampicillin or amoxicillin, but about a third produce a β-lactamase and are therefore resistant to these antibiotics. β-Lactamase–negative ampicillin-resistant isolates have been identified and manifest resistance by production of a β-lactam–insensitive cell wall synthesis enzyme called PBPs.

Amoxicillin-clavulanate is uniformly active against \textit{H. influenzae} clinical isolates except for the rare β-lactamase–negative ampicillin-resistant isolates. Among macrolides, azithromycin has in vitro activity against a high percentage of \textit{H. influenzae} isolates; in contrast, the activity of erythromycin and clarithromycin against \textit{H. influenzae} clinical isolates is poor. \textit{H. influenzae} resistance to third-generation cephalosporins has not been documented. Resistance to trimethoprim-sulfamethoxazole is infrequent (≈10%), and resistance to quinolones is believed to be rare.

**Immunity**

In the prevaccine era, the most important known element of host defense was antibody directed against the type b capsular polysaccharide polyribosylribitol phosphate (PRP). Anti-PRP antibody is acquired in an age-related fashion and facilitates clearance of \textit{H. influenzae} type b from blood, in part related to opsonic activity. Antibodies directed against antigens such as outer membrane proteins or lipopolysaccharide may also have a role in opsonization. Both the classic and alternative complement pathways are important in defense against \textit{H. influenzae} type b.

Before the introduction of vaccination, protection from \textit{H. influenzae} type b infection was presumed to correlate with the concentration of circulating anti-PRP antibody at the time of exposure. A serum antibody concentration of 0.15-1.0 μg/mL was considered protective against invasive infection. Unimmunized infants older than 6 mo of age and young children usually lacked an anti-PRP antibody concentration of this magnitude and were susceptible to disease after encountering \textit{H. influenzae} type b. This lack of antibody in infants and young children may have reflected a maturational delay in the immunologic response to thymus-independent type 2 antigens such as unconjugated PRP, presumably explaining the high incidence of type b infections in infants and young children in the pre-vaccine era.

The conjugate vaccines (Table 194-1) act as thymus-dependent antigens and elicit serum antibody responses in infants and young children. These vaccines are believed to prime memory antibody responses on subsequent encounters with PRP. The concentration of circulating anti-PRP antibody in a child primed by a conjugate vaccine may not correlate precisely with protection, presumably because a memory response may occur rapidly on exposure to PRP and provide protection.

Much less is known about immunity to other \textit{H. influenzae} serotypes or to nontypable isolates. For nontypable isolates, evidence suggests that antibodies directed against 1 or more outer membrane proteins...
are bactericidal and protect against experimental challenge. A variety of antigens have been evaluated in an attempt to identify vaccine candidates for nontypable *H. influenzae*, including outer membrane proteins (P1, P2, P4, P5, P6, D15, and Tbp A/B), lipopolysaccharide, various adhesins, and lipoprotein D.

**DIAGNOSIS**

Presumptive identification of *H. influenzae* is established by direct examination of the collected specimen after staining with Gram reagents. Because of its small size, pleomorphism, and occasional poor uptake of stain, as well as the tendency for proteinaceous fluids to have a red background, *H. influenzae* is sometimes difficult to visualize. Furthermore, given that identification of microorganisms on smear by either technique requires at least 10^3 bacteria/mL, failure to visualize them does not preclude their presence.

Culture of *H. influenzae* requires prompt transport and processing of specimens because the organism is fastidious. Specimens should not be exposed to drying or temperature extremes. Primary isolation of *H. influenzae* can be accomplished on chocolate agar or on blood agar plates using the staphylococcus streak technique.

Serotyping of *H. influenzae* is accomplished by slide agglutination with type-specific antisera. Accurate serotyping is essential to monitor progress toward elimination of type b invasive disease. Timely reporting of cases to public health authorities should be ensured.

**CLINICAL MANIFESTATIONS AND TREATMENT**

The initial antibiotic therapy of invasive infections possibly caused by *H. influenzae* should be a parenterally administered antimicrobial agent effective in sterilizing all foci of infection and effective against ampicillin-resistant strains, usually an extended-spectrum cephalosporin such as cefotaxime or ceftriaxone. These antibiotics have achieved popularity because of their relative lack of serious adverse effects and ease of administration. After the antimicrobial susceptibility of the isolate has been determined, an appropriate agent can be selected to complete the therapy. Ampicillin remains the drug of choice for the therapy of infections caused by susceptible isolates. If the isolate is resistant to ampicillin, ceftriaxone can be administered once daily in selected circumstances for outpatient therapy.

Oral antimicrobial agents are sometimes used to complete a course of therapy initiated by the parenteral route and are typically initial therapy for noninvasive infections such as otitis media and sinusitis. If the organism is susceptible, amoxicillin is the drug of choice. An oral second- or third-generation cephalosporin or amoxicillin-clavulanate may be used when the isolate is resistant to ampicillin.

**Meningitis**

In the prevaccine era, meningitis accounted for more than half of all cases of invasive *H. influenzae* disease. Clinically, meningitis caused by *H. influenzae* type b cannot be differentiated from meningitis caused by *Neisseria meningitidis* or *Streptococcus pneumoniae* (see Chapter 603.1). It may be complicated by other foci of infection such as the lungs, joints, bones, and pericardium.

Antimicrobial therapy should be administered intravenously for 7-14 days for uncomplicated cases. Cefotaxime, ceftriaxone, and ampicillin cross the blood–brain barrier during acute inflammation in concentrations adequate to treat *H. influenzae* meningitis. Intramuscular therapy with ceftriaxone is an alternative in patients with normal organ perfusion.

The prognosis of *H. influenzae* type b meningitis depends on the age at presentation, duration of illness before appropriate antimicrobial therapy, cerebrospinal fluid capsular polysaccharide concentration, and rapidity with which organisms are cleared from cerebrospinal fluid, blood, and urine. Clinically manifested inappropriate secretion of antidiuretic hormone and evidence of focal neurologic deficits at presentation are poor prognostic features. Approximately 6% of patients with *H. influenzae* type b meningitis are left with some hearing impairment, probably because of inflammation of the cochlea and the labyrinth. Dexamethasone (0.6 mg/kg/day divided every 6 hr for 2 days), particularly when given shortly before or concurrent with the initiation of antimicrobial therapy, decreases the incidence of hearing loss. Major neurologic sequelae of *H. influenzae* type b meningitis include behavior problems, language disorders, impaired vision, mental retardation, motor abnormalities, ataxia, seizures, and hydrocephalus.

**Cellulitis**

Children with *H. influenzae* type b cellulitis often have an antecedent upper respiratory tract infection. They usually have no prior history of trauma, and the infection is thought to represent seeding of the organism to the involved soft tissues during bacteremia. The head and neck, particularly the cheek and preseptal region of the eye, are the most common sites of involvement. The involved region generally has indistinct margins and is tender and inured. Buccal cellulitis is classically erythematous with a violaceous hue, although this sign may be absent. *H. influenzae* may often be recovered directly from an aspirate of the leading edge, although this procedure is seldom performed. The blood culture may also reveal the causative organism. Other foci of infection may be present concomitantly, particularly in children younger than 18 mo of age. A diagnostic lumbar puncture should be considered at the time of diagnosis in these children.

Parenteral antimicrobial therapy is indicated until patients become afebrile, after which an appropriate orally administered antimicrobial agent may be substituted. A 7-10 day course is customary.

**Preseptal Cellulitis**

Infection involving the superficial tissue layers anterior to the orbital septum is termed preseptal cellulitis, which may be caused by *H. influenzae*. Uncomplicated preseptal cellulitis does not imply a risk for visual impairment or direct central nervous system extension. However, concurrent bacteremia may be associated with the development of meningitis. *H. influenzae* preseptal cellulitis is characterized by fever, edema, tenderness, warmth of the lid, and, occasionally, purple discoloration. Evidence of interruption of the integument is usually absent. Conjunctival drainage may be associated. *S. pneumoniae*, *Staphylococcus aureus*, and group A streptococcus cause

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**Table 194-1  *Haemophilus influenzae* Type B Conjugate Vaccines Available in the United States**

<table>
<thead>
<tr>
<th>VACCINE</th>
<th>TRADE NAME</th>
<th>COMPONENTS</th>
<th>MANUFACTURER</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRP-T*</td>
<td>Hiberix*</td>
<td>PRP conjugated to tetanus toxoid</td>
<td>GlaxoSmithKline Biologicals</td>
</tr>
<tr>
<td>PRP-OMP</td>
<td>PedvaxHIB</td>
<td>PRP conjugated to OMP</td>
<td>Merck &amp; Co., Inc.</td>
</tr>
<tr>
<td>PRP-OMP-HepB</td>
<td>Comvax</td>
<td>PRP-OMP + hepatitis B vaccine</td>
<td>Merck &amp; Co., Inc.</td>
</tr>
<tr>
<td>PRP-T/DTaP-IPV</td>
<td>Pentacel</td>
<td>PRP-T + DTaP-IPV vaccines</td>
<td>Sanofi Pasteur</td>
</tr>
<tr>
<td>PRP-T</td>
<td>MenHibRix</td>
<td>PRP-T + MenCY</td>
<td>GlaxoSmithKline Biologicals</td>
</tr>
</tbody>
</table>

*PRP-T (Hiberix) is licensed only for the final (booster) dose of the Hib vaccine series and should not be used for primary immunization in infants at 2, 4, or 6 mo of age.

DTaP, diphtheria and tetanus toxoids and acellular pertussis vaccine; HepB, hepatitis B vaccine; Hib, *H. influenzae* type b; IPV, trivalent inactivated polio vaccine; OMP, outer membrane protein complex from *Neisseria meningitidis; PRP, polyribosylribitol phosphate.*
clinically indistinguishable preseptal cellulitis. The latter 2 pathogens are more likely when fever is absent and the integument is interrupted (e.g., an insect bite or trauma).

Children with preseptal cellulitis in whom *H. influenzae* and *S. pneumoniae* are etiologic considerations (young age, high fever, intact integument) should undergo blood culture, and a diagnostic lumbar puncture should be considered.

Parenteral antibiotics are indicated for preseptal cellulitis. Because methicillin-susceptible and methicillin-resistant *S. aureus*, *S. pneumoniae*, and group A β-hemolytic streptococci are other causes, empirical therapy should include agents active against these pathogens. Patients with preseptal cellulitis without concurrent meningitis should receive parenteral therapy for about 5 days, until fever and erythema have abated. In uncomplicated cases, antimicrobial therapy should be given for 10 days.

**Orbital Cellulitis**

Infections of the orbit are infrequent and usually develop as complications of acute ethmoid or sphenoid sinusitis. Orbital cellulitis may manifest as lid edema but is distinguished by the presence of proptosis, chemosis, impaired vision, limitation of the extraocular movements, decreased mobility of the globe, or pain on movement of the globe. The distinction between preseptal and orbital cellulitis may be difficult and is best delineated by CT.

Orbital infections are treated with parenteral therapy for at least 14 days. Underlying sinusitis or orbital abscess may require surgical drainage and more prolonged antimicrobial therapy.

**Supraglottitis or Acute Epiglottitis**

Supraglottitis is a cellulitis of the tissues comprising the laryngeal inlet (see Chapter 385). It has become exceedingly rare since the introduction of conjugate type b vaccines. Direct bacterial invasion of the involved tissues is probably the initiating pathophysiologic event. This dramatic, potentially lethal condition can occur at any age. Because of the risk of sudden, unpredictable airway obstruction, supraglottitis is a medical emergency. Other foci of infection, such as meningitis, are rare. Antimicrobial therapy directed against *H. influenzae* and other etiologic agents should be administered parenterally but only after the airway is secured, and therapy should be continued until patients are able to take fluids by mouth. The duration of antimicrobial therapy is typically 7 days.

**Pneumonia**

The true incidence of *H. influenzae* pneumonia in children is unknown because invasive procedures required to obtain culture specimens are seldom performed (see Chapter 400). In the prevaccine era, type b bacteria were believed to be the usual cause. The signs and symptoms of pneumonia caused by *H. influenzae* cannot be differentiated from those of pneumonia caused by many other microorganisms. Other foci of infection may be present concomitantly.

Children younger than 12 mo of age in whom *H. influenzae* pneumonia is suspected should receive parenteral antimicrobial therapy initially because of their increased risk for bacteremia and its complications. Older children who do not appear severely ill may be managed with an orally administered antimicrobial. Therapy is continued for 7-10 days. Uncomplicated pleural effusion associated with *H. influenzae* pneumonia requires no special intervention. However, if empyema develops, surgical drainage is indicated.

**Suppurative Arthritis**

Large joints, such as the knee, hip, ankle, and elbow, are affected most commonly (see Chapter 685). Other foci of infection may be present concomitantly. Although single joint involvement is the rule, multiple joint involvement occurs in approximately 6% of cases. The signs and symptoms of septic arthritis caused by *H. influenzae* are indistinguishable from those of arthritis caused by other bacteria.

Uncomplicated septic arthritis should be treated with an appropriate antimicrobial administered parenterally for at least 5-7 days. If the clinical response is satisfactory, the remainder of the course of antimicrobial treatment may be given orally. Therapy is typically given for 3 wk for uncomplicated septic arthritis, but it may be continued beyond 3 wk, until the C-reactive protein concentration is normal.

**Pericarditis**

*H. influenzae* is a rare cause of pericarditis (see Chapter 440). Affected children often have had an antecedent upper respiratory tract infection. Fever, respiratory distress, and tachycardia are consistent findings. Other foci of infection may be present concomitantly.

The diagnosis may be established by recovery of the organism from blood or pericardial fluid. Gram stain or detection of PRP in pericardial fluid, blood, or urine (when type b organisms are the cause) may aid the diagnosis. Antimicrobials should be provided parenterally in a regimen similar to that used for meningitis (see Chapter 603.1). Pericardectomy is useful for draining the purulent material effectively and preventing tamponade and constrictive pericarditis.

**Bacteremia Without an Associated Focus**

Bacteremia caused by *H. influenzae* may be associated with fever without any apparent focus of infection (see Chapter 177). In this situation, risk factors for “occult” bacteremia include the magnitude of fever (≥39°C [102.2°F]) and the presence of leukocytosis (≥15,000 cells/μL). In the prevaccine era, meningitis developed in approximately 25% of children with occult *H. influenzae* type b bacteremia if left untreated. In the vaccine era, this *H. influenzae* infection has become exceedingly rare. When it does occur, the child should be reevaluated for a focus of infection and a second blood culture performed. The child should be hospitalized and given parenteral antimicrobial therapy after a diagnostic lumbar puncture and chest radiograph are obtained.

**Miscellaneous Infections**

Urinary tract infection, epididymoorchitis, cervical adenitis, acute glossitis, infected thyroglossal duct cysts, uveitis, endocarditis, endophthalmitis, primary peritonitis, osteomyelitis, and periappendiceal abscess are rarely caused by *H. influenzae*.

**Invasive Disease in Neonates**

Neonates rarely have invasive *H. influenzae* infection. In the infant with illness within the 1st 24 hr of life, especially in association with maternal chorioamnionitis or prolonged rupture of membranes, transmission of the organism to the infant is likely to have occurred through the maternal genital tract, which may be (<1%) colonized with nontypable *H. influenzae*. Manifestations of neonatal invasive infection include bacteremia with sepsis, pneumonia, respiratory distress syndrome with shock, conjunctivitis, scalp abscess or cellulitis, and meningitis. Less commonly, mastoiditis, septic arthritis, and congenital vesicular eruption may occur.

**Otitis Media**

Acute otitis media is one of the most common infectious diseases of childhood (see Chapter 640). It results from the spread of bacteria from the nasopharynx through the eustachian tube into the middle ear cavity. Usually because of a preceding viral upper respiratory tract infection, the mucosa in the area becomes hyperemic and swollen, resulting in obstruction and an opportunity for bacterial multiplication in the middle ear.

The most common bacterial pathogens are *H. influenzae*, *S. pneumoniae*, and *Moraxella catarrhalis*. Most *H. influenzae* isolates causing otitis media are nontypable. Ipsilateral conjunctivitis may also be present. Amoxicillin (80-90 mg/kg/day) is a suitable first-line oral antimicrobial agent, because the probability that the causative isolate is resistant to amoxicillin and the risk for invasive potential are sufficiently low to justify this approach. Alternatively, in certain cases, a single dose of cefixime constitutes adequate therapy.

In the case of treatment failure or if a β-lactamase-producing isolate is obtained by tympanocentesis or from drainage fluid, amoxicillin-clavulanate (Augmentin) is a suitable alternative.
Conjunctivitis

Acute infection of the conjunctivae is common in childhood (see Chapter 626). In neonates, *H. influenzae* is an infrequent cause. However, it is an important pathogen in older children. Most *H. influenzae* isolates associated with conjunctivitis beyond the neonatal period usually consist of topical antimicrobial therapy with sulfacetamide. Topical fluoroquinolone therapy is to be avoided because of its broad spectrum, high cost, and high rate of emerging resistance among many bacterial species. Ipsilateral otitis media caused by the same organism may be present and requires oral antibiotic therapy.

Sinusitis

*H. influenzae* is an important cause of acute sinusitis in children, second in frequency only to *S. pneumoniae* (see Chapter 380). Chronic sinusitis lasting longer than 1 yr or severe sinusitis requiring hospitalization is often caused by *S. aureus* or anaerobes such as *Peptococcus*, *Peptostreptococcus*, and *Bacteroides*. Nontypable *H. influenzae* and viridans group streptococci are also frequently recovered.

For uncomplicated sinusitis, amoxicillin is acceptable initial therapy. However, if clinical improvement does not occur, a broader-spectrum agent, such as amoxicillin-clavulanate, may be appropriate. A 10-day course is sufficient for uncomplicated sinusitis. Hospitalization for parenteral therapy is rarely required; the usual reason is suspicion of progression to orbital cellulitis.

PREVENTION

Immunization with *H. influenzae* type b conjugate vaccine is recommended for all infants. Prophylaxis is indicated if close contacts of an index patient with type b disease are unvaccinated. The contagiousness of non–type b *H. influenzae* infections is not known, and prophylaxis is not recommended.

Vaccine

Several *H. influenzae* type b conjugate vaccines are currently marketed in the United States, containing either PRP–outer membrane protein (PRP-OMP) or PRP–tetanus toxoid (PRP-T), which differ in the carrier protein used and the method of conjugating the polysaccharide to the protein (see Table 194-1 and Chapter 172). One of the combination vaccines consists of PRP-OMP combined with hepatitis B vaccine (Comvax, Merck & Co., Inc., Whitehouse Station, NJ) and can be used for doses recommended at 2, 4, and 12-15 mo of age. Another consists of PRP-T combined with DTaP vaccine (diphtheria and tetanus toxoids and acellular pertussis) and IPV vaccine (trivalent, inactivated polio vaccine) (Pentacel, Sanofi Pasteur Inc., Swiftwater, PA) and can be used for doses recommended at 2, 4, 6, and 12-15 mo of age. A third consists of PRP-T combined with *N. meningitidis* serogroups C and Y (GlaxoSmithKline Biologicals) and can be used for doses recommended at 2, 4, 6, and 12-15 mo of age for children at increased risk for *N. meningitidis* disease. PRP-T by itself is licensed for doses scheduled for children 15 mo of age or older.

The *H. influenzae* type b conjugate vaccines stimulate circulating antcapsular antibody and provide long-term immunity via B-cell memory.

Prophylaxis

Unvaccinated children younger than 48 mo of age who are in close contact with an index case of invasive *H. influenzae* type b infection are at increased risk for invasive infection. The risk for secondary disease for children older than 3 mo of age is inversely related to age. About half of the secondary cases among susceptible household contacts occur in the 1st wk after hospitalization of the index case. Because many children are now protected against *H. influenzae* type b by prior immunization, the need for prophylaxis has greatly decreased. When prophylaxis is used, rifampin is indicated for all members of the household or close contact group, including the index patient, if the group includes 1 or more children younger than 48 mo of age who are not fully immunized.

Parents of children hospitalized for invasive *H. influenzae* type b disease should be informed of the increased risk for secondary infection in other young children in the same household if they are not fully immunized. Parents of children exposed to a single case of invasive *H. influenzae* type b disease in a childcare center or nursery school should be similarly informed, although there is disagreement about the need for rifampin prophylaxis for these children.

For prophylaxis, children should be given rifampin orally (0-1 mo of age, 10 mg/kg/dose; >1 mo of age, 20 mg/kg/dose, not to exceed 600 mg/dose) once a day for 4 consecutive days. The adult dose is 600 mg once daily. Rifampin prophylaxis is not recommended for pregnant women.

Bibliography is available at Expert Consult.
Bibliography
Chancroid is a sexually transmitted disease characterized by painful genital ulceration and inguinal lymphadenopathy.

**ETIOLOGY AND EPIDEMIOLOGY**

Chancroid is caused by *Haemophilus ducreyi*, a fastidious Gram-negative bacillus. It is prevalent in many developing countries but occurs sporadically in the developed world. Most Western cases occur in returning travelers (90% are male) from endemic areas or occasionally in localized urban outbreaks associated with commercial sex workers. It is a risk factor for transmission of HIV. Diagnosis of chancroid in infants and children is strong evidence of sexual abuse. Male circumcision lowers the risk for chancroid. The incidence of chancroid has declined significantly and remains low in the United States since 1981.

**CLINICAL MANIFESTATIONS.**

The incubation period is 4-7 days with a small inflammatory papule on the preputial orifice or frenulum in men and on the labia, fourchette, or perineal region in women. The lesion becomes pustular, eroded, and ulcerative within 2-3 days. The ulcer edge is classically ragged and undermined. Without treatment, the ulcers may persist for wk to mo. Painful, tender inguinal lymphadenitis occurs in more than 50% of cases, more often among men. The lymphadenopathy can become fluctuant to form buboes, which can spontaneously rupture.

**DIAGNOSIS**

Diagnosis is usually established by the clinical presentation and the exclusion of both syphilis (*Treponema pallidum*) and herpes simplex virus infections. Gram stain of ulcer secretions may show Gram-negative coccobacilli in parallel clusters (school of fish). Culture requires expensive, special media and has a sensitivity of only 80%. Polymerase chain reaction or indirect immunofluorescence using monoclonal antibodies remain either as research tools or are performed by some clinical laboratories using their own in-house CLIA (Clinical Laboratory Improvement Amendments) verified kits. There are currently no FDA-approved polymerase chain reaction tests for *H. ducreyi*. The ulcer of chancroid is accompanied by concurrent lymphadenopathy that is usually unilateral, unlike lymphogranuloma venereum (see Chapter 226.4). Genital herpes is characterized by vesicular lesions with a history of recurrence (see Chapter 252).
TREATMENT
Most *H. ducreyi* organisms are resistant to penicillin and ampicillin because of plasmid-mediated β-lactamase production. Spread of plasmid-mediated resistance among *H. ducreyi* has resulted in lack of efficacy of previously useful drugs such as sulfonamides and tetracyclines. Chancroid is easy to treat if recognized early. The current treatment recommendation is for azithromycin (1g as a single dose PO) or ceftriaxone (250 mg as a single dose IM). Alternative regimens include erythromycin (500 mg tid PO for 7 days), which is most often used in developing countries, and ciprofloxacin (500 mg bid PO for 3 days, for persons ≥18 yr of age). Fluctuant nodes may require drainage. Symptoms usually resolve within 3-7 days. Relapses can usually be treated successfully with the original treatment regimen. Patients with HIV infection may require longer duration of treatment. Persistence of the ulcer and the organism following therapy should raise suspicion of resistance to the prescribed antibiotic.

Patients with chancroid should be evaluated for other sexually transmitted infections, including syphilis, hepatitis B virus, HIV, chlamydia, and gonorrhea; an estimated 10% have concomitant syphilis or genital herpes. If initial HIV or syphilis testing is negative, they should be tested for again in 3 mo because of the high rates of coinfections. In developing countries, patients with a compatible genital ulcer are treated for both chancroid and syphilis. All sexual contacts of patients with chancroid should be evaluated and treated.

COMPLICATIONS
Complications include phimosis in men and secondary bacterial infection. Bubo formation may occur in untreated cases. Genital ulceration as a syndrome increases the risk for transmission of HIV.

Bibliography is available at Expert Consult.


**Chapter 196
Moraxella catarrhalis**

Timothy F. Murphy

*Moraxella catarrhalis* is an unencapsulated Gram-negative diplococcus and is a human-specific pathogen that colonizes the respiratory tract beginning in infancy. Colonization and infection with *M. catarrhalis* are increasing in countries in which pneumococcal conjugate vaccines are used widely. The most important clinical manifestation of *M. catarrhalis* infection in children is otitis media.

**ETIOLOGY**

*M. catarrhalis* has long been considered to be an upper respiratory tract commensal. Substantial genetic heterogeneity exists among strains of *M. catarrhalis*. Several outer membrane proteins demonstrate sequence differences among strains, particularly in regions of the proteins that are exposed on the bacterial surface. *M. catarrhalis* endotoxin lacks repeating polysaccharide side chains and is thus a lipooligosaccharide. In contrast to other Gram-negative respiratory pathogens, such as *Haemophilus influenzae* and *Neisseria meningitidis*, the lipooligosaccharide of *M. catarrhalis* is relatively conserved among strains; only 3 serotypes (A, B, and C) that are based on oligosaccharide structure have been identified. Genetic and antigenic differences among strains account for the observation that resolving an infection by 1 strain does not induce protective immunity to other strains. *M. catarrhalis* causes recurrent infections, which generally represent re infection by new strains.

**EPIDEMIOLOGY**

The ecologic niche of *M. catarrhalis* is the human respiratory tract. The bacterium has not been recovered from animals or environmental sources. Age is the most important determinant of the prevalence of upper respiratory tract colonization. Common throughout infancy, nasopharyngeal colonization is a dynamic process with active turnover as a result of acquisition and clearance of strains of *M. catarrhalis*. Some geographic variation in rates of colonization is observed. On the basis of monthly or bimonthly cultures, colonization during the 1st yr of life may range from 33-100%. Several factors likely account for this variability among studies, including living conditions, daycare attendance, hygiene, environmental factors (e.g., household smoking), and genetics of the population. The prevalence of colonization steadily decreases with age. Understanding nasopharyngeal colonization patterns is important, because the pathogenesis of otitis media involves migration of the bacterium from the nasopharynx to the middle ear via the eustachian tube.

The widespread use of pneumococcal polysaccharide vaccines in some countries has resulted in alteration of patterns of nasopharyngeal colonization in the population. A relative increase in colonization by nonvaccine pneumococcal serotypes, nontypable *H. influenzae*, and *M. catarrhalis* has occurred. These changes in colonization patterns may account for the increased rates of otitis media caused by nontypable *H. influenzae* and *M. catarrhalis*. Similar shifts in etiology are being observed in children with sinusitis as well.

**PATHOGENESIS OF INFECTION**

Strains of *M. catarrhalis* differ in their virulence properties. The species is composed of complement-resistant and complement-sensitive genetic lineages, the complement-resistant strains being more strongly associated with virulence. Strains that cause infection in children differ in several phenotypic characteristics from strains that cause infection in adults, in whom the most common clinical manifestation is lower respiratory tract infection in the setting of chronic obstructive pulmonary disease.

The presence of several adhesin molecules with differing specificities for various host cell receptors reflects the importance of adherence to the human respiratory epithelial surface in the pathogenesis of infection. *M. catarrhalis* has long been viewed as an exclusively extracellular pathogen. However, the bacterium is now known to invade multiple cell types, including bronchial epithelial cells, small airway cells, and type 2 alveolar cells. In addition, *M. catarrhalis* resides intracellularly in lymphoid tissue, providing a potential reservoir for persistence in the human respiratory tract. Like many Gram-negative bacteria *M. catarrhalis* sheds vesicles from its surface during growth. These vesicles are internalized by respiratory epithelial cells and mediate several virulence mechanisms including β-cell activation, induction of inflammation, and delivery of β-lactamases. Analysis of genomes reveals modest genetic heterogeneity among strains.

*M. catarrhalis* forms biofilms in vitro and in the middle ears of children with chronic and recurrent otitis media. Biofilms are communities of bacteria encased in a matrix attached to a surface. Bacteria in biofilms are more resistant to antibiotics and to host immune responses than bacteria growing individually in planktonic form.

**CLINICAL MANIFESTATIONS**

*M. catarrhalis* causes predominantly mucosal infections in children. The mechanism of infection is migration of the infecting strains from the nasopharynx to the middle ear in the case of otitis media or to the sinuses in the case of sinusitis. The inciting event for both otitis media and sinusitis is often a preceding viral infection.

**Acute Otitis Media**

Approximately 80% of children have 1 or more episodes of otitis media by age 3 yr. Otitis media is the most common reason for which children receive antibiotics. On the basis of culture of middle ear fluid obtained by tympanocentesis, the predominant causes of acute otitis media are *Streptococcus pneumoniae*, *H. influenzae*, and *M. catarrhalis* (Fig. 196-1). Overall, *M. catarrhalis* causes 15-20% of cases of otitis media. The distribution of the causative agents of otitis media is changing as a result of widespread administration of pneumococcal conjugate vaccines, with a relative increase in *H. influenzae* and *M. catarrhalis*. 

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**Moraxella catarrhalis**

**Chapter 196**

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Acute otitis media caused by *M. catarrhalis* is clinically milder than otitis media caused by *H. influenzae* or *S. pneumoniae*, with less fever and lower prevalence of a red, bulging tympanic membrane. However, substantial overlap in symptoms is seen, making it impossible to predict etiology in an individual child on the basis of clinical features. Tympanocentesis is required to make an etiologic diagnosis but is not performed routinely, and thus, treatment of otitis media is generally empirical.

**Recurrent Otitis Media and Otitis Media with Effusion**

*Otitis media with effusion* refers to the presence of fluid in the middle ear in the absence of signs and symptoms of acute infection. Children who experience 4 or more episodes of acute otitis media in a year or who have at least 8 mo of middle ear effusion in a year are defined as *otitis prone*. These children suffer conductive hearing loss, which may lead to delays in speech and language development. Analysis of middle ear fluid from children with otitis media with effusion using sensitive molecular techniques such as polymerase chain reaction indicates that bacterial DNA is present in up to 80% of samples from such children. Indeed, *M. catarrhalis* DNA is present in a larger proportion of cases of otitis media with effusion than of acute otitis media. Biofilms may account for these observations, although definitive evidence for this conclusion is lacking.

**Sinusitis**

A small proportion of viral upper respiratory tract infections are complicated by bacterial sinusitis. According to findings of studies that use sinus puncture, *M. catarrhalis* accounts for approximately 20% of cases of acute bacterial sinusitis in children and a smaller proportion in adults. Sinusitis caused by *M. catarrhalis* is clinically indistinguishable from that caused by *S. pneumoniae* or *H. influenzae*.

**Bacteremia**

*M. catarrhalis* rarely causes bacteremia or invasive infections in children. When bacteremia occurs, the usual source is the respiratory tract. Some children have underlying immunocompromising conditions, but no particular immunodeficiency is associated with invasive *M. catarrhalis* infections.

**DIAGNOSIS**

The clinical diagnosis of otitis media is made by demonstration of fluid in the middle ear by pneumatic otoscopy. A tympanocentesis is required to establish an etiologic diagnosis, but this procedure is not performed routinely. Thus, the choice of antibiotic for otitis media is empirical and generally based on guidelines. Management of bacterial sinusitis is also empirical, because determining the etiology of sinusitis requires a sinus puncture, also a procedure that is not performed routinely.

The key to making a microbiologic diagnosis is distinguishing *M. catarrhalis* from commensal *Neisseria* that are part of the normal upper respiratory tract flora. Indeed, the difficulty in distinguishing colonies of *M. catarrhalis* from *Neisseria* species explains in part why *M. catarrhalis* has been overlooked in the past as a respiratory tract pathogen. *M. catarrhalis* produces round, opaque colonies that can be slid across the agar surface without disruption, the “hockey puck sign.” In addition, after 48 hr, *M. catarrhalis* colonies tend to be larger than *Neisseria* and take on a pink color. A variety of biochemical tests distinguish *M. catarrhalis* from *Neisseria* species, and commercially available kits based on these tests are available.

Sensitive tests that employ polymerase chain reaction to detect respiratory tract bacterial pathogens in human respiratory tract secretions are in development. The application of such assays when they become available is likely to contribute new information about the epidemiology and disease patterns of *M. catarrhalis*.

**TREATMENT**

A proportion of cases of *M. catarrhalis* otitis media resolve spontaneously. Treatment of otitis media is empirical, and clinicians are advised to follow guidelines of the American Academy of Pediatrics (see Chapter 640).

Strains of *M. catarrhalis* rapidly acquired β-lactamase worldwide in the 1970s and 1980s, rendering essentially all strains resistant to amoxicillin. Antimicrobial susceptibility patterns have remained relatively stable since then. Most strains of *M. catarrhalis* are susceptible to amoxicillin/clavulanic acid, extended-spectrum cephalosporins, macrolides (azithromycin, clarithromycin), trimethoprim/sulfamethoxazole, and fluoroquinolones.

**PREVENTION**

Vaccines to prevent otitis media and other infections caused by *M. catarrhalis* are under development, but none is available yet.

*Bibliography is available at Expert Consult.*
Bibliography
Pertussis is an acute respiratory tract infection that was well described initially in the 1500s. Sydenham first used the term pertussis, meaning intense cough, in 1670; it is preferable to whooping cough because most infected individuals do not “whoop.”

**ETIOLOGY**

*Bordetella pertussis* is the cause of epidemic pertussis and the usual cause of sporadic pertussis. *Bordetella parapertussis* is an occasional cause of sporadic pertussis that contributes significantly to total cases of pertussis in Eastern and Western Europe but accounts for <5% of *Bordetella* isolates in the United States. *B. pertussis* and *B. parapertussis*
are exclusive pathogens of humans and some primates. *Bordetella holmesii*, first identified as a cause of bacteremia in immunocompromised hosts, is also reported to cause pertussis-like cough illness in healthy persons in Japan, France, and the United States. *Bordetella bronchiseptica* is a common animal pathogen. Occasional reports in humans describe a variety of body sites involved, and cases typically occur in immunocompromised persons or young children with intense exposure to animals. Protracted coughing (which in some cases is paroxysmal) can be caused by *Mycoplasma*, parainfluenza viruses, influenza viruses, enteroviruses, respiratory syncytial viruses, or adenoviruses.

### EPIDEMIOLOGY

Estimates from the World Health Organization suggest that in 2008, approximately 16 million cases of pertussis and 195,000 childhood deaths occurred worldwide, 95% of which were in developing countries. The World Health Organization also estimated that in 2008, 82% of infants worldwide received 3 doses of pertussis vaccine, and that global vaccination against pertussis averted 687,000 deaths. Before vaccination was available, pertussis was the leading cause of death from communicable disease among children younger than 14 yr of age in the United States, with 10,000 deaths annually. Widespread use of whole-cell pertussis vaccine (DTP) led to a >99% decline in cases. After the low number of 1,010 cases in the United States reported in 1976, there was an increase in annual pertussis incidence to 1.2 cases per 100,000 population from 1980 through 1989, with epidemic pertussis in many states in 1989-1990, 1993, and 1996. Since then, pertussis has become increasingly endemic, with shifting burden of disease to young infants, adolescents, and adults. By 2004, the incidence of reported pertussis in the United States was 8.9 cases per 100,000 in the general population and approximately 150 per 100,000 in infants younger than 2 mo of age, resulting in a total of 25,827 cases, the highest number since 1959. Prospective and serologic studies suggested that pertussis is underrecognized, especially among adolescents and adults, in whom the actual number of cases is estimated to be 600,000 annually. A number of studies documented pertussis in 13-32% of adolescents and adults with cough illness for longer than 7 days. A total of 40 pertussis-related deaths were reported in 2005, and 16 were reported in 2006; more than 90% of these cases occurred among young infants.

Universal recommendation of tetanus toxoid, reduced content diphtheria toxoid, and acellular pertussis antigens (Tdap) in 2006 for 11-12 year olds was aimed to enhance control. With >70% uptake of Tdap in adolescents, the burden of disease in young adolescents has fallen commensurately, but without evidence of herd protection of young infants or older adolescents or adults. In fact, a new epidemiology of pertussis has emerged in this decade, with substantial evidence of rapidly waning immunity following acellular pertussis vaccines (both DTap and Tdap) and especially in those who never received that, is not "primed" with, DTP (whole cell), which was replaced with DTap down to dose 1 in 1997 in the United States. The more than 42,000 cases of pertussis reported in 2012 was the highest number in more than 50 yr; increased numbers of cases were reported in all except 1 state; 10 yr old children had the highest age-related incidence after young infants.

Neither natural disease nor vaccination provides complete or life-long immunity against pertussis reinfection or disease. Subclinical reinfection undoubtedly contributed significantly to immunity against disease ascribed previously to both vaccine and prior infection. The resurgence of pertussis has been attributed to a variety of factors, including partial control of pertussis leading to less continuous exposure, increased awareness, improved diagnostics, suboptimal vaccines, waning vaccine-induced immunity, and pathogen adaptation. Pertussis is the only vaccine-preventable disease for which universal immunization in the United States is recommended that continues to be endemic.

### PATHOGENESIS

*Bordetella* organisms are small, fastidious, Gram-negative cocobacilli that colonize only ciliated epithelium. The exact mechanism of disease symptomatology remains unknown. *Bordetella* species share a high degree of DNA homology among virulence genes. Only *B. pertussis* expresses *pertussis toxin* (PT), the major virulence protein. PT has numerous proven biologic activities (e.g., histamine sensitivity, insulin secretion, leukocyte dysfunction). Injection of PT in experimental animals causes lymphocytosis immediately by rerouting lymphocytes to remain in the circulating blood pool but does not cause cough. PT appears to have a central, but not a singular, role in pathogenesis. *B. pertussis* produces an array of other biologically active substances, many of which are postulated to have a role in disease and immunity. After aerosol acquisition, *filamentous hemagglutinin*, some *agglutinogens* (especially fimbrins [Fim] types 2 and 3), and a 69-kDa non-fimbrial surface protein called *pertactin* (Prn) are important for attachment to ciliated respiratory epithelial cells. *Tracheal cytotoxin*, adenylate cyclase, and PT appear to inhibit clearance of organisms. Pertactin cytotoxin, demonecrotic factor, and adenylate cyclase are postulated to be predominantly responsible for the local epithelial damage that produces respiratory symptoms and facilitates absorption of PT. Both antibody and cellular immune responses follow infection and immunization. Antibody to PT neutralizes toxin, and antibody to Prn enhances opsonophagocytosis.

Pertussis is extremely contagious, with attack rates as high as 100% in susceptible individuals exposed to aerosol droplets at close range. High airborne transmission rates were shown in a baboon model of pertussis despite vaccinated with the acellular vaccine. *B. pertussis* does not survive for prolonged periods in the environment. Chronic carriage by humans is not documented. After intense exposure as in households, the rate of subclinical infection is as high as 80% in fully immunized or previously infected individuals. When carefully sought, a symptomatic source case can be found for most patients.

### CLINICAL MANIFESTATIONS

Classically, pertussis is a prolonged disease, divided into catarrhal, paroxysmal, and convalescent stages. The *catarrhal stage* (1-2 wk) begins insidiously after an incubation period ranging from 3-12 days with non distintinctive symptoms of congestion and rhinorrhea variably accompanied by low-grade fever, sneezing, lacrimation, and conjunctival suffusion. As initial symptoms wane, coughing marks the onset of the *paroxysmal stage* (2-6 wk). The cough begins as a dry, intermit tent, irritating hack and evolves into the inexorable paroxysms that are the hallmark of pertussis. A well-appearing, playful toddler with insig nificant provocation suddenly expresses an anxious aura and may cluch a parent or comforting adult before beginning a machine-gun burst of uninterrupted cough on a single exhalation, chin and chest held forward, tongue protruding maximally, eyes bulging and water ing, face purple, until coughing ceases and a loud whoop follows as inspired air traverses the still partially closed airway. *Posttussive emesis* is common, and exhaustion is universal. The number and severity of paroxysms escalate over days to a week and remain at that plateau for days to weeks. At the peak of the paroxysmal stage, patients may have more than 1 episode hourly. As the paroxysmal stage fades into the *convalescent stage* (≥22 wk), the number, severity, and duration of episodes diminish.

Infants younger than 3 mo of age do not display the classic stages. The catarrhal phase lasts only a few days or is unnoticed, and then, after the most insignificant startle from a draft, light, sound, sucking, or stretching, a well-appearing young infant begins to choke, gasp, gag, and flail the extremities, with face reddened. Cough may not be prominent, especially in the early phase. Whoop infrequently occurs in infants younger than 3 mo of age who at the end of a paroxysm lack stature or muscular strength to create sudden negative intrathoracic pressure. Apnea and cyanosis can follow a coughing paroxysm, or apnea can occur without a cough. Apnea may be the only symptom. Apnea and cyanosis both are more common with pertussis than with neonatal infections from viruses, including respiratory syncytial virus. The paroxysmal and convalescent stages in young infants are lengthy. Paradoxically, in infants, cough and whooping may become louder and more classic in convalescence. Convalescence includes intermittent paroxysmal coughing throughout the 1st yr of life, including “exacerbations” with subsequent respiratory illnesses; these are not a result of recurrent infection or reactivation of *B. pertussis*. 

Pertussis is extremely contagious, with attack rates as high as 100% in susceptible individuals exposed to aerosol droplets at close range. High airborne transmission rates were shown in a baboon model of pertussis despite vaccinated with the acellular vaccine. *B. pertussis* does not survive for prolonged periods in the environment. Chronic carriage by humans is not documented. After intense exposure as in households, the rate of subclinical infection is as high as 80% in fully immunized or previously infected individuals. When carefully sought, a symptomatic source case can be found for most patients.
Adolescents and previously immunized children have foreshortening of all stages of pertussis. Adults have no distinct stages. Classically, adolescents and adults describe a sudden feeling of strangulation followed by uninterrupted coughs, feeling of suffocation, bursting headache, diminished awareness, and then a gasping breath, usually without a whoop. Posttussive emesis and intermittency of paroxysms separated by hours of well-being are specific clues to the diagnosis in adolescents and adults. At least 30% of older individuals with pertussis have non-specific cough illness, distinguished only by duration, which usually is longer than 21 days.

Findings on physical examination generally are uninformative. Signs of lower respiratory tract disease are not expected unless complicating secondary bacterial pneumonia is present. Conjunctival hemorrhages and petechiae on the upper body are common.

**DIAGNOSIS**

Pertussis should be suspected in any individual who has a pure or predominant complaint of cough, especially if the following features are absent: fever, malaise or myalgia, exanthem or enanthem, sore throat, hoarseness, tachypnea, wheeze, and rales. For sporadic cases, a clinical case definition of cough of 14 days or longer duration with at least 1 associated symptom of paroxysms, whoop, or posttussive vomiting has a sensitivity of 81% and a specificity of 58% for confirmation of pertussis. Pertussis should be suspected in older children whose cough illness is escalating at 7-10 days and whose coughing episodes are not continuous. Pertussis should be suspected in infants younger than 3 mo of age with gagging, gasping, apnea, cyanosis, or an apparent life-threatening event. Sudden infant death occasionally is caused by *B. pertussis*.

Adenoviral infections usually are distinguishable by associated features, such as fever, sore throat, and conjunctivitis. *Mycoplasma* causes protracted episodic coughing, but patients usually have a history of fever, headache, and systemic symptoms at the onset of disease as well as more continuous cough and frequent finding of rales on auscultation of the chest. Epidemics of *Mycoplasma* and *B. pertussis* in young adults can be difficult to distinguish on clinical grounds. Although pertussis often is included in the laboratory evaluation of young infants with afebrile pneumonia, *B. pertussis* is not associated with staccato cough (breath with every cough), purulent conjunctivitis, tachypnea, rales or wheezes that typify infection by *Chlamydia trachomatis*, or predominant lower respiratory tract signs that typify infection by respiratory syncytial virus. Unless an infant with pertussis has secondary pneumonia (and then appears ill), the findings on examination between paroxysms including respiratory rate are entirely normal.

Leukocytosis (15,000-100,000 cells/µL) caused by absolute lymphocytosis is characteristic in the catarrhal stage. Lymphocytes are of T- and B-lymphocyte origin and are normal small cells, rather than the large atypical lymphocytes seen with viral infections. Adults, partially immune children, and, occasionally, young infants may have less impressive lymphocytosis. Absolute increase in neutrophils suggests a different diagnosis or secondary bacterial infection. Eosinophilia is not a manifestation of pertussis. A severe course and death are correlated with rapid-rise and extreme leukocytosis (median peak white blood cell count in fatal vs nonfatal cases, 94,000 vs 18,000/µL, respectively) and thrombocytosis (median peak platelet count in fatal vs nonfatal cases, 782,000 vs 556,000/µL, respectively). Chest radiographic findings are only mildly abnormal in the majority of hospitalized infants, showing perihilar infiltrate or edema (sometimes with a butterfly appearance) and variable atelectasis. Parenchymal consolidation suggests secondary bacterial infection. Pneumothorax, pneumomediastinum, and subcutaneous emphysema can be seen occasionally.

Current methods for confirmation of infection by *B. pertussis* (i.e., culture, polymerase chain reaction [PCR], and serology) have limitations in sensitivity, specificity, or practicality, and relative value depends on the setting, phase of disease, and purpose of use (e.g., as clinical diagnostic vs epidemiologic tool). For culture, careful attention must be directed to specimen collection, transport, and isolation technique. The specimen is obtained with deep nasopharyngeal aspiration or with the use of a flexible swab, preferably a Dacron or calcium alginate–tipped swab, held in the posterior nasopharynx for 15-30 sec (or until cough occurs). A 1% casamino acid liquid is acceptable for holding a specimen up to 2 hr; Stainer-Scholte broth or Regan-Lowe semisolid transport medium is used for longer transport periods, up to 4 days. The preferred isolation media are Regan-Lowe charcoal agar with 10% horse blood and 5-40 µg/mL cephalxin, and Stainer-Scholte media with cyclodextrin resins. Cultures are incubated at 35-37°C in a humid environment and examined daily for 7 days for slow-growing, tiny, glistening colonies. Direct fluorescent antibody testing of potential isolates using specific antibody for *B. pertussis* and *B. parapertussis* maximizes recovery rates. PCR testing on nasopharyngeal wash specimens has a sensitivity similar to that of culture and averts difficulties of isolation, but only standardized validated primers should be used. Results of culture and PCR are expected to be positive in unimmunized, untreated children during the catarrhal and early paroxysmal stages of disease. However, fewer than 20% of culture or PCR tests have positive results in partially or remotely immunized individuals tested in the paroxysmal stage. Serologic tests for detection of change in antibodies to *B. pertussis* antigens in acute and convalescent samples are the most sensitive tests in immunized individuals and are useful epidemiologically. A single serum sample showing immunoglobulin (Ig) G antibody to PT elevated >2 SD above the mean of the immunized population (>90 IU/mL) indicates recent symptomatic infection and usually is positive in the mid paroxysmal phase. Tests for IgA and IgM pertussis antibody, or antibody to antigens other than PT, are not reliable methods for serologic diagnosis of pertussis.

**TREATMENT**

Infants younger than 3 mo of age with suspected pertussis usually are admitted to hospital, as are many between 3 and 6 mo of age unless witnessed paroxysms are not severe, as well as are patients of any age if significant complications occur. Prematurely born young infants have a high risk for severe, potentially fatal disease, and children with underlying cardiac, pulmonary, muscular, or neurologic disorders have increased risk of poor outcome beyond infancy. Table 197-1 lists caveats in assessment and care of infants with pertussis. The specific, limited goals of hospitalization are to: (1) assess progression of disease and likelihood of life-threatening events at peak of disease; (2) maximize nutrition; (3) prevent or treat complications; and (4) educate parents in the natural history of the disease and in care that will be given at home. Heart rate, respiratory rate, and pulse oximetry are monitored continuously with alarm settings so that paroxysms can be witnessed and recorded by healthcare personnel. Detailed cough records and documentation of feeding, vomiting, and weight change provide data to assess severity. Typical paroxysms that are not life-threatening have the following features: duration <45 sec; red but not blue color change; tachycardia, bradycardia (not <60 beats/min in

<table>
<thead>
<tr>
<th>Table 197-1 Caveats in Assessment and Care of Infants with Pertussis</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Infants with potentially fatal pertussis may appear well between episodes.</td>
</tr>
<tr>
<td>• A paroxysm must be witnessed before a decision is made between hospital and home care.</td>
</tr>
<tr>
<td>• Only analysis of carefully compiled cough record permits assessment of severity and progression of illness.</td>
</tr>
<tr>
<td>• Suctioning of nose, oropharynx, or trachea should not be performed on a “preventive” schedule.</td>
</tr>
<tr>
<td>• Feeding in the period following a paroxysm may be more successful than after napping.</td>
</tr>
<tr>
<td>• Family support begins at the time of hospitalization with empathy for the child’s and family’s experience to date, transfer of the burden of responsibility for the child’s safety to the healthcare team, and delineation of assessments and treatments to be performed.</td>
</tr>
<tr>
<td>• Family education, recruitment as part of the team, and continued support after discharge are essential.</td>
</tr>
</tbody>
</table>
infants), or oxygen desaturation that spontaneously resolves at the end of the paroxysm; whooping or strength for brisk self-rescue at the end of the paroxysm; self-expectorated mucus plug; and posttussive exhaustion but not unresponsiveness. Assessing the need to provide oxygen, stimulation, or suctioning requires skilled personnel who can watchfully observe an infant’s ability for self-rescue but who will intervene rapidly and expertly when necessary. The benefit of a quiet, dimly lighted, undisturbed, comforting environment cannot be overestimated or forfeited in a desire to monitor and intervene. Feeding children with pertussis is challenging. The risk of precipitating cough by nipple feeding does not warrant nasogastric, nasojejunal, or parenteral alimentation in most infants. The composition or thickness of formula does not affect the quality of secretions, cough, or retention. Large-volume feedings are avoided.

Within 48-72 hr, the direction and severity of disease are obvious from analysis of recorded information. Many infants have marked improvement upon hospitalization and antibiotic therapy, especially if they are hospitalized early in the course of disease or have been removed from aggravating environmental smoke, excessive stimulation, or a dry or polluting heat source. Hospital discharge is appropriate if over a 48-hr period disease severity is unchanged or diminished, intervention is not required during paroxysms, nutrition is adequate, no complication has occurred, and parents are adequately prepared for care at home. Apnea and seizures occur in the incremental phase of illness and in patients with complicated disease. Portable oxygen, monitoring, or suction apparatus should not be needed at home.

Infants who have apnea, paroxysms that repeatedly lead to life-threatening events despite passive delivery of oxygen, or respiratory failure require intubation, pharmacologically induced paralysis, and ventilation.

**Antibiotics**

An antimicrobial agent always is given when pertussis is suspected or confirmed, primarily to limit the spread of infection and secondarily for possible clinical benefit. Macrolides are preferred agents and are similar to one another in terms of in vitro activity (Table 197-2). Resistance has been reported rarely. A 7-10-fold relative risk for infantile hypertrophic pyloric stenosis has been reported in neonates treated with orally administered erythromycin. Azithromycin is the preferred agent in all age groups; rare cases of infantile hypertrophic pyloric stenosis have followed its use in neonates. All young infants treated with any macrolide should be monitored for symptoms of pyloric stenosis. Benefits of postexposure prophylaxis for infants far outweigh risk of infantile hypertrophic pyloric stenosis. The FDA also warns of risk of fatal heart rhythms with use of azithromycin in patients already at risk for cardiovascular events, especially those with prolongation of the QT interval.

**Adjunct Therapies**

No rigorous clinical trial has demonstrated a beneficial effect of β2-adrenergic stimulants such as salbutamol and albuterol. Fusing associated with aerosol treatment triggers paroxysms. No randomized, blinded clinical trial of sufficient size has been performed to evaluate the usefulness of corticosteroids in the management of pertussis; their clinical use is not warranted. A randomized, double blind, placebo-controlled trial of pertussis intravenous immunoglobulin was halted prematurely because of expiration/lack of additional supply of study product; there was no indication of clinical benefit. Standard intravenous immunoglobulin has not been studied and should not be used for treatment or prophylaxis.

**Isolation**

Patients with suspected pertussis are placed in isolation with droplet precautions to reduce close respiratory or mucous membrane contact with respiratory secretions. All healthcare personnel should wear a mask upon entering the room. Screening for cough should be performed upon entrance of patients to emergency departments, offices, and clinics to begin isolation immediately and until 5 days after initiation of macrolide therapy. Children and staff with pertussis in childcare facilities or schools should be excluded until macrolide has been taken for 5 days.

**Care of Household and Other Close Contacts**

A macrolide agent should be given promptly to all household contacts and other close contacts, such as those in daycare, regardless of age, history of immunization, and symptoms (see Table 197-2). The same drugs and age-related doses used for treatment are used for prophylaxis. Visitation and movement of coughing family members in the

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**Table 197-2**

Recommended Antimicrobial Treatment and Postexposure Prophylaxis for Pertussis, By Age Group

<table>
<thead>
<tr>
<th>AGE GROUP</th>
<th>AZITHROMYCIN</th>
<th>ERYTHROMYCIN</th>
<th>CLARITHROMYCIN</th>
<th>TMP-SMZ</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1 mo</td>
<td>Recommended agent 10 mg/kg/day in a single dose for 5 days (only limited safety data available)</td>
<td>Not preferred Erythromycin is substantially associated with infantile hypertrophic pyloric stenosis Use if azithromycin is unavailable; 40-50 mg/kg/day in 4 divided doses for 14 days</td>
<td>Not recommended (safety data unavailable)</td>
<td>Contraindicated for infants &lt;2 mo of age (risk for kernicterus)</td>
</tr>
<tr>
<td>1-5 mo</td>
<td>10 mg/kg/day in a single dose for 5 days</td>
<td>40-50 mg/kg/day in 4 divided doses for 14 days</td>
<td>15 mg/kg/day in 2 divided doses for 7 days</td>
<td>Contraindicated at age &lt;2 mo For infants age ≥2 mo: TMP 8 mg/kg/day plus SMZ 40 mg/kg/day in 2 divided doses for 14 days</td>
</tr>
<tr>
<td>Infants age ≥6 mo and children</td>
<td>10 mg/kg in a single dose on day 1 (maximum: 500 mg), then 5 mg/kg/day (maximum: 250 mg) on days 2-5</td>
<td>40-50 mg/kg/day (maximum: 2 g/day) in 4 divided doses for 14 days</td>
<td>15 mg/kg/day in 2 divided doses (maximum: 1 g/day) for 7 days</td>
<td>TMP 8 mg/kg/day plus SMZ 40 mg/kg/day in 2 divided doses (maximum TMP: 320 mg/day) for 14 days</td>
</tr>
<tr>
<td>Adults</td>
<td>500 mg in a single dose on day 1 then 250 mg/day on days 2-5</td>
<td>2 g/day in 4 divided doses for 14 days</td>
<td>1 g/day in 2 divided doses for 7 days</td>
<td>TMP 320 mg/day, SMZ 1,600 mg/day in 2 divided doses for 14 days</td>
</tr>
</tbody>
</table>

*Trimethoprim-sulfamethoxazole (TMP-SMZ) can be used as an alternative agent to macrolides in patients age ≥2 mo who are allergic to macrolides, who cannot tolerate macrolides, or who are infected with a rare macrolide-resistant strain of Bordetella pertussis.

hospital must be assiduously controlled until a macrolide has been taken for 5 days. In close contacts younger than 7 yr of age who have received fewer than 4 doses of pertussis-containing vaccines, DTaP should be initiated or continued to complete the recommended series. Children younger than 7 yr of age who received a 3rd dose more than 6 mo before exposure or a 4th dose 3 yr or more before exposure should receive a DTaP booster dose. Individuals 9 yr of age or older should be given Tdap if they have not received Tdap previously. Unmasked healthcare personnel exposed to untreated cases should be evaluated for postexposure prophylaxis and follow-up. Coughing healthcare personnel with or without known exposure to pertussis should be promptly evaluated for pertussis.

**COMPLICATIONS**

Infants younger than 6 mo of age have excessive mortality and morbidity; infants younger than 2 mo of age have the highest reported rates of pertussis-associated hospitalization (82%), pneumonia (25%), seizures (4%), encephalopathy (1%), and death (1%). Infants younger than 4 mo of age account for 90% of cases of fatal pertussis. Preterm birth and young maternal age are significantly associated with fatal pertussis. Neonates with pertussis have substantially longer hospitalizations, greater need for oxygen, and greater need for mechanical ventilation than neonates with viral respiratory tract infection.

The principal complications of pertussis are apnea, secondary infections (such as otitis media and pneumonia), and physical sequelae of forceful coughing. Fever, tachypnea or respiratory distress between paroxysms, and absolute neutropenia are clues to pneumonia. Expected pathogens include *Staphylococcus aureus*, *Streptococcus pneumoniae*, and bacteria of oropharyngeal flora. Increased intrathoracic and intraabdominal pressure during coughing can result in conjunctival and scleral hemorrhages, petechiae on the upper body, epistaxis, hemorrhage in the central nervous system and retina, pnuemothorax and subcutaneous emphysema, and umbilical and inguinal hernias. Laceration of the lingual frenulum occurs occasionally.

The need for intensive care and mechanical ventilation usually is limited to infants younger than 3 mo of age and infants with underlying conditions. Respiratory failure from apnea may precipitate need for intubation and ventilation through the days when disease peaks; prognosis is good. Progressive pulmonary hypertension in very young infants and secondary bacterial pneumonia are severe complications of pertussis and are the usual causes of death. Pulmonary hypertension and cardiogenic shock with fatal outcome are associated with extreme elevations of lymphocyte and platelet counts. Autopsies in fatal cases show luminal aggregates of leukocytes in the pulmonary vasculature. Extracorporeal membrane oxygenation of infants with pertussis in whom mechanical ventilation failed has been associated with >80% mortality (questioning the advisability of this procedure). Exchange transfusion or leukapheresis, however, is associated with drops in lymphocyte and platelet counts, with recovery in several reported cases. Echocardiography should be performed in critically ill infants with pertussis to detect presence of pulmonary hypertension and to intervene expeditiously.

Central nervous system abnormalities occur at a relatively high frequency in pertussis and are almost always a result of hypoxemia or hemorrhage associated with coughing or apnea in young infants. Apnea or bradycardia or both may result from apparent laryngospasm or vagal stimulation just before a coughing episode, from obstruction during an episode, or from hypoxemia following an episode. Seizures usually are a result of hypoxemia, but hypotension from excessive secretion of antidiuretic hormone during pneumonia can occur. The only neuropathology documented in pertussis is parenchymal hemorrhage and ischemic necrosis.

Bronchiectasis has been reported rarely after pertussis. Children who have pertussis before the age of 2 yr may have abnormal pulmonary function into adulthood.

**PREVENTION**

Universal immunization of children with pertussis vaccine, beginning in infancy with reinforcing dose(s) through adolescence and adulthood, is central to the control of pertussis. Prevention of pertussis in young infants depends on universal maternal immunization during every pregnancy and focused full immunization of contacts, both children and adults of all ages (see Chapter 172).

**DTaP Vaccines**

Several diphtheria and tetanus toxoids combined with acellular pertussis vaccines (DTaP) or combination products currently are licensed in the United States for children younger than 7 yr of age. DTaP vaccines have fewer adverse effects than the vaccines containing whole-cell pertussis (DTP), which are not available in the United States but are given to infants and children in many other countries. Acellular pertussis vaccines all contain inactivated PT and 2 or more other bacterial components (filamentous hemagglutinin, Prn, and Fim 2 and 3). Clinical efficacy against severe pertussis, defined as paroxysmal cough for longer than 21 days, is approximately 85%. Mild local and systemic adverse events as well as more serious events (including high fever, persistent crying for 3 hr or longer, hypotonic hyporesponsive episodes, and seizures) occur significantly less frequently among infants who receive DTaP than in those who receive DTP vaccine. DTaP-containing vaccines can be administered simultaneously with any other vaccines used in standard schedules for children.

Four doses of DTaP should be administered during the 1st 2 yr of life, generally at ages 2, 4, 6, and 15-18 mo of age. The 4th dose may be administered as early as 12 mo of age, provided that 6 mo have elapsed since the 3rd dose. The 5th dose of DTaP is recommended for children at 4-6 yr of age; a 5th dose is not necessary if the 4th dose in the series is administered on or after the 4th birthday. DTaP should not be given to a neonate because of interference with subsequent infant immunizations, but commencement of vaccination at 6 wk of age, with monthly doses through the 3rd dose, can be considered in high-risk settings.

When feasible, the same DTaP product is recommended for all doses of the primary vaccination series. Local reactions increase in rate and severity with successive doses of DTaP, although never reaching the magnitude of reactions following similar doses of DTP. Swelling of the entire thigh or upper arm, sometimes accompanied by pain, erythema, and fever, has been reported in 2-3% of vaccinees after the 4th or 5th dose of a variety of DTaP products. Limitation of activity is less than might be expected. Swelling subsides spontaneously without sequelae. The pathogenesis is unknown. Extensive limb swelling after the 4th dose of DTaP usually is not associated with a similar reaction to the 5th dose and is not a contraindication to subsequent dose(s) of pertussis vaccines.

Exempting children from pertussis immunization should be considered only within the narrow limits as recommended. Exemptors have significantly increased risk for pertussis and play a role in outbreaks of pertussis among immunized populations. Although well-documented pertussis confers short-term protection, the duration of protection is unknown; immunization should be completed on schedule in children diagnosed with pertussis. Improper vaccine storage reduces immunity.

**Tdap Vaccines**

Two tetanus toxoid, reduced-diphtheria toxoid, and acellular pertussis antigen vaccine (Tdap) products were licensed in 2005 and were recommended universally in 2006 for use in individuals 11-18 yr of age and in older individuals as a single-dose booster vaccine to provide protection against tetanus, diphtheria, and pertussis. The preferred age for Tdap vaccination is 11-12 yr. Recommendations for Tdap have expanded through 2012. All adolescents and adults of any age (including 65 yr of age and older) who have not received Tdap should receive a single dose of Tdap regardless of interval since Td. Pregnant women should be given Tdap during every pregnancy to provide passive antibody protection to the infant until administration of DTaP. Optimal timing of maternal Tdap is 26 through 37 wk of gestation but Tdap can be given at any time during pregnancy. Special effort should be made to ensure that contacts of infants have received DTaP or Tdap as is universally recommended. There is no recommendation for Tdap
revaccination of persons other than pregnant women. Relatively lower burden of pertussis in older adolescents and adults, modest Tdap effectiveness, and rapidly waning protection do not support cost-effectiveness of routine revaccination. There is no contraindication to concurrent administration of any other indicated vaccine. A single dose of Tdap is recommended for children 7-10 yr old who had incomplete pertussis vaccination prior to age 7 yr.

_Bibliography is available at Expert Consult._
Bibliography


Chapter 198  
Salmonella  
Zulfiqar Ahmed Bhutta

Salmonellosis is a common and widely distributed foodborne disease that is a global major public health problem affecting millions of individuals and resulting in significant mortality.

Salmonellae live in the intestinal tracts of warm- and cold-blooded animals. Some species are ubiquitous, whereas others are specifically adapted to a particular host.

The sequencing of the *Salmonella enterica* serovar Typhi (previously called *Salmonella typhi*) and *Salmonella typhimurium* genomes indicates an almost 95% genetic homology between the organisms. However, the clinical diseases caused by the 2 organisms differ considerably. Orally ingested salmonellae survive at the low pH of the stomach and evade the multiple defenses of the small intestine so as to gain access to the epithelium. Salmonellae preferentially enter M cells, which transport them to the lymphoid cells (T and B) in the underlying Peyer patches. Once across the epithelium, *Salmonella* serotypes that are associated with systemic illness enter intestinal macrophages and disseminate throughout the reticuloendothelial system. By contrast, nontyphoidal *Salmonella* (NTS) serovars induce an early local inflammatory response, which results in the infiltration of polymorphonuclear leukocytes into the intestinal lumen and diarrhea. The NTS serovars cause a gastroenteritis of rapid onset and brief duration, in contrast to typhoid fever, which has a considerably longer incubation period and duration of illness and in which systemic illness predominates and only a small proportion of children get diarrhea. These differences in the manifestations of infection by the 2 groups of pathogens, 1 predominantly causing intestinal inflammation and the other leading to systemic disease, may be related to specific genetic pathogenicity islands in the organisms. NTS serovars are unable to overcome defense mechanisms that limit bacterial dissemination from the intestine to systemic circulation in immunocompetent individuals and produce a self-limiting gastroenteritis. In contrast, *S. typhi* may possess unique virulence traits that allow it to overcome mucosal barrier functions in immunocompetent hosts, resulting in a severe systemic illness. Interestingly, the frequencies of typhoid fever in immunocompetent and immunocompromised individuals do not differ. Nonetheless, invasive nontyphoidal salmonellae strains have been noted in Africa among HIV-positive adults and among children with either HIV, malaria, or malnutrition. The presentation may be more like typhoid fever than gastroenteritis.

The nomenclature of *Salmonella* reflects the species name *Salmo-

*erralia enterica* with a number of serovars. *Salmonella* nomenclature has undergone considerable alterations. The original taxonomy was based on clinical syndromes (*S. typhi*, *Salmonella choleraesuis*, *Salmonella paratyphi*). With adoption of serologic analysis, a *Salmonella* species was defined subsequently as “a group of related fermentation phage-type,” with the result that each *Salmonella* serovar was regarded as a species in itself. Although this classification is simplistic, its use until 2004 resulted in identification of 2,501 serovars of *Salmonella*, which led to the need for further categorization to aid communication among scientists, public health officials, and the public.

All *Salmonella* serovars form a single DNA hybridization group, a single species called *S. enterica* composed of several subspecies (Table 198-1). Each subspecies contains various serotypes defined by the O and H antigens. To further simplify the nomenclature for physicians and epidemiologists, the names for the common serovars are kept for subspecies I strains, which represent >99.5% of the *Salmonella* strains isolated from humans and other warm-blooded animals.

### Table 198-1  
*Salmonella* Species, Subspecies, and Serotypes and Their Usual Habitats

<table>
<thead>
<tr>
<th><em>Salmonella</em> Species and Subspecies</th>
<th>No. of Serotypes Within Subspecies</th>
<th>Usual Habitat</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>S. enterica</em> subsp. <em>enterica</em> (I)</td>
<td>1504</td>
<td>Warm-blooded animals</td>
</tr>
<tr>
<td><em>S. enterica</em> subsp. <em>salmiae</em> (II)</td>
<td>502</td>
<td>Cold-blooded animals and the environment*</td>
</tr>
<tr>
<td><em>S. enterica</em> subsp. <em>arizonae</em> (IIIa)</td>
<td>95</td>
<td>Cold-blooded animals and the environment*</td>
</tr>
<tr>
<td><em>S. enterica</em> subsp. <em>dianznoae</em> (IIIb)</td>
<td>333</td>
<td>Cold-blooded animals and the environment*</td>
</tr>
<tr>
<td><em>S. enterica</em> subsp. <em>houtenae</em> (IV)</td>
<td>72</td>
<td>Cold-blooded animals and the environment*</td>
</tr>
<tr>
<td><em>S. enterica</em> subsp. <em>indica</em> (V)</td>
<td>13</td>
<td>Cold-blooded animals and the environment*</td>
</tr>
<tr>
<td><em>S. bongori</em> (VI)</td>
<td>22</td>
<td>Cold-blooded animals and the environment*</td>
</tr>
<tr>
<td>Total</td>
<td>2541</td>
<td></td>
</tr>
</tbody>
</table>

*Isolates of all species and subspecies have occurred in humans.*


### 198.1 Nontyphoidal Salmonellosis  
Zulfiqar Ahmed Bhutta

**ETIOLOGY**

Salmonellae are motile, nonsporulating, nonencapsulated, Gram-negative rods that grow aerobically and are capable of facultative anaerobic growth. They are resistant to many physical agents but can be killed by heating to 54.4°C (130°F) for 1 hr or 60°C (140°F) for 15 min. They remain viable at ambient or reduced temperatures for days and may survive for weeks in sewage, dried foodstuffs, pharmaceutical agents, and fecal material. Like other members of the family Enterobacteriaceae, *Salmonella* possesses somatic O antigens and flagellar H antigens.

With the exception of a few serotypes that affect only 1 or a few animal species, such as *Salmonella dublin* in cattle and *S. choleraesuis* in pigs, most serotypes have a broad host spectrum. Typically, such strains cause gastroenteritis that is often uncomplicated and does not need treatment but can be severe in the young, the elderly, and patients with weakened immunity. The causes are typically *Salmonella Enteritidis* (*Salmonella enterica* serotype Enteritidis) and *Salmonella Typhimurium* (*S. enterica* serotype Typhimurium), the 2 most important serotypes for salmonellosis transmitted from animals to humans.

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**Table 198-1**  
*Salmonella* Species, Subspecies, and Serotypes and Their Usual Habitats

<table>
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<td>1504</td>
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<tr>
<td><em>S. enterica</em> subsp. <em>salmiae</em> (II)</td>
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<tr>
<td><em>S. enterica</em> subsp. <em>dianznoae</em> (IIIb)</td>
<td>333</td>
<td>Cold-blooded animals and the environment*</td>
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<td><em>S. enterica</em> subsp. <em>houtenae</em> (IV)</td>
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<td><em>S. enterica</em> subsp. <em>indica</em> (V)</td>
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<td>Total</td>
<td>2541</td>
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*Isolates of all species and subspecies have occurred in humans.*

Nontyphoidal salmonellae have emerged as a major cause of bacteremia in Africa, especially among populations with a high incidence of HIV infection.

**EPIDEMIOLOGY**

Salmonellosis constitutes a major public health burden and represents a significant cost to society in many countries. Typhoid fever caused by this organism is a global problem, with more than 27 million cases worldwide each year, culminating in an estimated 217,000 deaths. Although there is little information on the epidemiology and the burden of *Salmonella* gastroenteritis in developing countries, *Salmonella* infections are recognized as major causes of childhood diarrheal illness. With the growing burden of HIV infections and malnutrition in Africa, NTS bacteremic infections have emerged as a major cause of morbidity and mortality among children and adults.

NTS infections have a worldwide distribution, with an incidence proportional to the standards of hygiene, sanitation, availability of safe water, and food preparation practices. In the developed world, the incidence of *Salmonella* infections and outbreaks has increased several-fold over the past few decades, which may be related to modern practices of mass food production that increase the potential for epidemics. The incidence of infections with NTS serovars, such as *S. enterica* serovar Typhimurium and *S. Enteritidis* cause a significant disease burden, with an estimated 93.8 million cases worldwide and 155,000 deaths each year. *Salmonella* gastroenteritis accounts for more than half of all episodes of bacterial diarrhea in the United States, with incidence peaks at the extremes of age, among young infants and the elderly. Most human infections have been caused by *S. Enteritidis*, the prevalence of this organism has decreased over the past decade, with *S. Typhimurium* overtaking it in some countries.

The rise in *Salmonella* infections in many parts of the world over the past 3 decades may also be related to intensive animal husbandry practices, which selectively promote the rise of certain strains, especially drug-resistant varieties that emerge in response to the use of antimicrobials in food animals. Poultry products were traditionally regarded as a common source of salmonellosis, but consumption of a range of foods is now associated with outbreaks, including fruits and vegetables. Although this change in epidemiology may be related to selective pressure from the use of antimicrobials, there may be other factors, such as the rise of strains with a selective propensity to develop resistance and virulence. It appears that multidrug-resistant strains of *Salmonella* are more virulent than susceptible strains and that poorer outcome does not simply relate to the delay in treatment response because of empirical choice of an ineffective antibiotic. Strains of multidrug-resistant *Salmonella*, such as *S. Typhimurium* phage type DT104, harbor a genomic island that contains many of the drug-resistance genes. It is possible that these integrons also contain genes that encode virulence factors. The global spread of multidrug-resistant *S. Typhimurium* phage type DT104 in animals and humans may be related to the growing use of antimicrobials and may be facilitated by international and national trade of infected animals.

Several risk factors are associated with outbreaks of *Salmonella* infections. Animals constitute the principal source of human NTS disease, and cases have occurred in which individuals have had contact with infected animals, including domestic animals such as cats, dogs, reptiles, pet rodents, and amphibians. Specific serotypes may be associated with particular animal hosts; children with *S. enterica* serovar Marina typically have exposure to pet lizards. NTS serovars usually cause self-limiting diarrhea with secondary bacteremia occurring in less than 10% of patients. The NTS serovars have a broad host range, including poultry and cattle, and NTS infection is commonly from food poisoning in developed countries.

Domestic animals probably acquire the infection in the same way that humans do, through consumption of contaminated raw meat, poultry, or poultry-derived products. Animal feeds containing fish-meal or bone meal contaminated with *Salmonella* are an important source of infection for animals. Moreover, subtherapeutic concentrations of antibiotics are often added to animal feed to promote growth. Such practices promote the emergence of antibiotic-resistant bacteria, including *Salmonella*, in the gut flora of the animals, with subsequent contamination of their meat. There is strong evidence to link resistance of *S. Typhimurium* to fluoroquinolones with the use of this group of antimicrobials in animal feeds. Animal-to-animal transmission can occur, but most infected animals are asymptomatic.

An increasing number of produce-associated foodborne outbreaks in the United States that are associated with bacterial contamination are primarily from *Salmonella*. Although almost 80% of *Salmonella* infections are discrete, outbreaks can pose an inordinate burden on public health systems. During 1998-2008, a total of 1,491 outbreaks of *Salmonella* infections were reported to the Foodborne Disease Outbreak Surveillance System, and 80% of these were caused by a single serotype. Of the single-serotype outbreaks, 50% had an implicated food and 34% could be assigned to a single food commodity. Of the 47 serotypes reported, the 4 most common, causing more than two-thirds of the outbreaks, included Enteritidis, Typhimurium, Newport, and Heidelberg. Overall, eggs were the most commonly implicated food, followed by chicken, pork, beef, fruit, and turkey. *Salmonella* infections in chickens increase the risk for contamination of eggs, and both poultry and eggs are regarded as a dominant cause of common-source outbreaks. However, a growing proportion of *Salmonella* outbreaks are also associated with other food sources. The food sources include many fruits and vegetables, such as tomatoes, sprouts, watermelon, cantaloupe, lettuce, and mangoes.

In addition to the effect of antibiotic use in animal feeds, the relationship of *Salmonella* infections to prior antibiotic use among children in the previous month is well recognized. This increased risk for infection in people who have received antibiotics for an unrelated reason may be related to alterations in gut microbial ecology, which predispose them to colonization and infection with antibiotic-resistant *Salmonella* isolates. These resistant strains of *Salmonella* are also more virulent. The Centers for Disease Control and Prevention (CDC) reports resistance to ceftriaxone in approximately 3% of NTS tested and some level of resistance to ciprofloxacin in approximately 3% of isolates. Approximately 5% of NTS tested by the CDC are resistant to 5 or more types of drugs. Consequently, costs are also expected to be higher for resistant than for susceptible infections because of the severity of the former. Those patients are more likely to be hospitalized, and treatment is rendered less effective. The CDC is seeing some level of resistance to ciprofloxacin in two-thirds of *Salmonella* Typhi tested. The CDC has not yet detected resistance to ceftriaxone or azithromycin in the United States, but resistance to these antibiotics has been seen in other parts of the world.

Given the ubiquitous nature of the organism, nosocomial infections with NTS strains can also occur through contaminated equipment and diagnostic or pharmacologic preparations, particularly those of animal origin (non-sterile extracts, puruatory extracts, bile salts). Hospitalized children are at increased risk for severe and complicated *Salmonella* infections, especially with drug-resistant organisms.

**PATHOGENESIS**

The estimated number of bacteria that must be ingested to cause symptomatic disease in healthy adults is $10^8-10^9$ *Salmonella* organisms. The gastric acidity inhibits multiplication of salmonellae, and most organisms are rapidly killed at gastric pH ≤2.0. Achlorhydria, buffering medications, rapid gastric emptying after gastrectomy or gastroenterostomy, and a large inoculum enable viable organisms to reach the small intestine. Neonates and young infants have hypochlorhydria and rapid gastric emptying, which contribute to their increased vulnerability to symptomatic salmonellosis. In infants who typically take fluids, the inoculum size required to produce disease is also comparatively smaller because of faster transit through the stomach.

Once they reach the small and large intestines, the ability of *Salmonella* organisms to multiply and cause infection depends on both the infecting dose and competition with normal flora. Prior antibiotic therapy may alter this relationship, as might factors such as coadministration of antimotility agents. The typical intestinal mucosal response to NTS infection is an enterocolitis with diffuse mucosal inflammation and edema, sometimes with erosions and microabscesses.
organisms are capable of penetrating the intestinal mucosa, although destruction of epithelial cells and ulcers are usually not found. Intestinal inflammation with polymorphonuclear leukocytes and macrophages usually involves the lamina propria. Underlying intestinal lymphoid tissue and mesenteric lymph nodes enlarge and may demonstrate small areas of necrosis. Such lymphoid hypertrophy may cause interference with the blood supply to the gut mucosa. Hyperplasia of the reticuloendothelial system is also found within the liver and spleen. If bacteremia develops, it may lead to localized infection and suppuration in almost any organ.

Both *S. Typhi* and NTS possess overlapping and distinct virulence systems (Fig. 198-1). Although *S. Typhimurium* can cause systemic disease in humans, intestinal infection usually results in a localized enteritis that is associated with a secretory response in the intestinal epithelium. Intestinal infection also induces secretion of interleukin-8 from the basolateral surface and other chemoattractants from the apical surface, directing recruitment and transmigration of neutrophils into the gut lumen and thus preventing the systemic spread of the bacteria (Fig. 198-2).

Central to *S. Typhimurium* pathogenesis are 2 type III secretion systems encoded within the pathogenicity islands SPI-1 and SPI-2 that are responsible for the secretion and translocation of a set of bacterial proteins termed effectors into host cells with the intention of altering host cell physiology for bacterial entry and survival. Thus, once delivered by the type III secretion systems, the secreted effectors play critical roles in manipulating the host cell to allow for bacterial invasion, induction of inflammatory responses, and the assembly of an intracellular protective niche created for bacterial survival and replication. The type III secretion system encoded on SPI-1 mediates invasion of the intestinal epithelium, whereas the type III secretion system encoded on SPI-2 is required for survival within macrophages. In addition, the expression of strong agonists of innate pattern recognition receptors (lipopolysaccharide and flagellin) is important for triggering a Toll-like receptor (TLR)–mediated inflammatory response. These observations suggest that *S. Typhimurium* must have acquired additional factors that further modulate the host response during infection.

*Salmonella* species invade epithelial cells in vitro by a process of bacteria-mediated endocytosis involving cytoskeletal rearrangement, disruption of the epithelial cell brush-border, and the subsequent formation of membrane ruffles (Fig. 198-3). An adherent and invasive phenotype of *S. Enterica* is activated under conditions similar to those found in the human small intestine (high osmolarity, low oxygen). The invasive phenotype is mediated in part by SPI-1, a 40-kb region that encodes regulator proteins such as HilA, the type III secretion systems in invasion of epithelial cells, and a variety of other products. In humans the Toll-like receptor–dependent IL-12/interferon (IFN)–λ is a major immunoregulatory system that bridges innate and adaptive immunity and is responsible for restricting the systemic spread of nontyphoidal *Salmonella*.

Shortly following invasion of the gut epithelium, invasive *Salmonella* organisms encounter macrophages within the gut-associated lymphoid tissue. The interaction between *Salmonella* and macrophages results in alteration in the expression of a number of host genes, including those encoding proinflammatory mediators (inducible nitric oxide synthase, chemokines, IL-1β), receptors or adhesion molecules (tumor necrosis factor [TNF]-α receptor, CD40, intercellular adhesion molecule 1), and antiinflammatory mediators (transforming growth factor–β1 and transforming growth factor–β2). Other upregulated genes include those involved in cell death or apoptosis (intestinal epithelial cell protease, TNF-R1, Fas) and transcription factors (early growth response 1, IFN regulatory factor 1). *S. Typhimurium* can induce rapid macrophage death in vitro, which depends on the host cell protein caspase-1 and is mediated by the effector protein SipB (*Salmonella* invasion protein B). Intracellular *S. Typhimurium* is found within specialized vacuoles that have diverged from the normal endocytic pathway. This ability to survive within monocytes/macrophages is essential for *S. Typhimurium* to establish a systemic infection in the mouse. The mucosal proinflammatory response to *S. Typhimurium* infection and the subsequent recruitment of phagocytic cells to the site may also facilitate systemic spread of the bacteria.

Some virulence traits are shared by all *salmonellae*, but others are serotype restricted. These virulence traits have been defined in tissue...
culture and murine models, and it is likely that clinical features of human *Salmonella* infection will eventually be related to specific DNA sequences. With most diarrhea-associated nontyphoidal *Salmonella* infections, the infection does not extend beyond the lamina propria and the local lymphatics. Specific virulence genes are related to the ability to cause bacteremia. These genes are found significantly more often in strains of *S.* *Typhimurium* isolated from the blood than in strains recovered from stool. Although both *S. dublin* and *S. choleraesuis* have a greater propensity to rapidly invade the bloodstream with little or no intestinal involvement, the development of disease after infection with *Salmonella* depends on the number of infecting organisms, their virulence traits, and several host defense factors. Various host factors may also affect the development of specific complications or clinical syndromes (Table 198-2) and of these, HIV infections are assuming greater importance in Africa in all age groups.

**Bacteremia** is possible with any *Salmonella* serotype, especially in individuals with reduced host defenses and especially in those with altered reticuloendothelial or cellular immune function. Thus, children with HIV infection, chronic granulomatous disease, and leukemia are more likely to develop bacteremia after *Salmonella* infection, although the majority of children with *Salmonella* bacteremia in Africa are HIV-negative. Children with *Schistosoma mansoni* infection and hepatosplenic involvement, as well as chronic malarial anemia, are also at a

**Table 198-2**

<table>
<thead>
<tr>
<th>Host Factors and Conditions Predisposing to the Development of Systemic Disease with Nontyphoidal <em>Salmonella</em> Strains</th>
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<tr>
<td>Neonates and young infants (≤3 mo of age)</td>
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<tr>
<td>HIV/AIDS</td>
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<tr>
<td>Other immunodeficiencies and chronic granulomatous disease</td>
</tr>
<tr>
<td>Immunosuppressive and corticosteroid therapies</td>
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<tr>
<td>Malignancies, especially leukemia and lymphoma</td>
</tr>
<tr>
<td>Hemolytic anemia, including sickle cell disease, malaria, and bartonellosis</td>
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<tr>
<td>Collagen vascular disease</td>
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<tr>
<td>Inflammatory bowel disease</td>
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<tr>
<td>Achlorhydria or use of antacid medications</td>
</tr>
<tr>
<td>Impaired intestinal motility</td>
</tr>
<tr>
<td>Schistosomiasis, malaria</td>
</tr>
<tr>
<td>Malnutrition</td>
</tr>
</tbody>
</table>

**Figure 198-2** On contact with the epithelial cell, salmonellae assemble the *Salmonella* pathogenicity island 1-encoded type III secretion system (TTSS-1) and translocate effectors (yellow spheres) into the eukaryotic cytoplasm. Effectors such as SopE, SopE2, and SopB then activate host Rho guanosine triphosphatase (GTPase), resulting in the rearrangement of the actin cytoskeleton into membrane ruffles, induction of mitogen-activated protein kinase (MAPK) pathways, and destabilization of tight junctions. Changes in the actin cytoskeleton, which are further modulated by the actin-binding proteins SipA and SipC, lead to bacterial uptake. MAPK signaling activates the transcription factors activator protein-1 (AP-1) and nuclear factor-κB (NF-κB), which turn on production of the proinflammatory polymorphonuclear leukocyte (PMN) chemokine interleukin (IL)-8. SipB induces caspase-1 activation in macrophages, with the release of IL-1β and IL-18, augmenting the inflammatory response. In addition, SopB stimulates Cl− secretion by its inositol phosphatase activity. The destabilization of tight junctions allows the transmigration of polymorphonuclear leukocytes (PMNs) from the basolateral to the apical surface, paracellular fluid leakage, and access of bacteria to the basolateral surface. However, the transmigration of PMNs also occurs in the absence of tight-junction disruption and is further promoted by SopA. The actin cytoskeleton is restored, and MAPK signaling is turned off by the enzymatic activities of SptP. This also results in the down-modulation of inflammatory responses, to which SspH1 and AvrA also contribute by inhibiting activation of NF-κB. (From Haraga A, Ohlson MB, Miller SI: *Salmonellae interplay with host cells*, Nat Rev Microbiol 6:53–66, 2008.)
greater risk for development of chronic salmonellosis. Children with sickle cell disease are at increased risk for Salmonella septicemia and osteomyelitis. This risk may be related to the presence of numerous infarcted areas in the gastrointestinal tract, bones, and reticuloendothelial system, as well as reduced phagocytic and opsonizing capacity of patients, which allow the organism to flourish.

Some inherited defects, such as IL-12 deficiency (IL-12β1 chain deficiency, IL-12p40 subunit deletion) are associated with increased risk for Salmonella infections, suggesting a key role for IL-12 in the clearance of Salmonella. IL-12 is produced by activated macrophages and is a potent inducer of IFN-γ by natural killer cells and T lymphocytes. Given the putative protective role of IL-12 against malarial infection, Salmonella infection of phagocytes may secondarily affect IL-12 production and thus produce a vicious circle of chronic malaria and Salmonella coinfection.

**CLINICAL MANIFESTATIONS**

**Acute Enteritis**
The most common clinical presentation of salmonellosis is acute enteritis. After an incubation period of 6-72 hr (mean: 24 hr), there is an abrupt onset of nausea, vomiting, and crampy abdominal pain, located primarily in the periumbilical area and right lower quadrant, followed by mild to severe watery diarrhea and sometimes by diarrhea containing blood and mucus. A large proportion of children with acute enteritis are febrile, although younger infants may exhibit a normal or subnormal temperature. Symptoms usually subside within 2-7 days in healthy children, and fatalities are rare. However, some children experience severe disease with a septicemia-like picture (high fever, headache, drowsiness, confusion, meningismus, seizures, abdominal distention). The stool typically contains a moderate number of polymorphonuclear leukocytes and occult blood. Mild leukocytosis may be detected.

**Bacteremia**
Although the precise incidence of bacteremia following Salmonella gastroenteritis is unclear, transient bacteremia can occur in 1-5% of children with Salmonella diarrhea. Bacteremia can occur with minimal associated symptoms in newborns and very young infants, but in older infants it typically follows gastroenteritis and can be associated with fever, chills, and septic shock. In patients with AIDS, recurrent septicemia appears despite antibiotic therapy, often with a negative stool culture result for Salmonella and sometimes with no identifiable focus of infection. NTS gastrointestinal infections commonly cause bacteremia in developing countries. High rates of invasive disease with S. Typhimurium and S. Enteritidis reported from Africa (38-70% of isolates) suggest an association with HIV infections and malaria.

**Extraintestinal Focal Infections**
Following bacteremia, salmonellae have the propensity to seed and cause focal supplicative infection of many organs. The most common focal infections involve the skeletal system, meninges, intravascular sites, and sites of preexisting abnormalities. The peak incidence of Salmonella meningitis is in infancy, and the infection may be...
associated with a florid clinical course, high mortality, and neurologic sequelae in survivors.

COMPLICATIONS
Salmonella gastroenteritis can be associated with acute dehydration and complications that result from delayed presentation and inadequate treatment. Bacteremia in younger infants and immunocompromised individuals can have serious consequences and potentially fatal outcomes. Salmonella organisms can seed many organ systems, leading to osteomyelitis in children with sickle cell disease, among other infections. Reactive arthritis may follow Salmonella gastroenteritis, usually in adolescents with the HLA-B27 antigen.

In certain high-risk groups, especially those with impaired immunity, the course of Salmonella gastroenteritis may be more complicated. Neonates, infants younger than 6 mo, and children with primary or secondary immunodeficiency may have symptoms that persist for several weeks. The course of illness and complications may also be affected by coexisting pathologies. In children with AIDS, Salmonella infection frequently becomes widespread and overwhelming, causing multisystem involvement, septic shock, and death. In patients with inflammatory bowel disease, especially active ulcerative colitis, Salmonella gastroenteritis may lead to rapid development of toxic megacolon, bacterial translocation, and sepsis. In children with schistosomiasis, the Salmonella may persist and multiply within schistosomes, leading to chronic infection unless the schistosomiasis is effectively treated. Prolonged or intermittent bacteremia is associated with low-grade fever, anorexia, weight loss, diaphoresis, and myalgias and may occur in children with underlying problems and a reticuloendothelial system dysfunction such as hemolytic anemia or malaria.

DIAGNOSIS
Clinical features that are specific to Salmonella gastroenteritis and thus would allow differentiation from other bacterial causes of diarrhea are few. Definitive diagnosis of Salmonella infection is based on clinical correlation of the presentation and culture of and subsequent identification of Salmonella organisms from feces or other body fluids. In children with gastroenteritis, cultures of stools have higher yields than rectal swabs. In children with NTS gastroenteritis, prolonged fever lasting 5 or more days and young age should be recognized as risk factors closely associated with development of bacteremia. In patients with sites of local suppuration, aspirated specimens should be Gram-stained and cultured. Salmonella organisms grow well on nonselective or enriched media, such as blood agar, chocolate agar, and nutrient broth, but stool specimens containing mixed bacterial flora require a selective medium, such as MacConkey, xylose-lysine-deoxycholate, bismuth sulfite, or Salmonella-Shigella (SS) agar for isolation.

Although other rapid diagnostic methods, such as latex agglutination and immunofluorescence, have been developed for rapid diagnosis of Salmonella in cultures, there are few comparable tests for rapid serologic detection. Polymerase chain reaction techniques may offer a rapid alternative to classic cultures but are as yet not in widespread use in clinical settings.

TREATMENT
Appropriate therapy relates to the specific clinical presentation of Salmonella infection. In children with gastroenteritis, rapid clinical assessment, correction of dehydration and electrolyte disturbances, and supportive care are key (see Chapter 340). Antibiotics are not generally recommended for the treatment of isolated uncomplicated Salmonella gastroenteritis because they may suppress normal intestinal flora and prolong both the excretion of Salmonella and the remote risk for creating the chronic carrier state (usually in adults). However, given the risk for bacteremia in infants (<3 mo of age) and the risk of disseminated infection in high-risk groups with immune compromise (HIV, malignancies, immunosuppressive therapy, sickle cell anemia, immunodeficiency states), these children must receive an appropriate empirically chosen antibiotic until culture results are available (Table 198-3). The S. Typhimurium phage type DT104 strain is usually resistant to the following 5 drugs: ampicillin, chloramphenicol, streptomycin, sulfonamides, and tetracycline. An increasing proportion of S. Typhimurium phage type DT104 isolates also have reduced susceptibility to fluoroquinolones. Given the higher mortality associated with multidrug-resistant Salmonella infections, it is necessary to perform susceptibility tests on all human isolates. Infections with suspected drug-resistant Salmonella should be closely monitored and treated with appropriate antimicrobial therapy.

PROGNOSIS
Most healthy children with Salmonella gastroenteritis recover fully. However, malnourished children and children who do not receive optimal supportive treatment (see Chapters 58 and 340) are at risk for development of prolonged diarrhea and complications. Young infants and immunocompromised patients often have systemic involvement, a prolonged course, and extraintestinal foci. In particular, children with HIV infection and Salmonella infections can have a florid course.

After infection, NTS are excreted in feces for a median of 5 wk. A prolonged carrier state after nontyphoidal salmonellosis is rare (<1%) but may be seen in children with biliary tract disease and cholelithiasis after chronic hemolysis. Prolonged carriage of Salmonella organisms is rare in healthy children but has been reported in those with underlying immune deficiency. During the period of Salmonella excretion, the individual may infect others, directly by the fecal–oral route or indirectly by contaminating foods.

PREVENTION
Control of the transmission of Salmonella infections to humans requires control of the infection in the animal reservoir, judicious use of antibiotics in dairy and livestock farming, prevention of contamination of foodstuffs prepared from animals, and use of appropriate standards in food processing in commercial and private kitchens (Table 198-4). Because large outbreaks are often related to mass food production, it should be recognized that contamination of just 1 piece of machinery used in food processing may cause an outbreak; meticulous cleaning of equipment is essential. Clean water supply and education in handwashing and food preparation and storage are critical to reducing person-to-person transmission. Salmonella may remain viable when cooking practices prevent food from reaching a temperature greater than 65.5°C (150°F) for longer than 12 min. Parents should be advised of the risk of reptiles as pets in households with young infants.

In contrast to developed countries, relatively little is known about the transmission of NTS infections in developing countries, and it is likely that person-to-person transmission may be relatively more important in some settings. Although some vaccines have been used in animals, no human vaccine against NTS infections is currently available. Infections should be reported to public health authorities so that outbreaks can be recognized and investigated. Given the rapid rise of antimicrobial resistance among Salmonella isolates, it is imperative that there is rigorous regulation of the use of antimicrobials in animal feeds.

Table 198-3 Treatment of Salmonella Gastroenteritis

<table>
<thead>
<tr>
<th>ORGANISM AND INDICATION</th>
<th>DOSE AND DURATION OF TREATMENT</th>
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<tbody>
<tr>
<td>Salmonella infections in infants &lt;3 mo of age or immunocompromised persons (in addition to appropriate treatment for underlying disorder)</td>
<td>Cefotaxime 100-200 mg/kg/day every 6-8 hr for 5-14 days or Ceftriaxone 75 mg/kg/day once daily for 7 days or Ampicillin 100 mg/kg/day every 6-8 hr for 7 days or Cefixime 15 mg/kg/day for 7-10 days</td>
</tr>
</tbody>
</table>

Bibliography is available at Expert Consult.
Chapter 198  Salmonella  1387.e1

Bibliography

International Food Safety Authorities Network: Antimicrobial-resistant Salmonella. Available at: http://www.who.int/foodsafety/fs_management/No_03_Salmonella_Apr05_en.pdf.
Table 198-4  Recommendations for Preventing Transmission of Salmonella from Reptiles and Amphibians to Humans

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pet store owners, healthcare providers, and veterinarians should provide</td>
<td>Pet store owners, healthcare providers, and veterinarians should provide information to owners and potential purchasers of reptiles and amphibians about the risks for and prevention of salmonellosis from these pets.</td>
</tr>
<tr>
<td>information to owners and potential purchasers of reptiles and amphibians</td>
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<tr>
<td>about the risks for and prevention of salmonellosis from these pets.</td>
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</tr>
<tr>
<td>Persons at increased risk for infection or serious complications from</td>
<td>Persons at increased risk for infection or serious complications from salmonellosis (e.g., children &lt;5 yr of age and immunocompromised persons) should avoid contact with reptiles and amphibians and any items that have been in contact with reptiles and amphibians.</td>
</tr>
<tr>
<td>salmonellosis (e.g., children &lt;5 yr of age and immunocompromised persons)</td>
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<tr>
<td>should avoid contact with reptiles and amphibians and any items that have</td>
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<tr>
<td>been in contact with reptiles and amphibians.</td>
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<tr>
<td>Reptiles and amphibians should be kept out of households that include</td>
<td>Reptiles and amphibians should be kept out of households that include children &lt;5 yr of age or immunocompromised persons. A family expecting a child should remove any pet reptile or amphibian from the home before the infant arrives.</td>
</tr>
<tr>
<td>children &lt;5 yr of age or immunocompromised persons. A family expecting a</td>
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<tr>
<td>child should remove any pet reptile or amphibian from the home before the</td>
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<td>infant arrives.</td>
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<tr>
<td>Reptiles and amphibians should not be allowed in childcare centers.</td>
<td>Reptiles and amphibians should not be allowed in childcare centers.</td>
</tr>
<tr>
<td>Persons should always wash their hands thoroughly with soap and water</td>
<td>Persons should always wash their hands thoroughly with soap and water after handling reptiles and amphibians or their cages.</td>
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<td>after handling reptiles and amphibians or their cages.</td>
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<tr>
<td>Reptiles and amphibians should not be allowed to roam freely throughout</td>
<td>Reptiles and amphibians should not be allowed to roam freely throughout a home or living area.</td>
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<td>a home or living area.</td>
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<tr>
<td>Pet reptiles and amphibians should be kept out of kitchens and other</td>
<td>Pet reptiles and amphibians should be kept out of kitchens and other food preparation areas. Kitchen sinks should not be used to bathe reptiles and amphibians or to wash their dishes, cages, or aquariums. If bathtubs are used for these purposes, they should be cleaned thoroughly and disinfected with bleach.</td>
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<tr>
<td>food preparation areas.</td>
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<tr>
<td>Kitchen sinks should not be used to bathe reptiles and amphibians or to</td>
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<td>wash their dishes, cages, or aquariums. If bathtubs are used for these</td>
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<td>purposes, they should be cleaned thoroughly and disinfected with bleach.</td>
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<tr>
<td>Reptiles and amphibians in public settings (e.g., zoos and exhibits) should</td>
<td>Reptiles and amphibians in public settings (e.g., zoos and exhibits) should be kept from direct or indirect contact with patrons except in designated animal contact areas equipped with adequate handwashing facilities. Food and drink should not be allowed in animal contact areas.</td>
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<tr>
<td>be kept from direct or indirect contact with patrons except in</td>
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<tr>
<td>designated animal contact areas equipped with adequate handwashing</td>
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<td>facilities. Food and drink should not be allowed in animal contact areas.</td>
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198.2 Enteric Fever (Typhoid Fever)
Zulfiqar Ahmed Bhutta

Enteric fever (more commonly termed typhoid fever) remains endemic in many developing countries. Given the ease of modern travel, cases are regularly reported from most developed countries, usually from returning travelers.

ETIOLOGY

Typhoid fever is caused by S. enterica serovar Typhi (S. Typhi), a Gram-negative bacterium. A very similar but often less-severe disease is caused by Salmonella Paratyphi A and rarely by S. Paratyphi B (Schottmuller) and S. Paratyphi C (Hirschfeldii). The ratio of disease caused by S. Typhi to that caused by S. Paratyphi is approximately 10:1, although the proportion of S. Paratyphi A infections is increasing in some parts of the world for reasons that are unclear. Although S. Typhi shares many genes with Escherichia coli and at least 95% of genes with S. Typhimurium, several unique gene clusters known as pathogenicity islands and other genes have been acquired during evolution. The inactivation of single genes, as well as the acquisition or loss of single genes or large islands of DNA, may have contributed to host adaptation and restriction of S. Typhi.

One of the most specific gene products is the polysaccharide capsule Vi (virulence), which is present in approximately 90% of all freshly isolated S. Typhi and has a protective effect against the bactericidal action of the serum of infected patients.

EPIDEMIOLOGY

It is estimated that more than 26.9 million typhoid fever cases occur annually, of which 1% result in death. The vast majority of this disease burden is witnessed in Asia. Additionally, an estimated 5.4 million cases caused by paratyphoid occur each year. In 2010, 13.5 million cases of typhoid fever were recorded, and both typhoid and paratyphoid fevers together accounted for more than 12 million disability-adjusted life years. The mortality caused by typhoid fever in the same year was found to be 7.2 per 100,000 population for the sub-Saharan region of Africa. Given the paucity of microbiologic facilities in developing countries, these figures may be more representative of the clinical syndrome rather than of culture-proven disease. In most developed countries, the incidence of typhoid fever is <15 cases per 100,000 population, with most cases occurring in travelers. In contrast, the incidence may vary considerably in the developing world, with estimated rates ranging from 100-1,000 cases per 100,000 population. There are significant differences in the age distribution and population at risk. Population-based studies from South Asia also indicate that the age-specific incidence of typhoid fever may be highest in children younger than 5 yr of age, in association with comparatively higher rates of complications and hospitalization.

Typhoid fever is notable for the emergence of drug resistance. Following sporadic outbreaks of chloramphenicol-resistant S. Typhi infections, many strains of S. Typhi have developed plasmid-mediated multidrug resistance to all 3 of the primary antimicrobials: ampicillin, chloramphenicol, and trimethoprim-sulfamethoxazole. There is also a considerable increase in nalidixic acid–resistant isolates of S. Typhi, as well as the emergence of fluoroquinolone-resistant isolates. Nalidixic acid–resistant isolates first emerged in Southeast Asia and India, and now account for the majority of travel-associated cases of typhoid fever in the United States.

S. Typhi is highly adapted to infection of humans to the point that it has lost the ability to cause transmissible disease in other animals. The discovery of the large number of pseudogenes in S. Typhi suggests that the genome of this pathogen has undergone degeneration to facilitate a specialized association with the human host. Thus, direct or indirect contact with an infected person (sick or chronic carrier) is a prerequisite for infection. Ingestion of foods or water contaminated with S. Typhi from human feces is the most common mode of transmission, although waterborne outbreaks as a consequence of poor sanitation or contamination have been described in developing countries. In other parts of the world, oysters and other shellfish cultivated in water contaminated by sewage and the use of night soil as fertilizer may also cause infection.

PATHOGENESIS

Enteric fever occurs through the ingestion of the organism, and a variety of sources of fecal contamination have been reported, including street foods and contamination of water reservoirs.

Human volunteer experiments established an infecting dose of about 10^7–10^8 organisms, with an incubation period ranging from 4-14 days, depending on the inoculating dose of viable bacteria. After ingestion, S. Typhi organisms are thought to invade the body through the gut mucosa in the terminal ileum, possibly through specialized antigen-sampling cells known as M cells that overlie gut-associated lymphoid tissues, through enterocytes, or via a paracellular route. S. Typhi crosses the intestinal mucosal barrier after attachment to the microvilli by an intricate mechanism involving membrane ruffling, actin rearrangement, and internalization in an intracellular vacuole. In contrast to NTS, S. Typhi expresses virulence factors that allow it to downregulate the pathogen recognition receptor–mediated host inflammatory response. Within the Peyer patches in the terminal ileum, S. Typhi can traverse the intestinal barrier through several mechanisms, including the M cells in the follicle-associated epithelium, epithelial cells, and dendritic cells. At the villi, Salmonella can enter through the M cells or by passage through or between compromised epithelial cells.

On contact with the epithelial cell, S. typhi assembles type III secretion system encoded on SPI-1 and translocates effectors into the cytoplasm. These effectors activate host Rho guanosine triphosphatases, resulting in the rearrangement of the actin cytoskeleton into membrane ruffles, induction of mitogen-activated protein kinase pathways,
and destabilization of tight junctions. Changes in the actin cytoskeleton are further modulated by the actin-binding proteins SipA and SipC and lead to bacterial uptake. Mitogen-activated protein kinase signaling activates the transcription factors activator protein-1 and nuclear factor-κB, which turn on production of IL-8. The destabilization of tight junctions allows the transmigration of polymorphonuclear leukocytes from the basolateral surface to the apical surface, paracellular fluid leakage, and access of bacteria to the basolateral surface. Shortly after internalization of S. Typhi by macropinocytosis, salmonellae are enclosed in a spacious phagosome that is formed by membrane ruffles. Later, the phagosome fuses with lysosomes, acidifies, and shrinks to become adherent around the bacterium, forming the Salmonella-containing vacuole. Type III secretion system encoded on SPI-2 is induced within the Salmonella-containing vacuole and translocates effector proteins SifA and PipB2, which contribute to Salmonella-induced filament formation along microtubules. The S. Typhi toxin has been isolated and characterized composed of 2 A subunits, PltA and CdtB, which are homologs of the A subunits of the pertussis and cytotoxic lethal distending toxins, respectively. Its single B subunit, PltB, is a DNase that inflicts DNA damage and induces cell-cycle arrest. CdtB is a DNase that inflicts DNA damage and induces cell-cycle arrest. S. Typhi produces typhoid toxin only within mammalian cells, and the toxin is then ferried to the extracellular environment by a unique transport mechanism that involves vesicle carrier intermediates (Fig. 198-4). These findings open the door to future opportunities for developing diagnostic and preventive strategies.

After passing through the intestinal mucosa, S. Typhi organisms enter the mesenteric lymphoid system and then pass into the bloodstream via the lymphatics. This primary bacteremia is usually asymptomatic, and blood culture results are frequently negative at this stage of the disease. The bloodborne bacteria are disseminated throughout the body and are thought to colonize the organs of the reticuloendothelial system, where they may replicate within macrophages. After a period of bacterial replication, S. Typhi organisms are shed back into the blood, causing a secondary bacteremia that coincides with the onset of clinical symptoms and marks the end of the incubation period.

In vitro studies with human cell lines have shown qualitative and quantitative differences in the epithelial cell response to S. Typhi and S. Typhimurium with regard to cytokine and chemokine secretion. Thus, by avoiding the triggering of an early inflammatory response in the gut, S. Typhi could instead colonize deeper tissues and organ systems. Infection with S. Typhi produces an inflammatory response in the deeper mucosal layers and underlying lymphoid tissue, with hyperplasia of Peyer patches and subsequent necrosis and sloughing of overlying epithelium. The resulting ulcers can bleed but usually heal without scarring or stricture formation. The inflammatory lesion may occasionally penetrate the muscularis and serosa of the intestine and produce perforation. The mesenteric lymph nodes, liver, and spleen are hyperemic and generally have areas of focal necrosis as well. A mononuclear response may be seen in the bone marrow in association with areas of focal necrosis. The morphologic changes of S. Typhi infection are less prominent in infants than in older children and adults.

It is thought that several virulence factors, including type III secretion system encoded on SPI-2, may be necessary for the virulence properties and ability to cause systemic infection. The surface Vi polysaccharide capsular antigen found in S. Typhi interferes with phagocytosis by preventing the binding of C3 to the surface of the bacterium. The ability of organisms to survive within macrophages after phagocytosis is an important virulence trait encoded by the PhoP regulon and may be related to metabolic effects on host cells. The occasional occurrence of diarrhea may be explained by the presence of a toxin related to cholera toxin and E. coli heat-labile enterotoxin. The clinical syndrome of fever and systemic symptoms is produced by a release of proinflammatory cytokines (IL-6, IL-1β, and TNF-α) from the infected cells.

In addition to the virulence of the infecting organisms, host factors and immunity may also play an important role in predisposition to infection. There is an association between susceptibility to typhoid fever and human genes within the major histocompatibility complex class II and class III loci. Patients who are infected with HIV are at significantly higher risk for clinical infection with S. Typhi and S. Paratyphi. Similarly, patients with Helicobacter pylori infection have an increased risk of acquiring typhoid fever.

Infectious Diseases

Clinical Features

The incubation period of typhoid fever is usually 7-14 days but depends on the infecting dose and ranges between 3 and 30 days. The clinical presentation varies from a mild illness with low-grade fever, malaise, and slight, dry cough to a severe clinical picture with abdominal discomfort and multiple complications.

Many factors influence the severity and overall clinical outcome of the infection. They include the duration of illness before the initiation of appropriate therapy, choice of antimicrobial treatment, age, previous exposure or vaccination history, virulence of the bacterial strain, quantity of inoculum ingested, and several host factors affecting immune status.

The presentation of typhoid fever may also differ according to age. Although data from South America and parts of Africa suggest that typhoid may manifest as a mild illness in young children, presentation may vary in different parts of the world. There is emerging evidence from South Asia that the presentation of typhoid may be more dramatic in children younger than 5 yr of age, with comparatively higher rates of complications and hospitalization. Diarrhea, toxicity, and complications such as disseminated intravascular coagulopathy are also more common in infancy, resulting in higher case fatality rates. However, some of the other features and complications of typhoid fever seen in adults, such as relative bradycardia, neurologic manifestations, and gastrointestinal bleeding, are rare in children.

Typhoid fever usually manifests as high-grade fever with a wide variety of associated features, such as generalized myalgia, abdominal pain, hepatosplenomegaly, abdominal pain, and anorexia (Table 198-5). In children, diarrhea may occur in the earlier stages of the illness and may be followed by constipation. In the absence of localizing signs, the early stage of the disease may be difficult to differentiate from other endemic diseases such as malaria and dengue fever. The fever may rise gradually, but the classic stepladder rise of fever is relatively rare. In approximately 25% of cases, a macular or maculopapular rash (rose spots) may be visible around the 7th-10th day of the illness, and lesions may appear in crops of 10-15 on the lower chest and abdomen and last 2-3 days (Fig. 198-5). These lesions may be difficult to see in dark-skinned children. Patients managed as outpatients present with fever (99%) but have less emesis, diarrhea, hepatomegaly, splenomegaly, and myalgias than patients who require admission to the hospital.

The presentation of typhoid fever may be tempered by coexisting morbidities and early diagnosis and administration of antibiotics. In malaria-endemic areas and in parts of the world where schistosomiasis is common, the presentation of typhoid may also be atypical. It is also recognized that multidrug-resistant S. Typhi infection is a more severe clinical illness with higher rates of toxicity, complications, and case fatality rates, which may be related to the greater virulence as well as higher numbers of circulating bacteria. The emergence of typhoid infections resistant to nalidixic acid and fluoroquinolones is associated with higher rates of morbidity and treatment failure. These findings may have implications for treatment algorithms, especially in endemic areas with high rates of multidrug-resistant and nalidixic acid– or fluoroquinolone-resistant typhoid.

If no complications occur, the symptoms and physical findings gradually resolve within 2-4 wk; however, the illness may be associated with malnutrition in a number of affected children. Although enteric fever caused by S. Paratyphi organisms has been classically regarded as a milder illness, there have been several outbreaks of infection with drug-resistant S. Paratyphi A, suggesting that paratyphoid fever may also be severe, with significant morbidity and complications.

Complications

Although altered liver function is found in many patients with enteric fever, clinically significant hepatitis, jaundice, and cholecystitis are relatively rare and may be associated with higher rates of adverse outcome. Intestinal hemorrhage (<1%) and perforation (0.5-1%) are infrequent among children. Intestinal perforation may be preceded by a marked increase in abdominal pain (usually in the right lower quadrant), tenderness, vomiting, and features of peritonitis. Intestinal

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**Table 198-5** Common Clinical Features of Typhoid Fever in Children

<table>
<thead>
<tr>
<th>FEATURE</th>
<th>RATE (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High-grade fever</td>
<td>95</td>
</tr>
<tr>
<td>Coated tongue</td>
<td>76</td>
</tr>
<tr>
<td>Anorexia</td>
<td>70</td>
</tr>
<tr>
<td>Vomiting</td>
<td>39</td>
</tr>
<tr>
<td>Hepatomegaly</td>
<td>37</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>36</td>
</tr>
<tr>
<td>Toxicity</td>
<td>29</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>21</td>
</tr>
<tr>
<td>Pallor</td>
<td>20</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>17</td>
</tr>
<tr>
<td>Constipation</td>
<td>7</td>
</tr>
<tr>
<td>Headache</td>
<td>4</td>
</tr>
<tr>
<td>Jaundice</td>
<td>2</td>
</tr>
<tr>
<td>Obtundation</td>
<td>2</td>
</tr>
<tr>
<td>Ileus</td>
<td>1</td>
</tr>
<tr>
<td>Intestinal perforation</td>
<td>0.5</td>
</tr>
</tbody>
</table>

*Data collected in Karachi, Pakistan, from 2,000 children.

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**Figure 198-5 A**, A rose spot in a volunteer with experimental typhoid fever. **B**, A small cluster of rose spots is usually located on the abdomen. These lesions may be difficult to identify, especially in dark-skinned people. (From Huang DB, DuPont HL: Problem pathogens: extra-intestinal complications of Salmonella enterica serotype Typhi infection, Lancet Infect Dis 5:341–348, 2005.)
Extraintestinal Infectious Complications of Typhoid Fever Caused By Salmonella enterica Serotype Typhi

<table>
<thead>
<tr>
<th>ORGAN SYSTEM INVOLVED</th>
<th>PREVALENCE (%)</th>
<th>RISK FACTORS</th>
<th>COMPLICATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central nervous system</td>
<td>3-35</td>
<td>Residence in endemic region, malignancy, endocarditis, congenital heart disease, paranasal sinus infections, pulmonary infections, meningitis, trauma, surgery, and osteomyelitis of the skull</td>
<td>Encephalopathy, cerebral edema, subdural empyema, cerebral abscess, meningitis, ventriculitis, transient parkinsonism, motor neuron disorders, ataxia, seizures, Guillain-Barré syndrome, psychosis</td>
</tr>
<tr>
<td>Cardiovascular system</td>
<td>1-5</td>
<td>Cardiac abnormalities—e.g., existing valvular abnormalities, rheumatic heart disease, or congenital heart defects</td>
<td>Endocarditis, myocardiitis, pericarditis, arteritis, congestive heart failure</td>
</tr>
<tr>
<td>Pulmonary system</td>
<td>1-6</td>
<td>Residence in endemic region, past pulmonary infection, sickle cell anemia, alcohol abuse, diabetes, HIV infection</td>
<td>Pneumonia, empyema, bronchopleural fistula</td>
</tr>
<tr>
<td>Bone and joint</td>
<td>&lt;1</td>
<td>Sickle cell anemia, diabetes, systemic lupus erythematosus, lymphoma, liver disease, previous surgery or trauma, extremes of age, and steroid use</td>
<td>Osteomyelitis, septic arthritis</td>
</tr>
<tr>
<td>Hepatobiliary system</td>
<td>1-26</td>
<td>Residence in endemic region, pyogenic infections, intravenous drug use, splenic trauma, HIV, hemoglobinopathy</td>
<td>Cholecystitis, hepatitis, hepatic abscesses, splenic abscess, peritonitis, paralytic ileus</td>
</tr>
<tr>
<td>Genitourinary system</td>
<td>&lt;1</td>
<td>Urinary tract, pelvic pathologies, and systemic abnormalities</td>
<td>Urinary tract infection, renal abscess, pelvic infections, testicular abscess, prostatitis, epididymitis</td>
</tr>
<tr>
<td>Soft-tissue infections</td>
<td>At least 17 cases reported in the English language literature</td>
<td>Diabetes</td>
<td>Psos abscess, gluteal abscess, cutaneous vasculitis</td>
</tr>
<tr>
<td>Hematologic</td>
<td>At least 5 cases reported in the English language literature</td>
<td></td>
<td>Hemophagocytosis syndrome</td>
</tr>
</tbody>
</table>


perforation and peritonitis may be accompanied by a sudden rise in pulse rate, hypotension, marked abdominal tenderness and guarding, and subsequent abdominal rigidity. A rising white blood cell count with a left shift and free air on abdominal radiographs may be seen in such cases.

Rare complications include toxic myocarditis, which may manifest as arrhythmias, sinoatrial block, or cardiogenic shock (Table 198-6). Neurologic complications are also relatively uncommon among children; they include delirium, psychosis, increased intracranial pressure, acute cerebellar ataxia, chorea, deafness, and Guillain-Barré syndrome. Although case fatality rates may be higher with neurologic manifestations, recovery usually occurs with no sequelae. Other reported complications include fatal bone marrow necrosis, disseminated intravascular coagulopathy, hemolytic–uremic syndrome, pyelonephritis, nephrotic syndrome, meningitis, endocarditis, parotitis, orchitis, and suppurative lymphadenitis.

The propensity to become a carrier follows the epidemiology of gallbladder disease, increasing with patient age and the antibiotic resistance of the prevalent strains. Although limited data are available, rates of chronic carriage are generally lower in children than adults.

**DIAGNOSIS**

The mainstay of the diagnosis of typhoid fever is a positive result of culture from the blood or another anatomic site. Results of blood cultures are positive in 40-60% of the patients seen early in the course of the disease, and stool and urine culture results become positive after the 1st wk. The stool culture result is also occasionally positive during the incubation period. However, the sensitivity of blood cultures in diagnosing typhoid fever in many parts of the developing world is limited because widespread liberal antibiotic use may render bacteriologic confirmation difficult. Although bone marrow cultures may increase the likelihood of bacteriologic confirmation of typhoid, collection of the specimens is difficult and relatively invasive.

Results of other laboratory investigations are nonspecific. Although blood leukocyte counts are frequently low in relation to the fever and toxicity, there is a wide range in counts; in younger children leukocytosis is common and may reach 20,000-25,000 cells/µL. Thrombocytopenia may be a marker of severe illness and may accompany disseminated intravascular coagulopathy. Liver function test results may be deranged, but significant hepatic dysfunction is rare.

The classic Widal test measures antibodies against O and H antigens of S. Typhi but lacks sensitivity and specificity in endemic areas. Because many false-positive and false-negative results occur, diagnosis of typhoid fever by Widal test alone is prone to error. Other relatively newer diagnostic tests using monoclonal antibodies have been developed that directly detect S. Typhi–specific antigens in the serum or S. Typhi Vi antigen in the urine. However, few have proved sufficiently robust in large-scale evaluations. A nested polymerase chain reaction analysis using H1-d primers has been used to amplify specific genes of S. Typhi in the blood of patients; it is a promising means of making a rapid diagnosis, especially given the low level of bacteremia in enteric fever. Despite these innovations, the mainstay of diagnosis of typhoid remains clinical in much of the developing world, and several diagnostic algorithms have been evaluated in endemic areas.

**DIFFERENTIAL DIAGNOSIS**

In endemic areas, typhoid fever may mimic many common febrile illnesses without localizing signs. In children with multisystem features and no localizing signs, the early stages of enteric fever may be confused with alternative conditions, such as acute gastroenteritis,
bronchitis, and bronchopneumonia. Subsequently, the differential diagnosis includes malaria; sepsis with other bacterial pathogens; infections caused by intracellular microorganisms, such as tuberculosis, brucellosis, tularemia, leptospirosis, and rickettsial diseases; and viral infections such as Dengue fever, acute hepatitis, and infectious mononucleosis.

**TREATMENT**

An early diagnosis of typhoid fever and institution of appropriate treatment are essential. The vast majority of children with typhoid fever can be managed at home with oral antibiotics and close medical follow-up for complications or failure of response to therapy. Patients with persistent vomiting, severe diarrhea, and abdominal distention may require hospitalization and parenteral antibiotic therapy.

There are general principles of typhoid fever management. Adequate rest, hydration, and attention are important to correct fluid and electrolyte imbalance. Antipyretic therapy (acetaminophen 10-15 mg/kg every 4-6 hr PO) should be provided as required. A soft, easily digestible diet should be continued unless the patient has abdominal distention or ileus. Antibiotic therapy is critical to minimize complications (Table 198-7). It has been suggested that traditional therapy with either chloramphenicol or amoxicillin is associated with relapse rates of 5-15% and 4-8%, respectively, whereas use of the quinolones and third-generation cephalosporins is associated with higher cure rates. The antibiotic treatment of typhoid fever in children is also influenced by the prevalence of antimicrobial resistance. Over the past 2 decades, emergence of multidrug-resistant strains of S. Typhi (i.e., isolates fully resistant to amoxicillin, trimethoprim-sulfamethoxazole, and chloramphenicol) has necessitated treatment with fluoroquinolones, which are the antimicrobial drug of choice for treatment of salmonellosis in adults, with cephalosporins as an alternative. The emergence of resistance to quinolones places tremendous pressure on public health systems because alternative therapeutic options are limited.

Although some investigators suggest that children with typhoid fever should be treated with fluoroquinolones like adults, others question this approach on the basis of the potential development of further resistance to fluoroquinolones and the fact that quinolones are still not approved for widespread use in children. A Cochrane systematic review of the treatment of typhoid fever also indicates that there is little evidence to support the carte blanche administration of fluoroquinolones in all cases of typhoid fever. Azithromycin may be an alternative antibiotic for children with uncomplicated typhoid fever.

In addition to antibiotics, the importance of supportive treatment and maintenance of appropriate fluid and electrolyte balance must be underscored. Although additional treatment with dexamethasone (3 mg/kg for the initial dose, followed by 1 mg/kg every 6 hr for 48 hr) is recommended for severely ill patients with shock, obtundation, stupor, or coma; corticosteroids should be administered only under strict controlled conditions and supervision, because their use may mask signs of abdominal complications.

**PROGNOSIS**

The prognosis for a patient with enteric fever depends on the rapidity of diagnosis and institution of appropriate antibiotic therapy. Other factors are the patient’s age, general state of health, and nutrition, the causative Salmonella serotype, and the appearance of complications. Infants and children underling maternal malnutrition and patients infected with multidrug-resistant isolates are at higher risk for adverse outcomes.

Despite appropriate therapy, 2-4% of infected children may experience relapse after initial clinical response to treatment. Individuals who excrete S. Typhi for 3 mo or longer after infection are regarded as chronic carriers. The risk for becoming a carrier is low in children (<2% for all infected children) and increases with age. A chronic urinary carrier state can develop in children with schistosomiasis.

**PREVENTION**

Of the major risk factors for outbreaks of typhoid fever, contamination of water supplies with sewage is the most important. Other risk factors for development of typhoid fever are congestion, contact with another patient or a febrile individual, and lack of water and sanitation services. During outbreaks, central chlorination as well as domestic water purification is important. In endemic situations, consumption of street foods, especially ice cream and cut fruit, is recognized as an important risk factor. The human-to-human spread by chronic carriers is also important, and attempts should be made to target food handlers and

### Table 198-7

<table>
<thead>
<tr>
<th>SUSCEPTIBILITY</th>
<th>ANTIBIOTIC</th>
<th>DAILY DOSE (mg/kg/day)</th>
<th>DAYS</th>
<th>ANTI-BIOTIC</th>
<th>DAILY DOSE (mg/kg/day)</th>
<th>DAYS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>UNCOMPLICATED TYPHOID FEVER</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fully sensitive</td>
<td>Chloramphenicol</td>
<td>50-75</td>
<td>14-21</td>
<td>Fluoroquinolone, e.g., ofloxacin or ciprofloxacin</td>
<td>15</td>
<td>5-7*</td>
</tr>
<tr>
<td>Multidrug-resistant</td>
<td>Amoxicillin</td>
<td>75-100</td>
<td>14</td>
<td>Ceftriaxone</td>
<td>75</td>
<td>10-14</td>
</tr>
<tr>
<td>or</td>
<td>Fluoroquinolone</td>
<td>15</td>
<td>5-7</td>
<td>Azithromycin</td>
<td>8-10</td>
<td>7</td>
</tr>
<tr>
<td>or</td>
<td>Cefixime</td>
<td>15-20</td>
<td>7-14</td>
<td>Cefixime</td>
<td>15-20</td>
<td>7-14</td>
</tr>
<tr>
<td>or</td>
<td>Azithromycin</td>
<td>8-10</td>
<td>7</td>
<td>Cefixime</td>
<td>20</td>
<td>7-14</td>
</tr>
<tr>
<td>or</td>
<td>Ceftriaxone</td>
<td>75</td>
<td>10-14</td>
<td>Fluoroquinolone</td>
<td>100</td>
<td>14-21</td>
</tr>
<tr>
<td><strong>SEVERE TYPHOID FEVER</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fully sensitive</td>
<td>Fluoroquinolone, e.g., ofloxacin</td>
<td>15</td>
<td>10-14</td>
<td>Chloramphenicol</td>
<td>100</td>
<td>14-21</td>
</tr>
<tr>
<td>Multidrug-resistant</td>
<td>Fluoroquinolone</td>
<td>15</td>
<td>10-14</td>
<td>Azithromycin</td>
<td>60</td>
<td>10-14</td>
</tr>
<tr>
<td>Quinolone-resistant†</td>
<td>Ceftriaxone</td>
<td>60</td>
<td>10-14</td>
<td>Cefotaxime</td>
<td>80</td>
<td>10-14</td>
</tr>
</tbody>
</table>

*3-day course is also effective, particularly for epidemic containment.
†The optimum treatment for quinolone-resistant typhoid fever has not been determined. Azithromycin, third-generation cephalosporins, or high-dose fluoroquinolones for 10-14 days is effective.

high-risk groups for S. Typhi carriage screening. Once identified, chronic carriers must be counseled as to the risk for disease transmission and the importance of handwashing.

The classic heat-inactivated whole-cell vaccine for typhoid is associated with an unacceptably high rate of side effects and has been largely withdrawn from public health use. Globally, 2 vaccines are currently available for potential use in children. An oral, live-attenuated preparation of the Ty21a strain of S. Typhi has good efficacy (67-82%) for up to 5 yr. Significant adverse effects are rare. The Vi capsular polysaccharide can be used in people 2 yr of age and older. It is given as a single intramuscular dose, with a booster every 2 yr, and has a protective efficacy of 70-80%. The vaccines are currently recommended for anyone traveling into endemic areas, but a few countries have introduced large-scale vaccination strategies. Previous studies in South America have demonstrated protection against typhoid fever among schoolchildren with the use of an oral attenuated Ty21 strain vaccine.

Several large-scale demonstration projects using the Vi polysaccharide vaccine in Asia have demonstrated protective efficacy against typhoid fever across all age groups, but the data on protection among young children (<5 yr) showed important differences between studies. The recent Vi-conjugate vaccine has a protective efficacy exceeding 90% in younger children and may offer protection in parts of the world where a large proportion of preschool children are at risk for the disease enteric or typhoid fever.

_**Bibliography is available at Expert Consult.**_
Chapter 198  Salmonella 1393.e1

Bibliography
Chapter 199  Shigella  Theresa J. Ochoa and Thomas G. Cleary

Shigella causes an acute invasive enteric infection clinically manifested by diarrhea that is often bloody. The term *dysentery* is used to describe the syndrome of bloody diarrhea with fever, abdominal cramps, rectal pain, and mucoid stools. Bacillary dysentery is a term often used to distinguish dysentery caused by *Shigella* from amoebic dysentery caused by *Entamoeba histolytica*.

**ETIOLOGY**

Four species of *Shigella* are responsible for bacillary dysentery: *Shigella dysenteriae* (serogroup A), *Shigella flexneri* (serogroup B), *Shigella boydii* (serogroup C), and *Shigella sonnei* (serogroup D). There are 15 serotypes in group A, 19 serotypes in group B, 19 serotypes in group C, and one serotype in group D. Species classification has important therapeutic implications because the species differ in both geographic distribution and antimicrobial susceptibility.

**EPIDEMIOLOGY**

It is estimated that there are approximately 80-165 million cases of shigellosis each year worldwide, resulting in more than 1 million deaths; most of these cases and deaths occur in developing countries. Studies estimate similar illness rates but fewer deaths because of a decrease in the case-fatality rates. In the United States, approximately 14,000 cases per year are documented, although it is thought that the actual frequency of infection is 450,000 cases annually. *Shigella* is the third most important pathogen identified in the Foodborne Disease Active Surveillance Network in the United States. Although infection can occur at any age, it is most common in the 2nd and 3rd yr of life. Approximately 70% of all episodes and 60% of all *Shigella*-related deaths involve children younger than 5 yr of age. Infection in the 1st 6 mo of life is rare for reasons that are not clear. Breast milk from women living in endemic areas contains antibodies to both virulence plasmid-coded antigens and lipopolysaccharides, and breastfeeding might partially explain the age-related incidence.

Asymptomatic infection of children and adults occurs commonly in endemic areas. Infection with *Shigella* occurs most often during the warm months in temperate climates and during the rainy season in tropical climates. Both sexes are affected equally. In industrialized societies, *S. sonnei* is the most common cause of bacillary dysentery, with *S. flexneri* second in frequency; in preindustrial societies, *S. flexneri* is most common, with *S. sonnei* second in frequency. *S. boydii* is found primarily in India. *S. dysenteriae* serotype 1 tends to occur in massive epidemics, although it is also endemic in Asia and Africa, where it is associated with high mortality rates (5-15%). However, *Shigella* has shown temporal procession in serogroup dominance. Recently, epidemiologic transition has favored the emergence of *S. sonnei* as the dominant serogroup in some countries, although the reason for this is not clear.

Contaminated food (often a salad or other item requiring extensive handling of the ingredients) and water are important vectors. Exposure to both fresh and saltwater is a risk factor for infection. Rapid spread within families, custodial institutions, and childcare centers demonstrates the ability of shigellae to be transmitted from 1 individual to the next and the requirement for ingestion of very few organisms to cause illness. As few as 10 *S. dysenteriae* serotype 1 organisms can cause dysentery. In contrast, ingestion of 10^4-10^5 *Vibrio cholerae* is necessary to cause cholera.

**PATHOGENESIS**

*Shigella* has specialized mechanisms to survive the low gastric pH. *Shigella* survives the acid environment in the stomach and moves through the gut to the colon, its target organ. The basic virulence trait shared by all shigellae is the ability to invade colonic epithelial cells by turning on a series of temperature-regulated proteins. This invasion mechanism is encoded on a large (220 kb) plasmid that at body temperature synthesizes of a group of polypeptides involved in cell invasion and killing. Shigellae that lose the virulence plasmid are no longer pathogenic. Enteroinvasive *Escherichia coli* that harbor a closely related plasmid containing these invasion genes behave clinically like shigellae. The virulence plasmid encodes a type III secretion system required to trigger entry into epithelial cells and apoptosis in macrophages. This secretion system translocates effector molecules from the bacterial cytoplasm to the membrane and cytoplasm of target host cells. The type III secretion system is composed of approximately 50 proteins, including the Mxi and Spa proteins involved in assembly and regulation of the type III secretion system, chaperones (IpgA, IpgC, IpgE, and Spa15), transcription activators (VirF, VirB, and MxiE), translocators (IpaB, IpaC, and IpaD), and approximately 30 effector proteins. In addition to the major plasmid-encoded virulence traits, chromosomally encoded factors are also required for full virulence.

*Shigella* passes the epithelial cell barrier by transcytosis through M cells and encounters resident macrophages. The bacteria evade degradation in macrophages by inducing apoptosis, which is accompanied by proinflammatory signaling. Free bacteria invade the epithelial cells from the basolateral side, move into the cytoplasm by actin polymerization, and spread to adjacent cells. Proinflammatory signaling by macrophages and epithelial cells further activates the innate immune response involving natural killer cells and attracts polymorphonuclear leukocytes (PMNs). The influx of PMNs disintegrates the epithelial cell lining, which initially exacerbates the infection and tissue destruction by facilitating the invasion of more bacteria. Ultimately, PMNs phagocytose and kill *Shigella*, thus contributing to the resolution of the infection.

Some shigellae make toxins, including *Shiga* toxin and enterotoxins. *Shiga* toxin is a potent exotoxin that inhibits protein synthesis and is produced in significant amounts by *S. dysenteriae* serotype 1, by a subset of *E. coli*, which are known as enterohemorrhagic or *Shiga* toxin–producing *E. coli*, and occasionally by other organisms. *Shiga* toxin inhibits protein synthesis to injure vascular endothelial cells to trigger the severe complication of hemolytic-uremic syndrome.
Targeted deletion of the genes for other enterotoxins (ShET1 and ShET2) has decreased the incidence of fever and dysentery in volunteers during vaccine-development studies. Lipopolysaccharides are virulence factors for all shigellae; other traits are important for only a few serotypes (e.g., Shiga toxin synthesis by S. dysenteriae serotype 1 and ShET1 by S. flexneri 2a).

The pathologic changes of shigellosis take place primarily in the colon. The changes are most intense in the distal colon, although pan-colitis can occur. Shigellae cross the colonic epithelium through M cells in the follicle-associated epithelium overlying the Peyer patches. Grossly, localized or diffuse mucosal edema, ulcerations, friable mucosa, bleeding, and exudate may be seen. Microscopically, ulcerations, pseudomembranes, epithelial cell death, infiltration extending from the mucosa to the muscularis mucosae by PMNs and mononuclear cells, and submucosal edema occur.

**IMMUNITY**

Innate immunity to Shigella infection is characterized by the induction of acute inflammation with massive recruitment of PMNs and subsequently massive tissue destruction. In humans, analysis of cytokine expression in rectal biopsies of infected patients at the acute phase of the disease has revealed upregulation of proinflammatory genes, such as those encoding interleukin (IL)-1β, IL-6, IL-8, tumor necrosis factor-α, and tumor necrosis factor-β, although antiinflammatory genes encoding IL-10 and transforming growth factor-β are also upregulated. Control of Shigella invasion in intestinal epithelial cells depends on interferon-γ. Shigella-specific immunity elicited upon natural infection is characterized by the induction of a humoral response. Local secretory immunoglobulin A and serum immunoglobulin G are produced against lipopolysaccharide and some protein effectors (Ipsas). Protection is thought to be serotype specific. Natural protective immunity arises only after several episodes of infection, is of short duration, and seems to be effective in limiting reinfection, particularly in very young children.

**CLINICAL MANIFESTATIONS AND COMPLICATIONS**

**Bacillary dysentery is clinically similar regardless of infecting serotype.** There are some clinical differences, particularly relating to the greater severity and risk of complications with S. dysenteriae serotype 1 infection. Ingestion of shigellae is followed by an incubation period of 12 hr to several days before symptoms ensue. Severe abdominal pain, high fever, emesis, anorexia, generalized toxicity, urgency, and painful defecation characteristically occur. The diarrhea may be watery and of large volume initially, evolving into frequent, small-volume, bloody mucoid stools. Most children never progress to the stage of bloody diarrhea, but some have bloody stools from the outset. Significant dehydration is related to the fluid and electrolyte losses in feces and emesis. Untreated diarrhea can last 7–10 days; only approximately 10% of patients have diarrhea persisting for longer than 10 days. Persistent diarrhea occurs in malnourished infants, children with AIDS, and occasionally previously normal children. Even nondysenteric disease can be complicated by persistent illness.

Physical examination initially shows abdominal distention and tenderness, hyperactive bowel sounds, and a tender rectum on digital examination. Rectal prolapse may be present, particularly in malnourished children. Neurologic findings are among the most common extraintestinal manifestations of bacillary dysentery, occurring in as many as 40% of hospitalized children. Enteroinvasive E. coli can cause similar neurologic toxicity. Convulsions, headache, lethargy, confusion, nuchal rigidity, or hallucinations may be present before or after the onset of diarrhea. The cause of these neurologic findings is not understood. In the past, these symptoms were attributed to the neurotoxicity of Shiga toxin, but it is now clear that this explanation is wrong because the organisms isolated from children with Shigella-related seizures are usually not Shiga toxin producers. Seizures sometimes occur when little fever is present, suggesting that simple febrile convulsions do not explain their appearance. Hypocalcemia or hyponatremia may be associated with seizures in a small number of patients. Although symptoms often suggest central nervous system infection and cerebrospinal fluid pleocytosis with minimally elevated protein levels can occur, meningitis caused by shigellae is rare. Based on animal studies, it has been suggested that proinflammatory mediators, including tumor necrosis factor-α and IL-1β, nitric oxide, and corticotropin-releasing hormone, all play a role in the enhanced susceptibility to seizures caused by S. dysenteriae.

The most common complication of shigellosis is dehydration. Inappropriate secretion of antidiuretic hormone with profound hyponatremia can complicate dysentery, particularly when S. dysenteriae is the etiologic agent. Hypoglycemia and protein-losing enteropathy are common and are decreased by early appropriate antibiotic therapy. Severe protein-losing enteropathy is associated with prolonged illness and linear growth shortfalls. Bacteremia is uncommon except in girls or women infected with HIV, malnourished children, young infants, and children with S. dysenteriae serotype 1 infection. When bacteremia occurs with dysentery (<5%), it is as likely to be caused by other enteric bacteria as well as by the Shigella itself. The presence of E. coli, Klebsiella, and other enteric bacteria in blood cultures of children with shigellosis may reflect loss of the barrier function during severe colitis. The mortality rate is high (~20%) when sepsis occurs and is far more common in those with HIV than in non–HIV-infected persons. Other major complications include disseminated intravascular coagulation, particularly in very young, malnourished children. Given that shigellae penetrate the intestinal mucosal barrier, these events are surprisingly uncommon.

Neonatal shigellosis is rare. Neonates may have only low-grade fever with mild, nonbloody diarrhea. However, complications occur more commonly than in older children and include septicemia, meningitis, dehydration, colonic perforation, and toxic megacolon.

S. dysenteriae serotype 1 infection is commonly complicated by hemolysis, anemia, and hemolytic-uremic syndrome. This syndrome is caused by Shiga toxin–mediated vascular endothelial injury. E. coli that produce Shiga toxins (e.g., E. coli O157:H7, E. coli O111:NM, E. coli O26:H11, and less commonly in many other serotypes) also cause hemolytic-uremic syndrome (see Chapter 518).

Rectal prolapse, toxic megacolon or pseudomembranous colitis (usually associated with S. dysenteriae), cholestatic hepatitis, conjunctivitis, iritis, corneal ulcers, pneumonia, arthritis (usually 2–5 wk after enteritis), reactive arthritis, cystitis, myocarditis, and vaginitis (typically with a blood-tinged discharge associated with S. flexneri) are uncommon events. Although rare, surgical complications of shigellosis can be severe; the most common are intestinal obstruction and appendicitis with and without perforation.

On average, severity of illness and risk of death are least with disease caused by S. sonnei and greatest with infection by S. dysenteriae type 1. Risk groups for severe illness and poor outcomes include infants; adults older than age 50 yr; children who are not breastfed; children with HIV or who are recovering from measles; malnourished children and adults; and patients who develop dehydration, unconsciousness, or hypo- or hyperthermia, hyponatremia, lesser stool frequency, or have a history of convulsion when first seen. Death is a rare outcome in well-nourished older children. Multiple factors contribute to death in malnourished children with shigellosis, including illness in the 1st yr of life, altered consciousness, dehydration, hypothermia, thrombocytopenia, anemia, hyponatremia, renal failure, hyperkalemia hypoglycemia, bronchopneumonia, and bacteremia.

The rare syndrome of severe toxicity, convulsions, extreme hyperpyrexia, and headache followed by brain edema and a rapidly fatal outcome without sepsis or significant dehydration (Ekiri syndrome or “lethal toxic encephalopathy”) is not well understood.

**DIFFERENTIAL DIAGNOSIS**

Although clinical features suggest shigellosis, they are insufficiently specific to allow confident diagnosis. Infection by Campylobacter jejuni, Salmonella spp., enteroinvasive E. coli, Shiga toxin–producing E. coli (e.g., E. coli O157:H7), Yersinia enterocolitica, Clostridium difficile,
and *E. histolytica*, as well as inflammatory bowel disease, can cause confusion.

**DIAGNOSIS**

Presumptive data supporting a diagnosis of bacillary dysentery include the finding of fecal leukocytes (usually >50 or 100 PMNs per high-power field, confirming the presence of colitis), fecal blood, and demonstration in peripheral blood of leukocytosis with a dramatic left shift (often with more bands than segmented neutrophils). The total peripheral white blood cell count is usually 5,000-15,000 cells/µL, although leukopenia and leukemoid reactions occur.

Culture of both stool and rectal swab specimens optimizes the chance of diagnosing *Shigella* infection. Culture media should include MacConkey agar as well as selective media such as xylose-lysine-deoxycholate and *Salmonella-Shigella* agar. Transport media should be used if specimens cannot be cultured promptly. Appropriate media should be used to exclude *Campylobacter* spp. and other agents. Studies of outbreaks and illness in volunteers show that the laboratory is often not able to confirm the clinical suspicion of shigellosis even when the pathogen is present. Studies using molecular methods such as polymerase chain reaction suggest that culture significantly underestimates the true frequency of infection. Quantitative polymerase chain reaction improves ascertainment of *Shigella* burden in children with moderate-to-severe diarrhea in low-income countries. However, these methods are usually available only in research laboratories. Multiple fecal cultures improve the yield of *Shigella*. The diagnostic inadequacy of cultures makes it incumbent on the clinician to use judgment in the management of clinical syndromes consistent with shigellosis. In children who appear to be toxic, blood cultures should be obtained, especially in very young or malnourished infants because of their increased risk of bacteremia.

**TREATMENT**

As with gastroenteritis from other causes, the first concern in a child with suspected shigellosis should be for fluid and electrolyte correction and maintenance (see Chapter 340). Drugs that retard intestinal motility (e.g., diphenoxylate hydrochloride with atropine [Lomotil] or loperamide [Imodium]) should not be used because of the risk of prolonging the illness.

Nutrition is a key concern in areas where malnutrition is common. A high-protein and high-caloric diet during convalescence enhances growth in the following 6 mo. Controlled studies show that cooked green bananas, a food rich in amylase-resistant starches, significantly improves outcome in severe disease. A single large dose of vitamin A (200,000 IU) lessens severity of shigellosis in settings where vitamin A deficiency is common. Zinc supplementation (20 mg elemental zinc for 14 days) significantly decreases the duration of diarrhea, improves weight gain during recovery and immune response to the *Shigella*, and decreases diarrheal disease in the subsequent 6 mo in malnourished children.

The next concern is a decision about the use of antibiotics. Although some authorities recommend withholding antibacterial therapy because of the self-limited nature of the infection, the cost of drugs, and the risk of emergence of resistant organisms, there is a persuasive logic in favor of empirical treatment of all children in whom shigellosis is strongly suspected. Even if not fatal, the untreated illness can cause a child to be quite ill for weeks; chronic or recurrent diarrhea can ensue. Malnutrition can develop and worsen in prolonged illness, particularly in children in developing countries. The risk of continued excretion and subsequent infection of family contacts further argues against the strategy of withholding antibiotics.

*Shigella* species have variable antimicrobial susceptibility. In general, *S. flexneri* tends to be more resistant than *S. boydii*. There are major geographic variations in antibiotic susceptibility of *Shigella*. In the United States, strains are commonly resistant to ampicillin (74%) and trimethoprim-sulfamethoxazole (TMP-SMX) (36%), but infrequently resistant to nalidixic acid (2%) or ciprofloxacin (0.5%); however, antimicrobial resistance in the United States differs by race, ethnicity, age, travel history, and species. In general, the proportion of antibiotic-resistant isolates is lower in North America and Europe than in Asia or Africa. For example, in China, *S. sonnei* is commonly resistant to TMP-SMX (94.5%), ampicillin (40.3%), piperacillin (36.5%), and ceftriaxone (12.8%). In general, *Shigella* are susceptible in vitro to azithromycin, ceftriaxone, cefotaxime, cefixime, nalidixic acid, and quinolones. However, resistance to these antibiotics is being reported in several regions. For example, nalidixic acid–resistant *Shigella* has rapidly developed in Asia and Africa; resistance to ciprofloxacin is increasingly common in India; resistance to azithromycin and ceftriaxone is reported in some countries.

Currently, in most developed and developing countries, *Shigella* strains are often resistant to ampicillin and TMP-SMX; therefore, these drugs should not be used for empirical treatment of suspected shigellosis; they may be used only if the strain is known to be susceptible (e.g., in an outbreak from a defined strain). Given the frequent occurrence of resistant organisms, optimal empirical therapy in children with dysentery should include azithromycin, a third-generation cephalosporin, nalidixic acid or ciprofloxacin. Ceftriaxone (50 mg/kg/24 hr as a single daily dose IV or IM) can be used for empirical therapy, especially for small infants. The oral third-generation cephalosporin cefixime (8 mg/kg/24 hr divided every 12-24 hr) can also be used; however, oral first- and second-generation cephalosporins are inadequate as alternative drugs despite in vitro susceptibility. Nalidixic acid (55 mg/kg/24 hr orally divided 4 times/day) is also an acceptable alternative drug when available. Azithromycin (12 mg/kg/24 hr orally for the 1st day, followed by 6 mg/kg/24 hr for the next 4 days) has proven to be an effective alternative drug for shigellosis. Ciprofloxacin (20-30 mg/kg/24 hr divided into 2 doses) used to be a back-up drug to treat shigellosis but is now the drug of choice recommended by the World Health Organization for all patients with bloody diarrhea, irrespective of their ages.

Although quinolones are reported to cause arthropathy in immature animals, the risk of joint damage in children appears to be minimal and is outweighed by the value of these drugs for treatment of this potentially life-threatening disease. However, some experts recommend that these agents be reserved for seriously ill children with bacillary dysentery caused by an organism that is suspected or known to be resistant to other agents, because overuse of quinolones promotes development of resistance to these drugs.

Treatment of patients in whom *Shigella* infection is suspected on clinical grounds of should be initiated when they are first evaluated. Stool culture is obtained to exclude other pathogens and to assist in antibiotic changes should a child fail to respond to empirical therapy. A child who has typical dysentery and who responds to initial empiric antibiotic treatment should be reevaluated for other possible diagnoses. The child who fails to respond to therapy of a dysenteric syndrome in the presence of initially negative stool culture results, additional cultures should be obtained and the child should be reevaluated for other possible diagnoses.

**PREVENTION**

Numerous measures have been recommended to decrease the risk of *Shigella* transmission to children. Mothers should be encouraged to prolong breastfeeding of infants. Families and daycare personnel should be educated in proper handwashing techniques and encouraged to wash hands after using the toilet, changing diapers, or engaging in preparation of foods. They should be taught how to manage potentially contaminated materials such as raw vegetables, soiled diapers, and diaper-changing areas. Children with diarrhea should be excluded from childcare facilities. Children should be supervised when handwashing after they use the toilet. Caretakers should be informed of the risk of transmission if they prepare food when they are ill with diarrhea. Families should be educated regarding the risk of swallowing contaminated water from ponds, lakes, or untreated pools. In
developing countries, a safe water supply and appropriate sanitation systems are important measures for reducing the risk for shigellosis. There is not yet a vaccine that is effective for preventing infection by *Shigella*. Measles immunization can substantially reduce the incidence and severity of diarrheal diseases, including shigellosis. Every infant should be immunized against measles at the recommended age.

*Bibliography is available at Expert Consult.*
Chapter 199  Shigella 1396.e1

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Chapter 200
Escherichia coli
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*Escherichia coli* are important causes of enteric infections as well as urinary tract infections (see Chapter 538), sepsis and meningitis in the newborn (see Chapter 109), and bacteremia and sepsis in immunocompromised patients (see Chapter 178) and in patients with intravascular devices (see Chapter 179). In patients with non-diarrhea-associated *E. coli* infections, a significant number of these pathogens have acquired transferrable plasmids resulting in extended-spectrum β-lactamase production. This results in resistance to penicillins, cephalosporins and aztreonam; carbapenems remain effective. Because *E. coli* is normal fecal flora, pathogenicity is defined by the expression of virulence characteristics and association of those traits with illness (Table 200-1). The mechanism by which *E. coli* produces diarrhea typically involves adherence of organisms to a glycoprotein or glycolipid receptor, followed by production of some noxious substance that injures or disturbs the function of intestinal cells. The genes for virulence properties and for antibiotic resistance are often carried on transferable plasmids, pathogenicity islands, or bacteriophages. In the developing world, the various diarrheagenic *E. coli* cause frequent infections in the first few years of life; diarrheagenic *E. coli* as a group are responsible for 30-40% of all diarrhea cases in children worldwide. They occur with increased frequency during the warm months in temperate climates and during rainy season months in tropical climates. Most diarrheagenic *E. coli* strains (except STEC) require a large inoculum of organisms to induce disease. Infection is most likely when food-handling or sewage-disposal practices are sub-optimal. The diarrheagenic *E. coli* are also important in North America and Europe, although their epidemiology is less-well defined in these areas than in the developing world. In North America, the various diarrheagenic *E. coli* may be the etiology of as much as 30% of infectious diarrhea in children younger than 5 yr of age.

Many studies have found diarrheagenic *E. coli* pathotypes in a significant proportion of asymptomatic healthy children living in developing countries. Fecal contamination (human and animal), which is common in the underprivileged environments in which many young children live, facilitates the transmission of pathogens. In addition, with current modern, highly sensitive microbiologic methods, small numbers of bacteria can be detected in stool samples. Therefore, it is important to assess the prevalence of various enteropathogens in children with and without diarrhea, to interpret results. Excretion of enteropathogens by subjects without diarrhea may be explained by characteristics of the pathogens (virulence heterogeneity), the host (host susceptibility, age, nutritional status, breastfeeding, immunity), and environmental factors (inoculum size).

**ENTEROTOXIGENIC ESCHERICHIA COLI**

*ETEC* account for a sizeable fraction of dehydrating infantile diarrhea in the developing world (10-30%) and of traveler's diarrhea (20-60% of cases); *ETEC* is the most common cause of traveler's diarrhea. In a recent large multicenter diarrhea study (GEMS [global enteric multicenter study]) heat-stable enterotoxin (ST)-*ETEC* (with or without coexpression of heat-labile enterotoxin [LT]), was among the most important causes of diarrhea in young children in developing countries and was associated with increased risk of death. The typical signs and symptoms include explosive watery, nonmucoid, nonbloody diarrhea, abdominal pain, nausea, vomiting, and little or no fever. The illness is usually self-limited and resolves in 3-5 days but occasionally lasts longer than 1 wk.

*ETEC* cause few or no structural alterations in the gut mucosa. Diarrhea is caused by colonization of the small intestine and subsequent elaboration of enterotoxins. *ETEC* strains secrete an LT and/or an ST, a large molecule consisting of 5 receptor-binding subunits and 1 enzymatically active subunit, is structurally, functionally, and immunologically related to cholera toxin produced by *Vibrio cholerae*. LT stimulates adenylate cyclase, resulting in increased cyclic adenosine monophosphate. ST is a small molecule not related to cholera toxin. ST stimulates guanylate cyclase, resulting in increased cyclic guanosine monophosphate. The genes for these toxins are encoded on plasmids.

Colonization of the intestine requires fimbrial colonization factor antigens (CFAs), which promote adhesion to the intestinal epithelium. CFAs are antigenic fimbriae that are currently targets for vaccine development. There are at least 25 CFA types; these antigens are composed of coli surface (CS) antigens and can be expressed alone or in combination. Prevalent colonization factors include CFA/I, CS1-CS7, CS14, and CS17. However, CFAs have not been detected on all *ETEC* strains. Although 30-50% of *ETEC* isolates have no characterized CFA by phenotypic screening, novel CFAs continue to be identified. The multiple CFAs and their allelic variants have made definition of immunity and development of useful vaccines difficult. A large proportion of strains produce a type IV pilus called *longus*, which functions as a colonization factor and is found among several other Gram-negative bacterial pathogens. *ETEC* strains also have the common pilus, produced by commensal and pathogenic *E. coli* strains. Among the non-fimbrial adhesions, *TbIA* is a potent bacterial adhesin that mediates bacterial attachment and invasion of cells. For many years, the O serogroup was used to distinguish pathogenic from commensal *E. coli*. Because the pathogenic *E. coli* are now defined and classified by using probes or primers for specific virulence genes, determining the O serogroup has become less important. Of the more than 180 *E. coli* serogroups, only a relatively small number typically are *ETEC*. The most common O groups are O6, O8, O128, and O153, and based on some large retrospective studies, these serogroups only account for half of the *ETEC* strains.

**ENTEROINVASIVE ESCHERICHIA COLI**

Clinically, EIEC infections present either with watery diarrhea or a dysentery syndrome with blood, mucus, and leukocytes in the stools, as well as fever, systemic toxicity, crampy abdominal pain, tenesmus, and urgency. The illness resembles bacillary dysentery, because EIEC share virulence genes with *Shigella* spp. Sequencing of multiple housekeeping genes indicates that EIEC is more related to *Shigella* than to...
noninvasive \textit{E. coli}. EIEC are mostly described in outbreaks; however, endemic disease occurs in developing countries where these bacteria can be isolated. In some areas of the developing world as many as 5% of sporadic diarrhea episodes and 20% of bloody diarrhea cases are caused by EIEC strains.

EIEC cause colonic lesions with ulcerations, hemorrhage, mucosal and submucosal edema, and infiltration by polymorphonuclear leukocytes. EIEC strains behave like \textit{Shigella} in their capacity to invade gut epithelium and produce a dysentery-like illness. The invasive process involves initial entry into cells, intracellular multiplication, intracellular and intercellular spread, and host-cell death. All bacterial genes necessary for entry into the host cell are clustered within a 30-kb region of a large virulence plasmid; these genes are closely related to those necessary for entry into the host cell are clustered within a 30-kb region of a large virulence plasmid. The type III secretion apparatus is a system triggered by contact with host cells; bacteria use it to transport proteins into the host cell plasma membrane and inject toxins into the cytoplasm.

EIEC encompass a small number of serogroups (O28ac, O29, O112ac, O124, O136, O143, O144, O152, O159, O164, O167, and some untypable strains). These serogroups have LPS antigens related to \textit{Shigella} LPS, and, like shigellae, are nonmotile (they lack H or flagellar antigens) and are usually not lactose fermenting.

### ENTEROPATHOGENIC \textit{ESCHERICHIA COLI}

EPEC are a major cause of acute, prolonged, and persistent diarrhea in children younger than 2 yr of age in developing countries (20% of infant diarrhea). In developed countries, EPEC are responsible for occasional outbreaks in daycare centers and pediatric wards. Profuse watery, nonbloody diarrhea with mucus, vomiting, and low-grade fever are common symptoms. Prolonged diarrhea (>7 days) and persistent diarrhea (>14 days) can lead to malnutrition, a potentially serious outcome of EPEC infection in infants in the developing world. Studies show that breastfeeding is protective against diarrhea caused by EPEC.

EPEC colonization causes blunting of villi, inflammatory changes, and sloughing of superficial mucosal cells; these lesions can be found from the duodenum through the colon. EPEC induce a characteristic attaching and effacing histopathologic lesion, which is defined by the intimate attachment of bacteria to the epithelial surface and effacement of host cell microvilli. Factors responsible for the attaching and effacing lesion formation are encoded by the locus of enterocyte effacement, which is a pathogenicity island that contains the genes for a type III secretion system, the translocated intimin receptor (Tir) and intimin, and multiple effector proteins such as the \textit{E. coli}-secreted proteins...
attaching-effacing lesions like those seen with EPEC. The attachment mechanism has genes (intimin, Tir, EspA-D, etc.) very closely related to those of EPEC. However, in addition to enterocyte attachment, these bacteria produce toxins that kill cells. These toxins (Shiga toxins [Stx]) are the key virulence factors of STEC. In the past, these toxins were also called verotoxins or Shiga-like toxins. There are 2 major Shiga toxin families, Stx1 and Stx2, with multiple subtypes identified by letters (e.g., Stx2a, Stx2c, etc.). Some STEC produce only Stx1 and others produce only one of the variants of Stx2, but many STEC have genes for several toxins. Stx1 is essentially identical to Shiga toxin, the protein synthesis-inhibiting exotoxin of Shigella dysenteriae serotype 1. Stx2 and variants of Stx2 are more distantly related to Shiga toxin, although they share key sequences with it.

These toxins are composed of a single A subunit noncovalently associated with a pentamer composed of identical B subunits. The B subunits bind to globotriaosylceramide (Gb3), a glycosphingolipid receptor on host cells. The A subunit is taken up by endocytosis. The toxin target is the 28S rRNA, which is depurated by the toxin at an exact adenine residue, causing protein synthesis to cease and affected cells to die. These toxins are carried on lambdoid bacteriophages that are normally inactive when inserted into the bacterial chromosome; when the phages are induced to replicate (e.g., by the stress induced by many antibiotics), they cause lysis of the bacteria and release of large amounts of toxin. It is generally thought that the toxins enter the systemic circulation after translocation across the intestinal epithelium and damage vascular endothelial cells, resulting in activation of the coagulation cascade, formation of microthrombi, intravascular hemolysis, and ischemia.

Clinical outcome of STEC infection depends on both epithelial attachment and the toxin(s) produced by the infecting strain. The Stx2 family of toxins is associated with a higher risk of causing HUS. Strains that make only Stx1 often cause only watery diarrhea and are uncommonly associated with HUS.

The most common STEC serotypes are E. coli O157:H7, E. coli O111:NM, and E. coli O26:H11, although several hundred other STEC serotypes have also been described. E. coli O157:H7 is the most virulent serotype and the most frequently associated with HUS; however, other non-O157 serotypes also cause this illness.

### ENTEROAGGREGATIVE ESCHERICHIA COLI

EAEC are associated with (1) acute, prolonged and persistent pediatric diarrhea in developing countries, most prominently in children younger than 2 yr of age and in malnourished children; (2) acute and persistent diarrhea in HIV-infected adults and children; and (3) acute traveler’s diarrhea; EAEC is the second most common cause of travelers’ diarrhea after ETEC. Typical EAEC illness is manifested by watery, mucoid, secretory diarrhea with low-grade fever and little or no vomiting. The watery diarrhea can persist for 14 days or longer. In some studies, many patients have grossly bloody stools. EAEC are associated with growth retardation and malnutrition in infants in the developing world.

EAEC form a characteristic biofilm on the intestinal mucosa and induce shortening of the villi, hemorrhagic necrosis, and inflammatory responses. The proposed model of pathogenesis of EAEC involves 3 phases: adherence to the intestinal mucosa by way of the aggregative adherence fimbriae or related adhesins; enhanced production of mucus; and production of toxins and inflammation that results in damage of the mucosa and intestinal secretion. Diarrhea caused by EAEC is predominantly secretory. The intestinal inflammatory response (elevated fecal lactoferrin, interleukin [IL]-8 and IL-1β) may be related to growth impairment and malnutrition.

EAEC are recognized by adherence to HEP-2 cells in an aggregative, stacked-brick–like pattern, called aggregative adherence (AA). EAEC virulence factors include the AA fimbriae (AAFI, -II, and -III) that confers the AA phenotype. Some strains produce toxins, including the plasmid-encoded enterotoxin EAST1 (encoded by astA), homolog of the ETEC ST; an autotransporter toxin called Pet; other STATE toxins; other non-O157 serotypes also cause this illness.
secreted proteins such as dispersin (aap), and the dispersin transport complex (aatPABCd). EAEC is a heterogeneous group of *E. coli*. The original diagnostic criteria (HEP-2 cell adherence pattern) identified many strains that are probably not true pathogens; genetic criteria appear to more reliably identify true pathogens. A transcriptional activator called AggR controls expression of plasmid-borne and chromosomal virulence factors. Identification of AggR appears to reliably identify illness-associated pathogenic EAEC strains (“typical” EAEC). It has been documented that EAEC aggR-positive strains carrying 1, 2, or 3 of the genes *aap*, *astA*, and *setA* are significantly associated with diarrhea compared with EAEC isolates lacking these genes. Other than AAF and AggR, there is a great deal of genomic diversity among EAEC strains with corresponding heterogeneity in virulence.

Strains of *E. coli* categorized as EAEC belong to multiple serogroups, including O3, O7, O15, O44, O77, O86, O126, and O127.

**DIFFUSELY ADHERENT ESCHERICHIA COLI**

Although the status of DAEC as true pathogens has been in doubt, multiple studies in both developed and developing countries have associated these organisms with diarrhea, particularly in children after the 1st yr or 2 of life. DAEC strains isolated from children and adults seem to represent 2 different bacterial populations. Discrepancies among epidemiologic studies may be explained by age-dependent susceptibility to diarrhea or by the use of inappropriate detection methods. Data suggest that these organisms also cause traveler's diarrhea in adults. DAEC produces acute watery diarrhea that is usually not dysenteric but is often prolonged.

DAEC strains have been identified on the basis of their diffuse adherence pattern on cultured epithelial cells. Two putative adherence factors have been described for DAEC strains. One of the adherence factors is the surface fimbrae (designated F1845) that are responsible for the diffuse adherence phenotype in a prototype strain. These fimbrae are homologous with members of the *Afa/Dr* family of adhesins, which are identified by hybridization with a specific probe, *daaC*, common to operons encoding *Afa/Dr* adhesions. A second putative adhesin associated with the diffuse adherence pattern phenotype is an outer membrane protein, designated AIDA-I. The contribution of other putative effectors (*icuA, fimH, afa, agg-g3A, pap, astA, shET1*) to virulence is still under investigation. The only documented secreted factor associated with DAEC infection is the SPATE Sat. Bacteria expressing *Afa/Dr* adhesins interact with membrane-bound receptors, including decy-accelerating factor. The structural and functional lesions induced by DAEC include loss of microvilli and decrease in the expression and enzyme activities of functional brush-border–associated proteins. *Afa/Dr* DAEC isolates produce a secreted auto transporter toxin that induces marked fluid accumulation in the intestine. DAEC strains typically induce IL-8 production in vitro. Serogroups of DAEC strains are less well defined than are those of other diarrheagenic *E. coli*.

**ENTEROAGGREGATIVE HEMORRHAGIC ESCHERICHIA COLI**

In 2011, a massive outbreak of an unusual O104:H4 strain of diarrheagenic *E. coli* began in Germany. Eventually more than 4,000 individuals were sickened with hemorrhagic colitis; illness involved primarily adults (<100 ill children were identified). More than 800 individuals developed HUS and more than 50 died. DNA sequencing showed that this strain was an EAEc that had acquired a lambdoid bacteriophage with genes for producing Stx2a. It was thus a hybrid pathogen with colonization mechanisms like a typical EAEC strain and toxin production typical of an STEC strain. This outbreak strain carries Pic on the chromosome and a pAA-like plasmid encoding AAF, AggR, Pet, ShET1, and dispersin. A second virulence plasmid encodes multiple antibiotic resistances. The high morbidity and mortality associated with this strain may reflect the stronger adherence of EAEC compared with STEC, allowing more Stx to be transferred and more resultant pathology. Some have called this strain an enteroaggregative hemorrhagic *E. coli* or *Shiga* toxin-producing EAEC. Whether *Shiga* toxin production in an EAEC background merits separate classification is unclear. Organisms with *Shiga* toxin genes in an atypical EPEC background were designated as a separate group (referred to as STEC, EHEC or verotoxin-producing *E. coli*) before the relative importance of the various genes was clear. As noted above, EPEC are a heterogeneous group themselves. The important issue is not the nomenclature but rather the concept that virulence genes can move between *E. coli* and new variants can arise.

**DIAGNOSIS**

The clinical features of illness are seldom distinctive enough to allow confident diagnosis, and routine laboratory studies are of very limited value. Diagnosis currently depends heavily on laboratory studies that are not readily available to practitioners. Practical, non-DNA-dependent, methods for routine diagnosis of diarrheagenic *E. coli* have been developed primarily for the STEC. Serotype O157:H7 is suggested by isolation of an *E. coli* that fails to ferment sorbitol on MacConkey sorbitol medium; latex agglutination confirms that the organism contains O157 LPS. Other STEC can be detected in routine hospital laboratories using commercially available enzyme immunoassay or latex agglutination to detect *Shiga* toxins, although variable sensitivity of commercial immunoassays has limited their value.

Although some STEC (O157:H7 strains) can be detected in routine microbiology laboratories using selective media and appropriate anti sera, the diagnosis of other diarrheagenic *E. coli* infection is typically made based on tissue culture assays (e.g., HEP-2-cells assay for EPEC, EAEC, DAEC) or identification of specific virulence factors of the bacteria by phenotype (e.g., toxins) or genotype. DNA probes for genes encoding the various virulence traits are the best diagnostic tests but are currently available only as a research tool. Multiplex, real-time, or conventional polymerase chain reaction can be used for presumptive diagnosis of isolated *E. coli* colonies. The genes commonly used for diagnostic polymerase chain reaction are *lt* and *st* for ETEC, *IpaH* or *iaL* for EIEC, *eae* and *bpA* for STEC, *eae* and *Stx2* for STEC, AggR or the AA plasmid for EAEC, and *daaC* or *daaD* for DAEC. Suspected organisms can be forwarded to reference or research laboratories for definitive evaluation, although such effort is seldom necessary.

Serotyping does not provide definitive identification of pathotypes (except for selected cases such as O157:H7) because each pathotype contains many serotypes and some serotypes can belong to more than 1 pathotype. Consequently, serotyping should not be used routinely for diarrheagenic *E. coli* identification in clinical laboratories (e.g., to diagnose EPEC in infantile diarrhea), except during an outbreak investigation.

Other laboratory data are at best nonspecific indicators of etiology. Fecal leukocyte examination of the stool is often positive with EIEC or occasionally positive with other diarrheagenic *E. coli*. With EIEC and STEC there may be an elevated peripheral blood polymorphonuclear leukocyte count with a left shift. Determination of *Stx2* blood levels in the early postbloody diarrhea period may be useful to identify children at risk of HUS; however, this method requires further evaluation. Fecal lactoferrin, IL-8, and IL-1β can be used as inflammatory markers. Electrolyte changes are nonspecific, reflecting only fluid loss.

**TREATMENT**

The cornerstone of management is appropriate fluid and electrolyte therapy. In general, this therapy should include oral replacement and maintenance with rehydration solutions such as those specified by the World Health Organization. Pedialyte and other readily available oral maintenance with rehydration solutions such as those specified by the World Health Organization. The cornerstone of management is appropriate fluid and electrolyte therapy. In general, this therapy should include oral replacement and maintenance with rehydration solutions such as those specified by the World Health Organization. In general, this therapy should include oral replacement and maintenance with rehydration solutions such as those specified by the World Health Organization. In general, this therapy should include oral replacement and maintenance with rehydration solutions such as those specified by the World Health Organization.
pathogens and the unpredictability of antibiotic susceptibilities. Treatment is complicated by the fact that these organisms are often multiply resistant to antibiotics as a consequence of their previous exposure to inappropriate antibiotic therapy. Multiple studies in developing countries have found diarrheagenic E. coli strains to be commonly resistant to antibiotics such as trimethoprim-sulfamethoxazole (TMP-SMX) and ampicillin (60-70%). Most data come from case series or clinical trials in adults with traveler’s diarrhea. ETEC respond to antimicrobial agents such as TMP-SMX when the E. coli strains are susceptible. ETEC cases from traveler’s diarrhea trials respond to ciprofloxacin, azithromycin, and rifaximin. However, other than for a child recently returning from travel in the developing world, empirical treatment of severe watery diarrhea with antibiotics is seldom appropriate.

EIEC infections may be treated before the availability of culture results because the clinician suspects shigellosis and has begun empirical therapy. If the organisms prove to be susceptible, TMP-SMX is an appropriate choice. Although treatment of EPEC infection with TMP-SMX intravenously or orally for 5 days may be effective in speeding resolution, the lack of a rapid diagnostic test makes treatment decisions difficult. Ciprofloxacin or rifaximin are useful for EAEC traveler’s diarrhea, but pediatric data are sparse. Specific therapy for DAEC has not been defined.

The STEC represent a particularly difficult therapeutic dilemma; many antibiotics can induce toxin production and phage-mediated bacterial lysis with toxin release. Antibiotics should not be given for STEC infection because they can increase the risk of HUS (see Chapter 518).

**PREVENTION OF ILLNESS**

In the developing world, prevention of disease caused by diarrheagenic E. coli is probably best done by maintaining prolonged breastfeeding, paying careful attention to personal hygiene, and following proper food- and water-handling procedures. People traveling to these places can be best protected by handwashing, consuming only processed water, bottled beverages, breads, fruit juices, fruits that can be peeled, or foods that are served steaming hot.

Prophylactic antibiotic therapy is effective in adult travelers but has not been studied in children and is not recommended. Public health measures, including sewage disposal and food-handling practices, have made pathogens that require large inocula to produce illness relatively uncommon in industrialized countries. Foodborne outbreaks of STEC are a problem for which no adequate solution has been found. During the occasional hospital outbreak of EPEC disease, attention to enteric isolation precautions and cohorting may be critical.

The nature of protective immunity against diarrheagenic E. coli is not fully understood, and no vaccines are available for clinical use in children. There are multiple vaccine candidates based on bacterial toxins and colonization factors that have shown promise for prevention of ETEC in adult travelers, but long-term protection with these vaccines has not been optimal, particularly in children.

*Bibliography is available at Expert Consult.*
Bibliography
Cholera is a dehydrating diarrheal disease that can rapidly lead to death, if appropriate treatment is not immediately initiated. One of the most outbreak-prone diseases, cholera is substantially underreported, with 590,000 cases recorded in 2011 but an estimated 2 million cases and at least 94,000 deaths occurring annually. The past decade has seen an increase in the number of cholera cases, which have been reported in 58 countries affecting all regions of the world over this period. The ongoing outbreak in Haiti that began in 2010 emphasizes how infectious diseases, including cholera, can easily reemerge in areas that have long been considered free of the disease.

**ETIOLOGY**

The disease is caused by *Vibrio cholerae*, a Gram-negative, comma-shaped bacillus, subdivided into serogroups by its somatic O antigen. Of the more than 200 serogroups, only serogroups O1 and O139 have been associated with epidemics, although some non-O1, non-O139 *V. cholerae* strains (e.g., O75 and O141) are pathogenic and can cause small outbreaks. A flagellar H antigen is present but is not used for species identification. The O1 serogroup is further divided into classical and the El Tor biotypes based on its biochemical characteristics. Since the turn of the 21st century, only O1 El Tor has been reported; hybrids and variants of *V. cholerae* O1 El Tor possessing classical genes have been reported worldwide. These hybrid and variant strains have been associated with more-severe disease.

Each biotype may be further subdivided into Inaba, Ogawa, and Hikojima serotypes based on the antigenic determinants on the O antigen. Inaba strains have A and C antigenic determinants, whereas Ogawa strains have A and B antigenic determinants. Hikojima strains produce all 3 antigenic determinants but are unstable and rare.

**EPIDEMIOLOGY**

The 1st 6 cholera pandemics originated in the Indian subcontinent and were caused by classical O1 *V. cholerae*. The 7th pandemic is the most extensive of all and is caused by *V. cholerae* O1 El Tor. It began in 1961 in Sulawesi, Indonesia, and has spread to the Indian subcontinent, Southeast Asia, Africa, Oceania, Southern Europe, and the Americas. In 1991, *V. cholerae* O1 El Tor first appeared in Peru before rapidly spreading in the Americas. Cholera becomes endemic in areas following outbreaks when a large segment of the population develops immunity to the disease after recurrent exposure. The disease is now endemic in parts of Africa and Asia and will likely be endemic in Haiti.

In 1992, the first non-O1 *V. cholerae* that resulted in epidemics was identified in India and Bangladesh and was designated *V. cholerae* O139. From 1992-1994, this organism replaced O1 as the predominant cause of cholera in South Asia but has since been an uncommon etiologic agent.

The hybrid El Tor strains were first identified sporadically in Bangladesh. In 2004, during routine surveillance in Mozambique, isolates of *V. cholerae* O1 El Tor carrying classical genes were identified. Since then, hybrid and variant El Tor strains have been reported in other parts of Asia and Africa and have caused outbreaks in India and Vietnam. Although the classical biotype has virtually disappeared, its genes remain within the El Tor biotype. The current circulating strain in Haiti is closely related to the South Asian strain.

Humans are the only known hosts for *V. cholerae* but free-living and plankton-associated *V. cholerae* exist in the marine environment. The organism thrives best in moderately salty water but can survive in rivers and freshwater if nutrient levels are high, as occurs when there is organic pollution such as human feces. The formation of a biofilm on abiotic surfaces and the ability to enter a viable but nonculturable state have been hypothesized as factors that allow *V. cholerae* to persist in the environment. Surface sea temperature, pH, chlorophyll content, the presence of iron compounds and chitin, and climatic conditions such as amount of rainfall and sea level rise are all important environmental factors that influence the survival of *V. cholerae* in the environment and the expression of cholera toxin, an important virulence determinant.

Consumption of contaminated water and ingestion of undercooked shellfish are the main modes of transmission, with the latter more often seen in developed countries. In cholera-endemic areas, the incidence is highest among children <2 yr of age; however, in epidemics, all age groups are commonly affected. Persons with blood group O, decreased gastric acidity, malnutrition, immunocompromised state, and absence of local intestinal immunity (prior exposure by infection or vaccination) are at increased risk for developing severe disease. Household
contacts of cholera-infected patients are at high risk for the disease, because the stools of infected patients contain high concentrations of V. cholerae. Moreover, as V. cholerae organisms are shed, they enter into a hyperinfective state, requiring a 10-100 times lower infectious dose compared to organisms that were not shed by humans.

**PATHOGENESIS**

Following ingestion of V. cholerae from the environment, several changes occur in the vibrios as they traverse the human intestine: increased expression of genes required for nutrient acquisition, down-regulation of chemotactic response, and expression of motility factors. Together these changes allow the vibrios to reach a hyperinfectious state, leading to lower infectious doses required in secondarily infected persons. This hyperinfectivity may remain for 5-24 hr after excretion.

Large inocula of bacteria (>10⁷) are required for severe cholera to occur; however, for persons whose gastric barrier is disrupted, a much lower dose (10⁵) is required. If the vibrios survive gastric acidity, they then colonize the small intestine through various factors such as toxin coregulated pili and motility, leading to efficient delivery of cholera toxin. The cholera toxin consists of 5 binding B subunits and 1 active A subunit. The B subunits are responsible for binding to the GM₁ ganglioside receptors located in the small intestinal epithelial cells. After binding, the A subunit is then released into the cell, where it stimulates adenylate cyclase and initiates a cascade of events. An increase in cyclic adenosine monophosphate leads to an increase in chloride secretion by the crypt cells, which, in turn, leads to inhibition of absorption of sodium and chloride by the microvilli. These events eventually lead to massive purging of electrolyte rich isotonic fluid in the small intestine that exceeds the absorptive capacity of the colon, resulting in rapid dehydration and depletion of electrolytes, including sodium, chloride, bicarbonate, and potassium. Metabolic acidosis and hypokalemia then ensue.

**CLINICAL MANIFESTATIONS**

Most cases of cholera are mild or inapparent. Among symptomatic cases, approximately 20% develop severe dehydration that can rapidly lead to death. Following an incubation period of 1-3 days (range: several hours to 5 days), acute watery diarrhea and vomiting ensues. The onset may be sudden, with profuse watery diarrhea, but some patients have a prodrome of anorexia and abdominal discomfort and the stool may initially be brown. Diarrhea can progress to painless purging of profuse rice-water stools (suspended flecks of mucus) with a fishy smell, which is the hallmark of the disease (Fig. 201-1). Vomiting with clear watery fluid is usually present at the onset of the disease. **Cholera gravis**, the most severe form of the disease, results when purging rates of 500-1,000 mL/hr occur. This purging leads to dehydration manifested by decreased urine output, a sunken fontanel (in infants), sunken eyes, absence of tears, dry oral mucosa, shriveled hands and feet (washerwoman’s hands), poor skin turgor, tachycardia, hypotension, and vascular collapse (Fig. 201-2). Patients with metabolic acidosis can present with typical Kussmaul breathing. Although patients may be initially thirsty and awake, they rapidly progress to obtundation and coma. If fluid losses are not rapidly corrected, death can occur within hours.

**LABORATORY FINDINGS**

Findings associated with dehydration such as elevated urine specific gravity and hemoconcentration are evident. Hypoglycemia is a common finding that is caused by decreased food intake during the acute illness. Serum potassium may be initially normal or even high in the presence of metabolic acidosis; however, as the acidosis is corrected, hypokalemia can become evident. Metabolic acidosis due to bicarbonate loss is a prominent finding in severe cholera. Serum sodium and chloride levels may be normal or decreased, depending on the severity of the disease.

**DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS**

In children who have acute watery diarrhea with severe dehydration residing in a cholera endemic area or who have recently traveled to an area known to have cholera, the disease may be suspected pending laboratory confirmation. Cholera differs from other diarrheal disease in that it often occurs in large outbreaks affecting both adults and children.

Treatment of dehydration should begin as soon as possible. Diarrhea caused by other etiologic causes (e.g., enterotoxigenic Escherichia coli or rotavirus) may be difficult to distinguish from cholera clinically. Microbiologic isolation of V. cholerae remains the gold standard for diagnosis. Although definitive diagnosis is not required for treatment to be initiated, laboratory confirmation is necessary for epidemiologic surveillance. V. cholerae may be isolated from stools, vomitus, or rectal swabs. Specimens may be transported on Cary-Blair media, if they
cannot be processed immediately. Selective media such as thiosulfate-citrate-bile salts sucrose agar that inhibit normal flora should be used. Because most laboratories in industrialized countries do not routinely culture for \textit{V. cholerae}, clinicians should request appropriate cultures for clinically suspected cases.

Stool examination reveals few fecal leukocytes and erythrocytes because cholera does not cause inflammation. Dark-field microscopy may be used for rapid identification of typical “darting motility” in wet mounts of rice water stools, which disappears once specific antibodies against \textit{V. cholerae} O1 or O139 are added. Rapid diagnostic tests are currently available and in the future may be used in areas with limited laboratory capacity, allowing early identification of cases at the onset of an outbreak and facilitating a timely response. Molecular identification with the use of polymerase chain reaction and DNA probes is available but often not used in areas where cholera exists.

**COMPLICATIONS**

Delayed initiation of rehydration therapy or inadequate rehydration often leads to complications. Renal failure from prolonged hypotension can occur. Unless potassium supplementation is provided, hypokalemia can lead to nephropathy and focal myocardial necrosis. Hypoglycemia is common among children and can lead to seizures unless it is appropriately corrected.

**TREATMENT**

Rehydration is the mainstay of therapy (see Chapter 57). Effective and timely case management considerably decreases mortality. Children with mild or moderate dehydration may be treated with oral rehydration solution (ORS) unless the patient is in shock, is obtunded, or has intestinal ileus. Vomiting is not a contraindication to ORS. Severely dehydrated patients require intravenous fluid, ideally with lactated Ringer solution. When available, rice-based ORS should be used during rehydration, because this fluid has been shown to be superior to standard ORS in children and adults with cholera. Close monitoring is necessary, especially during the 1st 24 hr of illness, when large amounts of stool may be passed. After rehydration, patients have to be reassessed every 1-2 hr, or more frequently if profuse diarrhea is ongoing. Feeding should not be withheld during diarrhea. Frequent, small feedings are better tolerated than less-frequent, large feedings.

Antibiotics should only be given in cases with moderately severe to severe dehydration (Table 201-1). As soon as vomiting stops (usually within 4-6 hr after initiation of rehydration therapy), an antibiotic to which local \textit{V. cholerae} strains are sensitive must be administered. Antibiotics shorten the duration of illness, decrease fecal excretion of vibrios, decrease the volume of diarrhea, and reduce the fluid requirement during rehydration. Single-dose antibiotics increase compliance; doxycycline, ciprofloxacin, and azithromycin are effective against cholera. There are increasing reports of resistance to tetracyclines, trimethoprim-sulfamethoxazole, and other drugs. Because of these multidrug resistant strains, antibiotic treatment must be tailored based on available susceptibility results from the area. Cephalosporins and aminoglycosides are not clinically effective against cholera and therefore should not be used, even if in vitro tests show strains to be sensitive.

Zinc should be given as soon as vomiting stops. Zinc deficiency is common among children in many developing countries. Zinc supplementation among children younger than 5 yr of age shortens the duration of diarrhea and reduces subsequent diarrhea episodes when given daily for 14 days at the time of the illness. Children younger than 6 mo of age should receive 10 mg of oral zinc for 2 wk, and for children older than 6 mo, 20 mg of oral zinc may be given daily.

**PREVENTION**

Improved personal hygiene, access to clean water, and sanitation are the mainstays of cholera control. Appropriate case management substantially decreases case fatalities to <1%. Travelers from developed countries often have no prior exposure to cholera and are therefore at risk of developing the disease. Children traveling to cholera-affected areas should avoid drinking potentially contaminated water and eating high-risk foods such as raw or undercooked fish and shellfish. No country or territory requires vaccination against cholera as a condition for entry. There is no cholera vaccine licensed in the United States.

Alarmed by the increasing prevalence of cholera, in 2011, the World Health Assembly recommended the use of oral cholera vaccines to complement existing water, sanitation, and hygiene initiatives for cholera control. Older-generation parenteral cholera vaccines have not been recommended by World Health Organization because of the limited protection they confer and their high reactogenicity. Oral cholera vaccines are safe, protective for approximately 2-5 yr duration, and confer moderate herd protection. Two oral cholera vaccines are currently available internationally and recognized by World Health Organization (Table 201-2). An internationally licensed killed whole-cell oral cholera vaccine with recombinant B subunit (Dukoral, Crucell) has been available in more than 60 countries, including the European Union, and provides protection against cholera in endemic areas as well as cross-protection against certain strains of enterotoxigenic \textit{E.}

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**Table 201-1**  
**Recommended Antimicrobials for Cholera**

<table>
<thead>
<tr>
<th>RECOMMENDING BODY</th>
<th>ANTIBIOTIC OF CHOICE</th>
<th>ALTERNATIVE</th>
</tr>
</thead>
</table>
| **WHO** (antibiotics recommended for cases with severe dehydration) | Adults  
Doxycline 300 mg given as a single dose PO or Tetracycline 500 mg 4 times a day x 3 days PO  
Children  
Tetracycline 12.5 mg/kg/dose 4 times a day x 3 days (up to 500 mg per dose x 3 days) PO | Adults  
Erythromycin 250 mg 4 times a day x 3 days PO  
Children  
Erythromycin 12.5 mg/kg/dose 4 times a day x 3 days (up to 250 mg 4 times a day x 3 days) PO |
| **PAHO** (antibiotics recommended for cases with moderate to severe dehydration) | Adults  
Doxycline 300 mg PO given as a single dose  
Children  
Erythromycin 12.5 mg/kg/dose 4 times a day x 3 days (up to 500 mg per dose x 3 days) or Azithromycin, 20 mg/kg as a single dose (up to 1 g) | Adults  
Ciprofloxacin 1g PO single dose or Azithromycin 1g PO single dose  
Children  
Ciprofloxacin 20 mg/kg PO as a single dose or Doxycycline 2-4 mg/kg PO as a single dose |

*Antibiotic selection must be based on sensitivity patterns of strains of Vibrio cholerae O1 or O139 in the area.


coli. The 2nd vaccine (Shanchol, Shantha Biotech) is a variant of the 1st vaccine and contains both *V. cholerae* O1 and O139 antigens but does not contain the B-subunit. Because it does not contain the B-subunit, the vaccine does not require buffer for administration, thereby reducing administration costs and resources, making it easier to deploy.

Oral cholera vaccines have been available for more than 2 decades and are mostly used by travelers from industrialized countries going to cholera-affected regions. With the World Health Organization declaration, countries are now using oral cholera vaccines in mass vaccination campaigns where cholera remains a substantial problem. A cholera vaccine stockpile, established by WHO, is now available and can be accessed by countries at risk for cholera, supplementing efforts to lessen the impact of this ongoing cholera scourge.

*Bibliography is available at Expert Consult.*

<table>
<thead>
<tr>
<th>VACCINE TRADE NAME</th>
<th>CONTENTS</th>
<th>DOSING SCHEDULE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dukoral (Crucell)</td>
<td>1 mg of recombinant B subunit of cholera toxin plus ( 2.5 \times 10^{10} ) of the following strains of <em>V. cholerae</em>: - Formalin-killed El Tor Inaba (Phil 6973) - Heat-killed classical Inaba (Cairo 48) - Heat-killed classical Ogawa (Cairo 50) - Formalin-killed classical Ogawa (Cairo 50)</td>
<td>Children 2-6 yr: 3 doses, 1-6 wk apart Adults and children &gt;6 yr: 2 doses, 1-6 wk apart</td>
</tr>
<tr>
<td>Shanchol (Shantha Biotech)</td>
<td><em>V. cholerae</em> O1 - 600 EU Formalin-killed El Tor Inaba (Phil 6973) - 300 EU Heat-killed classical Inaba (Cairo 48) - 300 EU Heat-killed classical Ogawa (Cairo 50) - 300 EU Formalin-killed classical Ogawa (Cairo 50) <em>V. cholerae</em> O139-600 EU of Formalin-killed strain 4260B</td>
<td>Adults and children ≥1 year of age: 2 doses, 2 wk apart</td>
</tr>
</tbody>
</table>

*WHO prequalified vaccines.*
Bibliography
Campylobacter, most commonly *Campylobacter jejuni* and *Campylobacter coli*, are found globally and are among the most common causes of human intestinal infections. Clinical presentation varies by age and underlying conditions.

**ETIOLOGY**

Eighteen species and 6 subspecies of *Campylobacter* are recognized at this time. Most of these have been isolated from humans, and many are considered pathogenic. The most significant of these are *C. jejuni* and *C. coli*, which may cause the majority of human enteritis. More than 100 serotypes of *C. jejuni* have been identified. *C. jejuni* has been subspecciated into *C. jejuni* subspecies *jejuni* and *C. jejuni* subspecies *doylei*. Although *C. jejuni* subspecies *doylei* has been isolated from humans, it is much less common, less hearty, and more difficult to isolate. Other species, including *Campylobacter fetus*, *Campylobacter lari*, and *Campylobacter upsaliensis*, among others, have been isolated from patients with diarrhea, although much less frequently (Table 202-1). Additional *Campylobacter* species have been isolated from clinical specimens, but their roles as pathogens have not been established.

*Campylobacter* organisms are Gram-negative, curved, thin (0.2-0.4 µm wide), non–spore-forming rods (1.5-3.5 µm long) that usually have tapered ends. They are smaller than most other enteric bacterial pathogens and have variable morphology, including short comma-shaped or S-shaped organisms and long, multispiraled, filamentous, seagull-shaped organisms. Individual organisms are usually motile with a flagellum at 1 or both poles. Such morphology enables these bacteria to colonize the mucosal surfaces of both the gastrointestinal and respiratory tracts and move through them in a spiraling motion. Most *Campylobacter* organisms are microaerophilic, occasionally partially anaerobic, and oxidase positive. Most can transform into coccoid forms under adverse conditions, especially oxidation.

*C. jejuni* has a circular chromosome of 1.64 million base pairs that is predicted to encode 1,654 proteins and 54 stable RNA species. The genome is unusual in that there are almost no insertion sequences or phage-associated sequences and very few repeat sequences.

**EPIDEMIOLOGY**

Worldwide, *Campylobacter* enteritis is a leading cause of acute diarrhea. Efforts to reduce *Campylobacter* contamination and safe handling practices have caused decreased incidence. *Campylobacter* infections can be both foodborne and waterborne, and most commonly result from ingestion of contaminated poultry (chicken, turkey) or raw milk. Less commonly, they come from drinking water, household pets (cats, dogs, hamsters), and farm animals. Infections are more common in resource-limited settings, are prevalent year-round in tropical areas, and can exhibit seasonal peaks in temperate regions (late spring with a peak midsummer in most of the United States, with a smaller secondary peak in late fall). In industrialized countries, *Campylobacter* infections peak in early childhood and again in young adulthood (15-44 yr of age). The second peak is not seen with *Salmonella* and *Shigella* infections. In developing countries, repeated infections are common in childhood, leading to increased immunity and rare disease in adulthood. Each year in the United States, there are an estimated 2.5 million cases of *Campylobacter* infection. Of these, death is rare, with 50-150 reports annually. In the Netherlands, medical record review shows that on average each resident acquires asymptomatic *Campylobacter* infection every 2 yr, progressing to symptomatic infection in approximately 1% of colonized people.

Foodborne illness is most common and can be seen with the consumption of raw or undercooked meat, as well as by cross-contamination of other foods. Although chickens are the classic source of *Campylobacter*, many animal sources of human food can also harbor *Campylobacter*, including seafood. *C. coli* has been linked to swine. Poultry is more likely to be heavily contaminated while red meats often have fewer organisms. Unpasteurized milk products are also a documented source. Additionally, many pets can carry *Campylobacter*, and insects inhabiting contaminated environments can acquire the organism. Shedding from animals can contaminate water sources. Humans can acquire infection from water, although much less frequently than from contaminated food. Airborne transmission of *Campylobacter* has occurred in farm workers. Use of antimicrobials in animal foods may...
increase the prevalence of antibiotic-resistant Campylobacter isolated from humans.

Human infection can result from exposure to as few as 500 bacteria, although a higher dose (>9,000 bacteria) is often needed to cause illness. At times, C. jejuni and C. coli spread person to person, perinatally, and at childcare centers where diapered toddlers are present. People infected with C. jejuni usually shed the organism for weeks but can shed for months. Hand washing is key to preventing spread in these environments.

**PATHOGENESIS**

Most Campylobacter isolates are acid sensitive, and should, in theory, be eradicated in the stomach. Therefore, models for the pathogenesis of C. jejuni enteritis include mechanisms to transit the stomach, adhere to intestinal mucosal cells, and initiate intestinal lumen fluid accumulation. Host conditions associated with reduced gastric acidity, such as proton pump inhibitor use, and foods capable of shielding organisms in transit through the stomach may help allow Campylobacter to reach the intestine. Once there, Campylobacter are able to adhere to and invade intestinal mucosal cells through motility, including use of flagellae, as well as by the use of surface proteins (e.g., PEBI and CadF), large plasmids (e.g., pVir), surface adhesins (e.g., IlpA), and chemotactic factors. Lumen fluid accumulation is associated with direct damage to mucosal cells resulting from bacterial invasion and potentially from a cholera-like toxin and other cytotoxins. Additionally, C. jejuni has mechanisms that enable transit away from the mucosal surface. The factors that are used are dependent on the species involved.

Campylobacter differ from other enteric bacterial pathogens in that they have both N- and O-linked glycosylation capacities. N-linked glycosylation is associated with molecules expressed on the bacterial surface, and O-linked glycosylation appears limited to flagellae. Slipped-strand mispairing in glycosylation loci results in modified, antigenically distinct surface structures. It is hypothesized that antigenic variation provides a mechanism for immune evasion.

C. fetus possesses a high-molecular-weight S-layer protein that mediates high-level resistance to serum-mediated killing and phagocytosis and is therefore thought to be responsible for the propensity to produce bacteremia. C. jejuni and C. coli are generally sensitive to serum-mediated killing, but serum-resistant variants exist. It has been suggested that these serum-resistant variants may be more capable of systemic dissemination.

**Campylobacter** infections can be followed by Guillain-Barré syndrome, reactive arthritis, and erythema nodosum. Such complications are thought to be from molecular mimicry between nerve tissue and Campylobacter surface antigens. Most Campylobacter infections are not followed by immunoreactive complications, indicating that host conditions as well as other factors, in addition to molecular mimicry, are required for these complications. There is some evidence of an association between Campylobacter infection and irritable bowel syndrome. It is proposed that low-grade inflammation caused by Campylobacter below the threshold that can be detected by endoscopy, results in crosstalk with gut nerves, leading to symptoms.

**CLINICAL MANIFESTATIONS**

There are a variety of clinical presentations of Campylobacter infections, depending on host factors such as age, immunocompetence, and underlying conditions. Infection presents most commonly as gastroenteritis, but also as bacteremia, neonatal infections, and, occasionally, extraintestinal infections.

**Acute Gastroenteritis**

Diarrhea is most commonly caused by C. jejuni (90-95%) or C. coli, and rarely by C. lari, Campylobacter hyointestinalis, or C. upsaliensis. The average incubation period is 3 days (range: 1-7 days). One-third of symptomatic patients can have a prodrome with fever, headache, dizziness, and myalgias; 1-3 days later, they develop cramping abdominal pain and loose, watery stools or, less commonly, bloody, mucus-containing stools. In severe cases (approximately 15%), blood appears in the stools 2-4 days after the onset of symptoms. In younger children, more than 50% may develop blood in their stools. Some patients do not develop diarrhea at all, most commonly children 6-15 yr old. Fever may be the only manifestation initially and is most pronounced in patients older than 1 yr of age. Febrile seizures can also occur in this age group. Sixty percent to 90% of older children also complain of

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<tr>
<td>C. jejuni</td>
<td>Gastroenteritis, bacteremia, Guillain-Barré syndrome</td>
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<td>C. coli</td>
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<td>C. fetus</td>
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<td>Swine, cattle, deer, hamsters, raw milk, oysters</td>
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<tr>
<td>C. lari</td>
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<td>Seagulls, water, poultry, cattle, dogs, cats, monkeys, oysters, mussels</td>
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<tr>
<td>C. upsaliensis</td>
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<td>C. sputorum</td>
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<td>Head and neck abscesses, abdominal abscesses, empyema</td>
<td>Dogs</td>
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<td>C. cryaerophila</td>
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abdominal pain. The abdominal pain is most commonly periumbilical and sometimes persists after the stools return to normal. The abdominal pain can mimic appendicitis, colitis, or intussusception. Nausea is common, with up to 25% of adults developing vomiting. Vomiting tends to be more common the younger the patient and is most frequent in infants.

Diarrhea lasts around 7 days and will resolve spontaneously. More mild disease can last 1-2 days; 20-30% of patients will have symptoms for 2 wk and 5-10% are symptomatic for longer than 2 wk. Relapse can occur in 5-10% of patients. Persistent or recurrent Campylobacter gastroenteritis has been reported in immunocompetent patients, in patients with hypogammaglobulinemia (both congenital and acquired), and in patients with AIDS. Persistent infection can mimic chronic inflammatory bowel disease; therefore, Campylobacter infection should also be considered when evaluating for inflammatory bowel disease. There is some suggestion that infection may also be the trigger for the development of inflammatory bowel disease. Fecal shedding of the organisms in untreated patients usually lasts for 2-3 wk, with a range from a few days to several months. Shedding tends to occur longer in young children. Acute appendicitis, mesenteric lymphadenitis, and ileocolitis have been reported in patients who have had appendectomies during C. jejuni infection.

Bacteremia

Transient bacteremia has been shown in early acute infection in 0.1-1% of patients. With the exception of bacteremia caused by C. fetus, bacteremia with Campylobacter occurs most often among malnourished children, patients with chronic illnesses or immunodeficiency, such as HIV, and in the very old and very young. Bacteremia can also occur in patients without underlying disease. The majority of cases of bacteremia are asymptomatic. C. fetus causes bacteremia in adults with or without identifiable focal infection, usually in the setting of underlying conditions such as malignancy or diabetes mellitus. When symptomatic, C. jejuni bacteremia is associated with fever, headache, malaise, and abdominal pain. Relapsing or intermittent fever is associated with night sweats, chills, and weight loss when the illness is prolonged. Lethargy and confusion can occur, but focal neurologic signs are unusual without cerebrovascular disease or meningitis. A cough is present occasionally, without additional evidence of pulmonary involvement. Moderate leukocytosis may be found. Variable presentations, including transient asymptomatic bacteremia, rapidly fatal sepsis, and prolonged bacteremia of 8-13 wk, have been described.

Focal Extraintestinal Infections

Focal infections caused by C. jejuni are rare and occur mainly among neonates and immunocompromised patients. Multiple sites have been reported including meningitis, pneumonia, thrombophlebitis, pancreatitis, cholecystitis, ileocecal, urinary tract infection, arthritis, peritonitis, myocarditis, pericarditis, and endocarditis. C. fetus shows a predilection for vascular endothelium, leading to endocarditis, periarditis, thrombophlebitis, and mycotic aneurysms. C. hominis has been associated with proctitis; C. upsaliensis has been associated with breast abscesses; Campylobacter rectus has been associated with periodontitis.

Perinatal Infections

Perinatal infections are most often acquired at birth from a mother infected with or shedding Campylobacter. Maternal C. fetus and C. jejuni infections may be asymptomatic and can result in abortion, stillbirth, premature delivery, or neonatal infection with sepsis and meningitis. Severe perinatal infections are uncommon and are caused most often by C. fetus and rarely by C. jejuni. Neonatal infection with C. jejuni is associated with diarrhea that may be bloody. Nosocomial infections in nurseries have also been described.

DIAGNOSIS

The clinical presentation of Campylobacter enteritis can be similar to that of enteritis caused by other bacterial pathogens. The differential diagnosis includes Shigella, Salmonella, Escherichia coli, Yersinia enterocolitica, Aeromonas, Vibrio parahaemolyticus, and amebiasis. Fecal leukocytes are found in as many as 75% of cases, and fecal blood is present in 50% of cases. Campylobacter should be considered in patients with bloody stools, fever, and abdominal pain.

The diagnosis of Campylobacter enteritis is usually confirmed by identification of the organism in cultures of stool or rectal swabs. Isolation is most likely from selective media such as CAMPY agar grown in microaerophilic conditions (5-10% oxygen), 1-10% carbon dioxide, with some hydrogen. Some C. jejuni grow best at 42°C (107.6°F). Growth on solid media results in small (0.5-1.0 mm), slightly raised, smooth colonies. Organisms can be identified from stool under the microscope in approximately 50% of known Campylobacter cases. Gram stain is even less sensitive. Stool culture is greater than 90% sensitive and is the standard method of diagnosis. Visible growth on stool culture is most often present in 1-2 days. Visible growth in blood cultures is often not apparent until 5-14 days after inoculation.

Routine culture may be adequate for isolation of C. jejuni because of the large numbers of bacteria that are often present. However, because campylobacters grow more slowly under routine conditions than do other enteric bacteria, routine culture can result in failure because of overgrowth of other enteric bacteria. Culture for campylobacters can be enhanced, when necessary, with selective media. However, selective culture media developed to enhance isolation of C. jejuni may inhibit the growth of other Campylobacter species. Filtration methods are available and can preferentially enrich for Campylobacter by selecting for their small size. These methods allow subsequent culture of the enriched sample on antibiotic free media, enhancing rates of isolation of Campylobacter organisms inhibited by the antibiotics included in standard selective media. Isolation of Campylobacter from normally sterile sites does not require enhancement procedures. Clinically, it is not necessary to speciate Campylobacter, as clinical disease is the same. Speciation can be done, when needed, and specialized labs can perform strain typing when required for epidemiologic purposes.

For rapid diagnosis of Campylobacter enteritis, direct carbol fuchsin stain of fecal smear, indirect fluorescence antibody test, dark-field microscopy, or latex agglutination can be used. Enzyme immunoassay and polymerase chain reaction have been tested and used in research studies but are not currently available in the clinical setting. These tests are quite sensitive. However, there continues to be concern regarding the specificity of these tests. In a recent study published in 2013, enzyme immunoassay had a positive predictive value of 91% in verification studies, which dropped to 42% in routine diagnostic studies. Polymerase chain reaction seems to be more specific and currently is being studied regarding differentiation of species. At this time, the recommendation remains to confirm all positive rapid tests with culture. Serologic diagnosis is also possible. This is especially important in patients with late-onset reactive arthritis or Guillain-Barré syndrome, as these patients may have negative stool cultures.

COMPLICATIONS

Severe, prolonged C. jejuni infection can occur in patients with immunodeficiencies, including hypogammaglobulinemia and malnutrition. In patients with AIDS, increased frequency and severity of C. jejuni infection have been reported; severity correlates inversely with CD4 count. Complications can include acute complications, as described earlier, and late onset complications that may present after the acute infection has resolved. The most common late-onset complications include reactive arthritis and Guillain-Barré syndrome.

Reactive Arthritis

Reactive arthritis can accompany Campylobacter enteritis in adolescents and adults, especially in patients who are positive for HLA-B27. Reactive arthritis occurs in up to 3% of patients, though up to 13% may have joint symptoms. This manifestation appears most commonly 1-2 wk after the onset of diarrhea, but has been seen 5-40 days later. It involves mainly large joints and resolves without sequelae. The arthritis is typically migratory and occurs without fever. Synovial fluid lacks bacteria. The arthritis responds well to nonsteroidal antiinflammatory
Guillain-Barré Syndrome

Guillain-Barré syndrome (GBS) is an acute demyelinating disease of the peripheral nervous system characterized clinically by acute flaccid paralysis and is the most common cause of neuromuscular paralysis worldwide. GBS carries a mortality rate of approximately 2%, and approximately 20% of patients with this disease develop major neurologic sequelae. C. jejuni has been identified as the trigger in up to 45% of patients with GBS and is most closely linked to the serotypes Penner O19 and O14. It has been reported 1-12 wk after C. jejuni gastroenteritis in 1 of every 1,000 C. jejuni infections. Stool cultures obtained from patients with GBS at the onset of neurologic symptoms have yielded C. jejuni in greater than 25% of the cases. Serologic studies suggest that 20-45% of patients with GBS have evidence of recent C. jejuni infection. Molecular mimicry between nerve tissue GM1 ganglioside and Campylobacter surface antigens may be the triggering factor in Campylobacter-associated GBS. The Miller-Fisher variant, which more commonly affects cranial nerves, is characterized by ataxia, areflexia, and ophthalmoplegia, and is linked to cross-reacting antibodies to the GQ1b ganglioside found in cranial nerve myelin. The next common serotype is Penner O2. When associated with Campylobacter, GBS is more likely to be the axonal form and has a worse prognosis with slower recovery and more neurologic disability. The management of GBS includes supportive care, intravenous immunoglobulin, and plasma exchange.

Other Complications

Immunoglobulin A nephropathy and immune complex glomerulonephritis with C. jejuni antigens in the kidneys have been reported. Campylobacter infection has also been associated with hemolytic anemia.

TREATMENT

Fluid replacement, correction of electrolyte imbalance, and supportive care are the mainstays of treatment of children with Campylobacter gastroenteritis. Antimotility agents can cause prolonged or fatal disease and should not be used. The need for antibiotic therapy in patients with uncomplicated gastroenteritis is controversial. Data suggest a shortened duration of symptoms (by an average of 1.3 days) and intestinal shedding of organisms if antibiotics are initiated early in the disease.

Most Campylobacter isolates are susceptible to macrolides, fluoroquinolones, aminoglycosides, chloramphenicol, tetracyclines, and clindamycin, and are resistant to cephalosporins, rifampin, penicillins, trimethoprim, and vancomycin. Resistance to tetracyclines, macrolides, and fluoroquinolones has been described. Antibiotic resistance among C. jejuni has become a serious worldwide problem. Macrolide resistance is increased in areas such as Thailand and Ireland, whereas fluoroquinolone resistance has been reported in Spain, Hungary, and multiple developing countries in greater than 50% of cultured Campylobacter. Fluoroquinolone resistance continues to increase in the United States and is related to the use of quinolones in veterinary medicine and food products, as well as acquisition from travelers. Erythromycin-resistant Campylobacter isolates are uncommon; therefore, erythromycin or azithromycin is the drug of choice if therapy is required. Drug sensitivities should be determined for patients who do not respond to therapy. Antibiotics are recommended for patients with bloody stools, high fever, or a severe course, and for children who are immunosuppressed or have underlying diseases. Sepsis is treated with parenteral antibiotics such as an aminoglycoside, meropenem, or imipenem. Extraintestinal infections should also be treated with antibiotics. For extraintestinal infection caused by C. fetus, prolonged therapy is advised. C. fetus isolates resistant to erythromycin have been reported.

PROGNOSIS

Although Campylobacter gastroenteritis is usually self-limited, immunosuppressed children (including children with AIDS) can experience a protracted or severe course. Septicemia in newborns and immunocompromised hosts has a poor prognosis, with an estimated mortality rate of 30-40%. Additional prognosis is based upon the secondary sequelae that may develop.

PREVENTION

Most human Campylobacter infections are sporadic and are acquired from infected animals or contaminated foods. Interventions to minimize transmission include cooking meats thoroughly, preventing recontamination after cooking by not using the same surfaces, utensils, or containers for both uncooked and cooked food, and avoiding unpasteurized dairy products. Also, it is important to ensure that water sources are not contaminated and that water is kept in clean containers. Contact with infected animals should be avoided. No specific isolation is required; standard precautions are sufficient. However, children in diapers should be kept out of daycare until the diarrhea resolves. Breastfeeding appears to decrease symptomatic Campylobacter disease but does not reduce colonization.

Several approaches at immunization have been studied, including the use of live-attenuated organisms, subunit vaccines, and killed whole-cell vaccines. No vaccine is currently available.

Bibliography is available at Expert Consult.
Chapter 202  •  Campylobacter 1406.e1

Bibliography


The genus *Yersinia* is a member of the family Enterobacteriaceae and comprises more than 14 named species, 3 of which are established as human pathogens. *Y. enterocolitica* is by far the most common *Yersinia* species causing human disease and it produces fever, abdominal pain that can mimic appendicitis, and diarrhea. *Y. pseudotuberculosis* is most often associated with mesenteric lymphadenitis. *Y. pestis* is the agent of plague and most commonly causes an acute febrile lymphadenitis (bubonic plague) and less commonly occurs as septicemic, pneumonic, pharyngeal, or meningeval plague. Other *Yersinia* organisms are uncommon causes of infections of humans, and their identification is often an indicator of immunodeficiency. *Yersinia* is enzootic and can colonize pets. Infections in humans are incidental and most often result from contact with infected animals or their tissues; ingestion of contaminated water, milk, or meat; or, for *Y. pestis*, the bite of infected fleas. Association with human disease is less clear for *Y. frederiksenii, Y. intermedia, Y. kristensenii, Y. aldovae, Y. bercovieri, Y. mollaretii, Y. rohdei, and Y. ruckeri*. Some *Yersinia* isolates replicate at low temperatures (1-4°C [33.8-39.2°F]) or survive at high temperatures (50-60°C [122-140°F]). Thus, common food preparation and storage and common pasteurization methods might not limit the number of bacteria. Most are sensitive to oxidizing agents.

### 203.1 *Yersinia enterocolitica*

*Ramia Zakhour, Gloria P. Heresi, and James R. Murphy*

**ETIOLOGY**

*Y. enterocolitica* is a large, Gram-negative cocccobacillus that exhibits little or no bipolarity when stained with methylene blue and carbol
fuchsin. It ferments glucose and sucrose but not lactose, is oxidase-negative, and reduces nitrate to nitrite. These facultative anaerobes grow well on common culture media and are motile at 22°C (71.6°F) but not at 37°C (98.6°F). Optimal growth temperature is 25-28°C (77-82.4°F); however, the organism can grow at refrigerator temperature. *Y. enterocolitica* includes pathogenic and nonpathogenic members. It has 6 different biotypes (1A, 1B, and 2-5). *Y. enterocolitica* relies on other bacteria for iron uptake, and conditions associated with iron overload increase risk of infection.

**EPIDEMIOLOGY**

This agent is transmitted to humans through food, water, animal contact, and contaminated blood products. Transmission can occur from mother to newborn. *Y. enterocolitica* appears to have a global distribution but is seldom a cause of tropical diarrhea. In 2010, incidence of culture-confirmed *Y. enterocolitica* infection in the United States was 0.3 per 100,000 population (52% decrease from incidence in 1996-1998). Infection may be more common in Northern Europe. Prevalence in fecal samples from asymptomatic humans of nonvirulent *Y. enterocolitica* biotype 1A was 1.1% in 1 study. Most infections occur among children younger than 5 yr of age (incidence: 1.6-1.9 per 100,000 population), with the majority among children younger than 1 yr of age. It is estimated that *Y. enterocolitica* accounts for 5% of illnesses secondary to major bacterial enteric pathogens in children younger than 5 yr old in the United States. Cases are more common in colder months and among males.

Natural reservoirs of *Y. enterocolitica* include pigs, rodents, rabbits, sheep, cattle, horses, dogs, and cats, with pigs being the major animal reservoir. A recent publication estimated direct or indirect contact with animals, including pets, other domesticated animals, as well as wild animals, to be responsible for <1% of cases of enteric illnesses caused by *Y. enterocolitica*. Culture and molecular techniques have found the organism in a variety of foods and beverages, including vegetable juice, pasteurized milk, carrots, and water. Consumption of contaminated water or food, specially undercooked pork, is the most common form of transmission to humans. A source of sporadic *Y. enterocolitica* infections is pig offal (chitterlings). In 1 study, 71% of human isolates were indistinguishable from the strains isolated from pigs. *Y. enterocolitica* is an occupational threat to butchers. There is evidence that under conventional farm conditions pigs can be raised free of *Y. enterocolitica*.

In part because of its capacity to multiply at refrigerator temperatures, *Y. enterocolitica* can be transmitted by intravenous injection of contaminated fluids, including blood products.

Patients with conditions leading to iron overload are at higher risk of developing *Yersinia* infections.

**PATHOGENESIS**

The organisms most often enter by the alimentary tract and cause mucosal ulcerations in the ileum. Necrotic lesions of Peyer patches are also found in the ileum. Exudative pharyngitis, pneumonia, empyema, lung abscess, and acute respiratory distress syndrome uncommonly occur.

Reactive complications include erythema nodosum, reactive arthritis, and rarely uveitis. These manifestations may be more common in selected populations (northern Europeans), in association with HLA-B27, and in girls.

**DIAGNOSIS**

Diagnosis is made usually through isolation of the organism usually from the stool. *Y. enterocolitica* is easily cultured from normally sterile sites but requires special procedures for isolation from stool, where other bacteria can outgrow it. Cold enrichment, where a sample is held in buffered saline, can result in preferential growth of *Yersinia*, but the procedure takes weeks. Polymerase chain reaction (PCR) and DNA microarray are more sensitive than culture, with DNA microarray more sensitive and accurate than multiplex PCR. Many laboratories do not routinely perform the procedures required to detect *Y. enterocolitica*. Procedures targeted to this organism must be specifically requested. A history indicating contact with environmental sources of *Yersinia* and detection of fecal leukocytes are helpful indicators of a need to test for *Y. enterocolitica*. The isolation of a *Yersinia* from stool should be followed by tests to confirm that the isolate is a pathogen. Serodiagnosis is possible but not readily available.

**DIFFERENTIAL DIAGNOSIS**

The clinical presentation is similar to other forms of bacterial enterocolitis. The most common considerations include *Shigella*, *Salmonella*, *Campylobacter*, *Clostridium difficile*, enteroinvasive *Escherichia coli*, *Y. pseudotuberculosis*, and, occasionally, *Vibrio*-related diarrheal disease. Amebiasis, appendicitis, Crohn disease, ulcerative colitis, diverticulitis, and pseudomembranous colitis should also be considered.

**TREATMENT**

Enterocolitis in an immunocompetent patient is a self-limiting disease, and no benefit from antibiotic therapy is established. Patients with systemic infection and very young children (in whom septicemia is common) should be treated. *Yersinia* organisms are typically susceptible to trimethoprim-sulfamethoxazole (TMP-SMX), aminoglycosides, third-generation cephalosporins, and quinolones, although strains resistant to quinolones have been recently reported. *Y. enterocolitica* produces β-lactamas, which are responsible for resistance to penicillins and first-generation cephalosporins. TMP-SMX is the recommended empirical treatment in children for enterocolitis (generally a 5-day course), because it has activity against most strains and is well tolerated. In severe infections such as bacteremia, third-generation cephalosporins, with or without aminoglycosides, are effective, and usually a 3 wk course of therapy is administered with possible transition to oral therapy. Patients on deferexamine should discontinue iron chelation therapy during treatment for *Y. enterocolitica*, especially if they have complicated gastrointestinal infection or extraintestinal infection.

**COMPLICATIONS**

Reactive arthritis, erythema nodosum, erythema multiforme, hemorrhagic anemia, thrombocytopenia, and systemic dissemination of bacteria have been reported in association with *Y. enterocolitica* infection.
Septicemia is more common in younger children, and reactive arthritis is more common in older patients. Arthritis appears to be mediated by immune complexes, which form as a result of antigenic mimicry, and viable organisms are not present in involved joints.

PREVENTION
Prevention centers on reducing contact with environmental sources of Yersinia. Breaking or sterilization of the chain from animal reservoirs to humans holds the greatest potential to reduce infections, and the techniques applied must be tailored to the reservoirs in each geographic area. There is no licensed vaccine.

Bibliography is available at Expert Consult.

203.2 Yersinia pseudotuberculosis
Ramia Zakhour, Gloria P. Heresi, and James R. Murphy

Y. pseudotuberculosis has a worldwide distribution; Y. pseudotuberculosis disease is less common than Y. enterocolitica disease. The most common form of disease is a mesenteric lymphadenitis that produces an appendicitis-like syndrome. Y. pseudotuberculosis is associated with a Kawasaki disease–like illness in approximately 8% of cases.

ETIOLOGY
Y. pseudotuberculosis is a small Gram-negative aerobic and facultative anaerobic cocccobacillus. Like Y. enterocolitica, it ferments glucose and does not ferment lactose, is oxidase negative, is catalase producing, is urea splitting, and shares a number of morphologic and culture characteristics. It is differentiated biochemically from Y. enterocolitica on the basis of ornithine decarboxylase activity, fermentation of sucrose, sorbitol, and cellobiose, and other tests, although some overlap between species occurs. Antisera to somatic O antigens and sensitivity to Yersinia phages can also be used to differentiate the 2 species. Subspecies-specific DNA sequences that allow direct probe- and primer-specific differentiation of Y. pestis, Y. pseudotuberculosis, and Y. enterocolitica have been described. Y. pseudotuberculosis is more closely related phylogenetically to Y. pestis than to Y. enterocolitica.

EPIDEMIOLOGY
Y. pseudotuberculosis is zoonotic, with reservoirs in wild rodents, rabbits, deer, farm animals, various birds, and domestic animals, including cats and canaries. Transmission to humans is by consumption of or contact with contaminated animals or contact with an environment contaminated by animals (often water). Direct evidence of transmission of Y. pseudotuberculosis to humans by consumption of lettuce and raw carrots has been reported. The organism has a worldwide distribution; however, infections are more commonly reported in Europe, in boys, and in the winter. During 1996-2007 FoodNet reported 18 cases of infections secondary to Y. pseudotuberculosis in the United States, with an annual average incidence of 0.04 per 1,000,000 persons. When compared to Y. enterocolitica infections, those caused by Y. pseudotuberculosis are more likely to be invasive and occur in adolescents and adults. Iron-overloading conditions, HIV infection, and other debilitating diseases (including liver cirrhosis) may predispose to invasive Y. pseudotuberculosis infection.

PATEROGENESIS
Ileal and colonic mucosal ulceration and mesenteric lymphadenitis are hallmarks of the infection. Necrotizing epithelioid granulomas may be seen in the mesenteric lymph nodes, but the appendix is often grossly and microscopically normal. The mesenteric nodes are often the only source of isolation of the organism. Y. pseudotuberculosis antigens bind directly to human leukocyte antigen class II molecules and can function as superantigens, which might account for the clinical illness resembling Kawasaki disease.

CLINICAL MANIFESTATIONS
Pseudoappendicitis and mesenteric lymphadenitis with abdominal pain, right lower quadrant tenderness, fever, and leukocytosis is the most common clinical presentation. Enterocolitis and extraintestinal spread are uncommon. Iron overload, diabetes mellitus, and chronic liver disease are often found concomitantly with extraintestinal Y. pseudotuberculosis infection. Renal involvement with tubulointerstitial nephritis, azotemia, pyuria, and glucosuria can occur. Y. pseudotuberculosis can present as a Kawasaki disease-like illness with fever of 1-2 days duration; strawberry tongue; pharyngeal erythema; a scarlatiniform rash; cracked, red, swollen lips; conjunctivitis; sterile pyuria; periungual desquamation; and thrombocytosis. Other uncommon manifestations include septic arthritis, massive lower gastrointestinal bleeding, postanureysmal prosthetic vascular infection, and acute encephalopathy.

DIAGNOSIS
PCR of involved tissue can be used to identify the organism; isolation by culture can require an extended interval. Involved mesenteric lymph nodes removed at appendectomy can yield the organism by culture. Abdominal CT scan or ultrasound examination of children with unexplained fever and abdominal pain can reveal a characteristic picture of enlarged mesenteric nodes and thickening of the terminal ileum with or without peritoneal findings including appendicidal inflammation and periappendical fluid. Y. pseudotuberculosis is rarely recovered from stool. Serologic procedures are available, but not in most routine laboratories.

DIFFERENTIAL DIAGNOSIS
Appendicitis (most commonly), inflammatory bowel disease, and other intraabdominal infections should be considered. Kawasaki disease, staphylococcal or streptococcal disease, leptospirosis, Stevens-Johnson syndrome, and collagen vascular diseases, including acute-onset juvenile rheumatoid arthritis, can mimic the syndrome with prolonged fever and rash. C. difficile colitis, meningitis, encephalitis, enteropathic arthropathies, acute pancreatitis, sarcoidosis, toxic shock syndrome, typhoid fever, and ulcerative colitis may also be considered.

TREATMENT
Uncomplicated mesenteric lymphadenitis caused by Y. pseudotuberculosis is a self-limited disease, and antimicrobial therapy is not required. Few data exist on optimal treatment and duration of therapy. Infections with Y. pseudotuberculosis can generally be managed same as those caused by Y. enterocolitica. Culture-confirmed bacteremia should be treated with an aminoglycoside, ampicillin, TMP-SMX, a third-generation cephalosporin, a fluoroquinolones, or chloramphenicol.

COMPLICATIONS
Erythema nodosum and reactive arthritis can follow infection. Coronary aneurysm formation has been described with disease presenting as Kawasaki-like illness. Rare local complications of gastrointestinal disease include perforation, obstruction, and intussusception.

PREVENTION
Avoiding exposure to potentially infected animals and good food-handling practices can prevent infection. The sporadic nature of the disease makes application of targeted prevention measures difficult.

Bibliography is available at Expert Consult.

203.3 Plague (Yersinia pestis)
Ramia Zakhour, Gloria P. Heresi, and James R. Murphy

ETIOLOGY
Y. pestis is a Gram-negative, facultative anaerobe that is a pleomorphic nonmotile, non-spore-forming coccobacillus and is a potential agent...
Bibliography


Bibliography


of bioterrorism. It evolved from *Y. pseudotuberculosis* through acquisition of chromosomal changes and plasmid-associated factors that are essential to its virulence and survival in mammalian hosts and fleas. *Y. pestis* shares bipolar staining appearance with *Y. pseudotuberculosis* and can be differentiated by biochemical reactions, serology, phage sensitivity, and molecular techniques. The *Y. pestis* genome has been determined and is approximately 4,600,000 base pairs in size. *Y. pestis* exists in 3 biovars: Antigua (Africa), Medievalis (central Asia), and Orientalis (widespread).

**EPIDEMIOLOGY**

Plague is endemic in at least 24 countries. Approximately 3,000 cases are reported worldwide per year, with 100-200 deaths. Plague is uncommon in the United States (0-40 reported cases/yr); most of these cases occur west of a line from east Texas to east Montana, with 80% of cases in New Mexico, Arizona, and Colorado. The epidemic form of disease killed approximately 25% of the population of Europe in the Middle Ages in one of a number of epidemics and pandemics. The epidemiology of epidemic plague involves extension of infection from the zoonotic reservoirs to urban rats, *Rattus rattus* and *Rattus norvegicus*, and from fleas of urban rats to humans. Epidemics are no longer seen. Selective pressure exerted by plague pandemics in medieval Europe is hypothesized for enrichment of a deletion mutation in the gene encoding CCR5 (CCR5-Δ32). The enhanced frequency of this mutation in European populations endows approximately 10% of European descendants with resistance to HIV-1.

The most common mode of transmission of *Y. pestis* to humans is through flea bites. Historically, most human infections are thought to have resulted from bites of fleas that acquired infection from feeding on infected urban rats. Less commonly, infection is caused by contact with infectious body fluids or tissues or inhalation of respiratory secretions of infected animals. Nowadays most cases of plague secondary to direct animal contact or inhalation of animal secretions are related to domestic cats. Direct transmission from human to human through droplet inhalation is possible but extremely rare. Laboratory transmission of *Y. pestis* has been described as well. Sylvatic plague can exist as a stable enzootic infection or as an epizootic disease with high host mortality. Ground squirrels, rock squirrels, prairie dogs, rats, mice, bobcats, cats, rabbits, and chipmunks may be infected. Transmission among animals is usually by flea bite or by ingestion of contaminated tissue. *Xenopsylla cheopis* is the flea most commonly associated with transmission to humans, but more than 30 species of fleas have been demonstrated as vector competent, and *Pulex irritans*, the human flea, can transmit plague and might have been an important vector in some historical epidemics. Both sexes are similarly affected by plague, and transmission is more common in colder regions and seasons, possibly because of temperature effects on *Y. pestis* infections in vector fleas.

**PATHOGENESIS**

In the most common form of plague, infected fleas regurgitate organisms into a patient's skin during feeding. The bacteria translocate via lymphatics to regional lymph nodes, where *Y. pestis* exists. From 2-8 days after a flea bite, lymphadenitis develops in lymph nodes closest to the inoculation site, including the inguinal (most common), axillary, or cervical region. These buboes are remarkable for tenderness. Fever, chills, weakness, prostration, headache, and the development of septicemia are common. The skin might show insect bites or scratch marks. Purpura and gangrene of the extremities can develop as a result of disseminated intravascular coagulation. These lesions may be the origin of the name Black Death. Untreated plague results in death in more than 50% of symptomatic patients. Death can occur within 2-4 days after onset of symptoms.

Occasionally, *Y. pestis* establishes systemic infection and induces the systemic symptoms seen with bubonic plague without causing a bubo (primary septicemic plague). Because of the delay in diagnosis linked to the lack of the bubo, septicemic plague carries a higher case fatality rate than bubonic plague. In some regions, bubo-free septicemic plague accounts for 25% of cases.

**Pneumonic plague** is the least common but most dangerous and lethal form of the disease. Pneumonic plague can result from hematogenous dissemination, or, rarely, as primary pneumonic plague after inhalation of the organism from a human or animal with plague pneumonia or potentially from a biologic attack. Signs of pneumonic plague include severe pneumonia with high fever, dyspnea, and hemoptysis. Plague meningitis, tonsillitis, or gastroenteritis can occur. Meningitis tends to be a late complication following inadequate treatment. Tonsillitis and gastroenteritis can occur with or without apparent bubo formation or lymphadenopathy.

**DIAGNOSIS**

Plague should be suspected in patients with fever and history of exposure to small animals in endemic areas. Thus, bubonic plague is suspected in a patient with a painful swollen lymph node, fever, and prostration who has been exposed to fleas or rodents in the western United States. A history of camping or the presence of flea bites increases the index of suspicion. *Y. pestis* is readily transmitted to humans by some routine laboratory manipulations. Thus, it is imperative to clearly notify a laboratory when submitting a sample suspected of containing *Y. pestis*. Laboratory diagnosis is based on bacteriologic culture or direct visualization using Gram, Giemsa, or Wayson stains of lymph node aspirates, blood, sputum, or exudates. *Y. pestis* grows slowly under routine culture conditions and best at temperatures that differ from those used for routine cultures in many clinical laboratories. Enzyme-linked immunosorbent assay and PCR are available but are not in routine clinical use. A rapid antigen test detecting *Y. pestis* F1 antigen in sputum and serum samples exists as well. Suspected isolates of *Y. pestis* should be forwarded to a reference laboratory for confirmation. Special containment shipping precautions are required. Cases of plague should be reported to local and state health departments and the Centers for Disease Control and Prevention (CDC).

**DIFFERENTIAL DIAGNOSIS**

The Gram stain of *Y. pestis* may be confused with *Enterobacter agglomerans*. Mild and subacute forms of bubonic plague may be confused with other disorders causing localized lymphadenitis and lymphadenopathy. Septicemic plague may be indistinguishable from other forms of overwhelming bacterial sepsis like tularemia and cat-scratch disease. Pulmonary manifestations of plague are similar to those of anthrax, Q fever, and tularemia, all agents with bioterrorism and biological warfare potential. Thus, the presentation of a suspected case, and especially any cluster of cases, requires immediate reporting. Additional information on this aspect of plague and procedures can be found at http://www.bt.cdc.gov/agent/plague/.

**TREATMENT**

Patients with suspected plague should be placed on droplet isolation until pneumonia is ruled out, sputum cultures are negative, and antibiotic treatment has been administered for 48 hr. The treatment of choice for bubonic plague historically has been streptomycin (30 mg/kg/day, maximum 2 g/day, divided every 12 hr IM for 10 days). Intramuscular streptomycin is inappropriate for septicemia because absorption may be erratic when perfusion is poor. The poor central nervous...
system penetration of streptomycin makes this an inappropriate drug for meningitis. Furthermore, streptomycin might not be widely and immediately available. Gentamicin (children, 7.5 mg/kg IM or IV divided every 8 hr; adults, 5 mg/kg IM or IV once daily) has been shown to be as efficacious as streptomycin. Alternative treatments include doxycycline (in children who weigh <45 kg: 2-5 mg/kg/day every 12 hr IV; in children who weigh ≥45 kg, 100 mg every 12 hr PO), ciprofloxacin (30 mg/kg/day divided every 12 hr, maximum 400 mg every 12 hr IV), and chloramphenicol (50-100 mg/kg/day IV divided every 6 hr). Meningitis is usually treated with chloramphenicol or a fluoroquinolone. Resistance to these agents and relapses are rare. Y. pestis is susceptible to fluoroquinolones in vitro, which are effective in treating experimental plague in animals. Y. pestis is susceptible to penicillin in vitro, but penicillin is ineffective in treatment of human disease. Mild disease may be treated with oral chloramphenicol or tetracycline in children older than 8 yr of age. Clinical improvement is noted within 48 hr of initiating treatment. Typical duration of therapy is 7-10 days or a few days following clinical improvement.

**Postexposure prophylaxis** should be given to close contacts of patients with pneumonic plague. Antimicrobial prophylaxis is recommended within 7 days of exposure for persons with direct, close contact with patient with pneumonic plague or those exposed to an accidental or terrorist-induced aerosol. Recommended regimens include a 7-day course of tetracycline, doxycycline, or TMP-SMX. Contacts of cases of uncomplicated bubonic plague do not require prophylaxis. Y. pestis is a potential agent of bioterrorism that can require mass casualty prophylaxis.

**PREVENTION**

Avoidance of exposure to infected animals and fleas is the best method of prevention of infection. In the United States, special care is required in environments inhabited by rodent reservoirs of Y. pestis and their ectoparasites. Patients with plague should be isolated if they have pulmonary symptoms, and infected materials should be handled with extreme care. There is currently no available licensed vaccine for Y. pestis in the United States. Several vaccine development trials are underway, and recombinant subunit vaccines based on rF1 and rV antigens seem to be the most promising. Using baits containing live vaccines for oral immunization of wild animals may be a helpful alternative for control of epidemics.

*Bibliography is available at Expert Consult.*
Bibliography


Chapter 204

**Aeromonas and Plesiomonas**

Amanda N. Shaw and Gloria P. Heresi

_Aeromonas_ and _Plesiomonas_ are Gram-negative bacilli that include species capable of causing enteritis and less frequently cause skin and soft-tissue infections and septicemia. They are common in fresh and brackish aquatic sources and colonize animals and plants in these environments.

### 204.1 Aeromonas

_Aeromonas_ is a member of the Aeromonadaceae family and are oxidase-positive, facultative anaerobic, Gram-negative bacilli that ferment glucose. At least 24 phenotypic species are known, though there is controversy regarding species differentiation. Eleven are recognized as clinically significant human pathogens. _Aeromonas hydrophila_, _Aeromonas veronii_ biotype sobria, and _Aeromonas caviae_ are the species most often associated with human infection. _Aeromonas trota_ continues to be isolated with increasing frequency from human stool. _A. hydrophila_ strain ATCC 7966 has been sequenced and contains 5,195 predicted protein-encoding genes identified.

_Aeromonas_ infects many cold- and warm-blooded animals. There are 2 major groups of _Aeromonas_ isolates: the nonmotile psychrophilic organisms that infect cold-blooded animals, most commonly fish (optimal growth 22-25°C [71.6-77°F]), and the motile mesophilic organisms that infect humans and other warm-blooded animals (optimal growth 35-37°C [95-98.6°F]).

**Epidemiology**

_Aeromonas_ organisms are ubiquitous and are found in fresh and brackish aquatic sources, including rivers and streams, well water, both treated and bottled drinking water, and sewage. They are most often cultivated from aquatic sources during warm weather months, when they are able to attain large populations. The prevalence of human infection tends to exhibit seasonality, depending on local conditions. For example, _Aeromonas_ are isolated with increased frequency from May to October in the northern hemisphere. Some species can resist chlorination of water and show tolerance to high salt. _Aeromonas_ has been isolated from meats, milk, seafood, seaweed, and vegetables consumed by humans. Most human infections with _Aeromonas_ are associated with exposure to contaminated water. A systematic review of cases of traveler’s diarrhea worldwide implicated _Aeromonas_ in 0.8-3.3% of infections, with highest frequencies in travelers to Southeast Asia and Africa. A study in India of 3,500 stool samples from patients hospitalized with diarrhea found 4.7% positive for _Aeromonas_. _Aeromonas_ infections have also been acquired at various sites of natural disasters. Following the 2004 Thailand tsunami, 305 survivors with skin and soft-tissue infections were found to have _Aeromonas_, making it the most common bacterial pathogen causing skin infections following this disaster. Asymptomatic colonization occurs in humans and is more common in inhabitants of tropical regions.

**Pathogenesis**

Clinical and epidemiologic data seem to support that _Aeromonas_ organisms are enteric pathogens, although this is not universally accepted. Reasons for uncertainty include a lack of outbreaks with colonially distinct isolates, infrequent person to person transmission, absence of a good animal model, and overlapping prevalence in symptomatic and asymptomatic patients. Adult volunteers can ingest 10⁴-10⁶ colony-forming units without developing diarrhea or becoming colonized.

_Aeromonas_ isolates possess a variety of potential virulence factors, including: constitutive polar and inducible lateral flagella, fimbriae, outer membrane proteins, an S-layer, endotoxin (lipopolysaccharide), capsules, collagenase, elastase, nuclease, gelatinase, lipase, chitinase, enterotoxins, hemolysins, and multiple secretion systems. Polar flagella provide motility in liquid media, and lateral flagella act as adhesins. There are various hemolysins and heat labile- and heat-stable enterotoxins. _Aeromonas_ cytotoxoid enterotoxin (aerolysin) is secreted by a type II secretion system and is able to lyse erythrocytes, inhibit phagocytosis, and induce cytotoxicity in eukaryotic cells. _Aeromonas_ also has a type III secretion system with an effector protein that causes actin reorganization and eventual apoptosis in vitro. A few strains produce _Shiga_ toxin. _Aeromonas_ has serine proteases that can cause a cascade of inflammatory mediators leading to vascular leakage, and in vitro studies show induction of apoptosis in murine macrophages by human isolates of _Aeromonas_. _Aeromonas_ also has enzyme systems and efflux pumps that enable it to develop resistance to antibiotics. There are limited data on identified quorum-sensing molecules, which coordinate gene expression according to local density and may be involved in biofilm production or population control.
Human serum generally promotes phagocytosis and intracellular killing of Aeromonas. Absence of this serum action has been associated with a poor prognosis.

**CLINICAL MANIFESTATIONS**

Colonization with Aeromonas may be asymptomatic or cause illness, including enteritis, focal invasive infection, and septicemia. Although apparently immunologically normal individuals may present with any manifestation, invasive disease is more common among immunocompromised persons.

**Enteritis**

The most common clinical manifestation of infection with Aeromonas is enteritis, which occurs primarily among children younger than 3 yr of age. Aeromonas is the 3rd or 4th most common cause of childhood bacterial diarrhea and has been isolated from 2-10% of patients with diarrhea and 1-5% of asymptomatic control subjects. One study showed isolation from hospitalized neonates with diarrhea at rates of 0.1-19% depending on season. Diarrhea is often watery and self-limited, although a dysentery-like syndrome with blood and mucus in the stool has also been described. Fever, abdominal pain, and vomiting are common in children. Enteritis caused by A. hydrophila and A. sobria tends to be acute and self-limited, whereas 30% of the patients with A. caviae enteritis have chronic or intermittent diarrhea that may last 4-6 wk. A. sobria and A. caviae are most frequently associated with traveler’s diarrhea. Complications of Aeromonas enteritis include intussusception, failure to thrive, hemolytic-uremic syndrome, bacteremia, and strangulated intestinal hernia. A. caviae infection may mimic inflammatory bowel disease.

**Skin and Soft-Tissue Infections**

Skin and soft-tissue infections are the second most common presentation of Aeromonas. Predisposing factors include local trauma and exposure to contaminated fresh water. Aeromonas soft-tissue infections have been reported following animal bites, including alligator, tiger, bear, and snake bites, as well as tick bites. It has also been reported following sports injuries and following medicinal leech therapy. Antibiotic prophylaxis is currently used in conjunction with medicinal leech therapy because of the presence of symbiotic A. hydrophila. The spectrum of skin and soft-tissue infections is broad, ranging from a localized skin nodule to life-threatening necrotizing fasciitis, myonecrosis, and gas gangrene. Soft-tissue infections are most commonly found on the extremities and are 3 times more likely in men than in women. Aeromonas cellulitis, the most common skin manifestation, clinically presents like any other bacterial cellulitis but should be suspected in wounds following contact with a water source, especially during the summer.

**Septicemia**

Aeromonas septicemia is the third most frequent presentation of infection and is associated with a mortality rate of 27-73%. Patients often present with fever and gastrointestinal symptoms including abdominal pain, nausea, vomiting, and diarrhea. Multiple pediatric cases of septicemia from A. hydrophila have been reported; symptoms include diarrhea, pneumonia, and acute renal failure. Aeromonas septicemia usually occurs in patients with underlying conditions, such as hepatobiliary disease or malignancy, but may occur in apparently immunocompetent persons. Aeromonas may be the only organism isolated or may be part of a polymicrobial bacteremic illness. The source of the infection is frequently not identified, and in these cases is most likely from the gastrointestinal tract. A. sobria bacteremia has resulted in disseminated intravascular gas production and subsequent acute death in the absence of any underlying condition.

**Other Infections**

Aeromonas is a rare cause of gastrointestinal infections such as necrotizing gastroenteritis, peritonitis, cholecystitis, appendicitis, and liver and pancreas abscess formation, cardiovascular infections including endocarditis and septic embolism, and pulmonary infections including tracheobronchitis, pneumonia, empyema, and abscess formation. Aeromonas is also associated with musculoskeletal infections, including osteomyelitis, pyogenic arthritis, pyomyositis, and necrotizing fasciitis, as well as ear, nose and throat infections, including endophthalmitis, keratitis, orbital cellulitis, otitis media, and epiglottitis. Other infections include meningitis, urinary tract infection, pelvic inflammatory disease, lymphadenitis, hot tub folliculitis, and surgical wound infections. Aeromonas is associated with tracheobronchitis and aspiration pneumonia after near-drowning.

**DIAGNOSIS**

Diagnosis is established by culture isolation of Aeromonas. The organism is easily grown on standard media when the source material is normally sterile. Isolation of the organism from samples containing numerous bacteria is more difficult, possibly because competing bacteria outgrow Aeromonas. Often, Aeromonas is not identified by typical lab protocols for examining stool specimens. If Aeromonas is suspected, the yield will increase if the lab is notified prior to testing. Previously suggested use of ampicillin containing agars is no longer recommended, because a significant number of A. caviae and all A. trota are sensitive to ampicillin and will not grow. Most (~90%) strains produce β-hemolysis on blood agar. However, lack of hemolysis is not a reliable indicator of lack of hemolysin in the isolate. Lactose-fermenting strains of Aeromonas may not be identified if the clinical laboratory does not routinely perform oxidase tests on lactose fermenters isolated on MacConkey agar. Automated identification systems are more routinely being used and can identify most Aeromonas as a group. More specific identification is not done as often, and when it is done, is often incomplete or erroneous.

**TREATMENT**

Aeromonas enteritis is usually self-limited, and antimicrobial therapy may not be indicated. Nevertheless, data from uncontrolled trials suggest that antimicrobial therapy shortens the course of the illness. Antimicrobial therapy is reasonable to consider in patients with protracted diarrhea, dysentery-like illness, or underlying conditions such as hepatobiliary disease or an immunocompromised state. Antibiotic sensitivity varies between species. Therefore, it is important to identify the species and sensitivities when antibiotics are used. Most species produce an inducible β-lactamase which may not be detected by automated systems. There is near-uniform resistance to penicillins. Septicemia should be treated with a third-generation cephalosporin or an aminoglycoside. Other options include imipenem, meropenem, chloramphenicol, trimethoprim-sulfamethoxazole (TMP-SMZ), quinolones, and tetracyclines. Many species have developed multidrug resistance, especially to quinolones. Sensitivities vary by geographic region. For example, in Taiwan there is increasing resistance to TMP-SMZ, so travel history should be taken into consideration when planning treatment. There are no clinic trial data available to guide duration of treatment. As a consequence, treatment is typically guided by clinical response. In general, diarrhea is treated for 3 days, wound infections for 7-10 days, and bacteremia for 14 days.

**PREVENTION**

Reducing contact with contaminated environmental fresh and brackish water and contaminated foods should reduce the risk for Aeromonas infections. Aeromonas expresses LamB-like outer membrane proteins that facilitate bacterial adherence to extracellular matrix components. Outer membrane proteins are strongly immunogenic and have been target antigens for vaccine development.

**Bibliography is available at Expert Consult.**

### 204.2 Plesiomonas shigelloides

Amanda N. Shaw and Gloria P. Heresi

**ETIOLOGY**

Plesiomonas shigelloides is most commonly associated with acute enteritis and rarely with extraintestinal infections. The organism is a facultative anaerobic, Gram-negative non–spore-forming bacillus with more...
Bibliography
than 100 serotypes. It is catalase- and oxidase-positive, able to ferment xylose, and motile, with 2-5 polar flagellae. 

*P. shigelloides* is the only oxidase positive member of the Enterobacteriaceae family. A high level of diversity has been recognized within *P. shigelloides* strains, reflecting the frequency of homologous recombination and differing from other members of the Enterobacteriaceae.

**EPIDEMIOLOGY**

*P. shigelloides* is ubiquitous in fresh water and can be found in estuarine water. Historically, it has been found most often in warmer and tropical waters or during warmer months, although there are increasing reports of isolation from surface water in colder climates. *P. shigelloides* colonizes numerous cold- and warm-blooded animals, has been isolated from fish and seafood, and may cause disease in cats. Infection of humans is thought to be the result of consumption of contaminated water or raw seafood and possibly through contact with colonized animals. There have also been cases of immunocompromised patients who are injured in fresh water. A majority of symptomatic patients in North America have known exposure to potentially contaminated water or seafood or have traveled abroad. In general, enteric infections with *Plesiomonas* occur more commonly in areas where development and hygiene are inadequate and have been associated with large outbreaks.

**PATHOGENESIS**

Epidemiologic evidence indicates that *P. shigelloides* is an enteropathogen. However, the pathogenic capacity of *P. shigelloides* has not been confirmed when volunteers have been fed the organism. The mechanism of enteritis is not known, but it appears that the species can commonly cause secretory and less commonly invasive disease. In vitro studies show that isolates of *P. shigelloides* are capable of invading and inducing apoptosis in cells of enteric origin. Most strains of *P. shigelloides* secrete a β-hemolysin, which is thought to be a major virulence factor. They also produce a β-lactamase, which renders them resistant to the penicillins. Studies show evidence of modulation of host defenses through inhibition of cathepsins involved in antigen processing and presentation.

**CLINICAL MANIFESTATIONS**

Clinical disease in humans generally begins 24-48 hr after exposure to the organism, although there have been cases 4 days after exposure. Diarrhea is commonly secretory or watery and less often presents as invasive dysentery. In 13% of cases, diarrhea can last more than 2 wk and has been noted to last as long as 3 mo. The frequency of secretory vs dysenteric presentation seems to cluster by individual outbreak, suggesting that either the human populations or bacterial populations involved associate with their particular presentation. Symptoms include diarrhea (84-100%), vomiting (70%), fever (8-50%), headache, abdominal cramping (more common in adults), nausea, and transient arthralgias. Frequently, diarrhea is mild and watery without significant dehydration. Blood, mucus, or both may be passed with stool, and white blood cells may be visualized in stained preparations of stool.

Extraintestinal infections are rare and usually occur in patients with underlying conditions, such as immunodeficiency (including HIV), malignancy, sickle cell disease, thalassemia, splenectomy, or hepatobiliary disease. Traumatic wounds sustained in aquatic environments less commonly contain *P. shigelloides*. Rarely, bacteremia accompanying enteritis has been documented in apparently otherwise normal children. Extraintestinal disease includes septicemia, pneumonia, meningitis, osteomyelitis, septic arthritis, reactive arthritis, cellulitis with abscess formation, endophthalmitis, cholecystitis, pseudoparadepididymitis, pseudomembranous colitis, proctitis, epididymo-orchitis, and pyosalpinx. Early onset neonatal sepsis and meningitis are rare but make up most of the reported cases of *P. shigelloides* meningitis and have a very high mortality rate (80%). Septicemia has a high mortality rate in adults.

**DIAGNOSIS**

A history of foreign travel, ingestion of raw seafood, or exposure to contaminated water or an animal with diarrhea suggests possible *P. shigelloides* infection. Mixed infection with *Salmonella*, *Aeromonas*, rotavirus, or other enteric pathogens may occur in 30-50% of patients. *P. shigelloides* is a non-lactose fermenter and grows well on traditional enteric media, although selective techniques may be required to isolate the organism from mixed cultures and to differentiate *P. shigelloides* from *Shigella* species. Many strains cross react with *Shigella* on serologic testing, but can be differentiated easily as oxidase positive organisms. It may be underrecognized by clinical laboratories that do not routinely perform an oxidase test. Rapid identification systems are fairly accurate when identifying *P. shigelloides*.

**TREATMENT**

Enteritis caused by *P. shigelloides* is usually mild and self-limited. In cases associated with dehydration, patients respond favorably to oral rehydration solution. Antimicrobial therapy is reserved for those patients with prolonged or bloody diarrhea, those who are immunocompromised, the very old, and the very young. Data from uncontrolled studies suggest that antimicrobial therapy decreases the duration of symptoms, although no difference was found in an exclusively pediatric study. Most strains of *P. shigelloides* are susceptible to TMP-SMZ, cephalexin, carbenemem, and fluoroquinolones. *P. shigelloides* is commonly resistant to broad-spectrum penicillins, aminoglycosides, and tetracyclines. In some strains resistance has also been found to TMP-SMZ and fluoroquinolones. Resistance to gentamicin, chloramphenicol, and nalidixic acid has been demonstrated in strains of *P. shigelloides* isolated from tilapia.

Antibiotics are essential for therapy of extraintestinal disease. Empirical therapy with a third-generation cephalosporin is often first-line management, because most isolates are susceptible in vitro. Alternatives include imipenem, aztreonam, β-lactam/β-lactamase inhibitor combinations, and quinolones. Definitive therapy should be guided by the susceptibility of the individual isolate. Duration of therapy ranges from 1-2 wk, but may be extended depending on underlying chronic conditions and clinical response.

*Bibliography is available at Expert Consult.*
**Bibliography**


Chapter 205

Pseudomonas, Burkholderia, and Stenotrophomonas

205.1 Pseudomonas aeruginosa
Thomas S. Murray and Robert S. Baltimore

ETIOLOGY

Pseudomonas aeruginosa is a Gram-negative rod and is a strict aerobe. It can multiply in a great variety of environments that contain minimal amounts of organic compounds. Strains from clinical specimens do not ferment lactose, are oxidase positive, and may produce β-hemolysis on blood agar. Many strains produce pigments, including pyocyanin, pyoverdin, and pyorubrin, that diffuse into and color the surrounding medium. Strains of P. aeruginosa are differentiated for epidemiologic purposes by a variety of genotyping methods, including restriction fragment length polymorphisms using pulsed-field gel electrophoresis and multilocus sequence typing.
**Pathogenesis**

Invasiveness of *P. aeruginosa* is mediated by a host of virulence factors. Bacterial attachment is facilitated by pili that adhere to epithelium damaged by prior injury or infection. Extracellular proteins, proteases, elastases, and cytotoxins disrupt cell membranes, and in response, host-produced cytokines cause capillary vascular permeability and induce an inflammatory response. Dissemination and bloodstream invasion follow extension of local tissue damage and are facilitated by the antiphagocytic properties of endotoxin, the exopolysaccharide, and protease cleavage of immunoglobulin G. *P. aeruginosa* also produces numerous exotoxins, including *exotoxin A*, which causes local necrosis and facilitates systemic bacterial invasion. *P. aeruginosa* possesses a type III secretion system that is important for virulence in multiple animal models. This needle structure inserts into host cell membranes and allows secretion of exotoxins directly into host cells. *P. aeruginosa* strains with the gene encoding the type III secretion system–dependent phospholipase ExoU are associated with increased mortality compared with ExoU-negative strains in retrospective studies of patients with *P. aeruginosa* ventilator-associated pneumonia. The host responds to infection with a robust inflammatory response, recruiting neutrophils to the infection site and by producing antibodies to *P. aeruginosa* proteins such as exotoxin A and endotoxin. There is a lack of convincing data that these antibodies are protective against the establishment of infection.

In addition to acute infection, *P. aeruginosa* is also capable of chronic persistence thought to be partly a result of the formation of biofilms, organized communities of bacteria encased in an extracellular matrix that protects the organisms from the host immune response and the effects of antibiotics. Biofilm formation requires pilus-mediated attachment to a surface, proliferation of the organism, and production of exopolysaccharide as the main component of the extracellular matrix. A mature biofilm can persist despite an intense host immune response, is resistant to many antimicrobials, and is difficult to eradicate with current therapies.

**CLINICAL MANIFESTATIONS**

Most clinical patterns (Table 205-1) are related to opportunistic infections in immunocompromised hosts (see Chapter 178) or are...
associated with shunts and indwelling catheters (see Chapter 179). 

*P. aeruginosa* may be introduced into a minor wound of a healthy person as a secondary invader, and cellulitis and a localized abscess that exudes green or blue pus may follow. The characteristic skin lesions of *P. aeruginosa*, *ecthyma gangrenosum*, whether caused by direct inoculation or a metastatic focus secondary to septicemia, begin as pink macules and progress to hemorrhagic nodules and eventually to ulcers with erythematous and gangrenous centers with eschar formation, surrounded by an intense red areola (Fig. 205-1).

Outbreaks of dermatitis and urinary tract infections caused by *P. aeruginosa* have been reported in healthy persons after use of pools or hot tubs. Skin lesions of folliculitis develop several hours to 2 days after contact with these water sources. Skin lesions may be erythematous, macular, papular, or pustular. Illness may vary from a few scattered lesions to extensive truncal involvement. In some children, malaise, fever, vomiting, sore throat, conjunctivitis, rhinitis, and swollen breasts may be associated with dermal lesions. Urinary tract infections caused by *P. aeruginosa* are most often nosocomial and are commonly associated with the presence of an indwelling urinary catheter, urinary tract malformations, and previous antibiotic use. Urinary tract infections may be minimized or prevented by prompt removal of the catheter and by early identification and corrective surgery of obstructive lesions when present.

**Burns and Wound Infection**

The surfaces of burns or wounds are frequently populated by *P. aeruginosa* and other Gram-negative organisms; this initial colonization with a low number of adherent organisms is a necessary prerequisite to invasive disease. *P. aeruginosa* colonization of a burn site may develop into burn wound sepsis, which has a high mortality rate when the density of organisms reaches a critical concentration. Administration of antibiotics may diminish the susceptible microbiologic flora, permitting strains of relatively resistant *P. aeruginosa* to flourish. Multiplication of organisms in devitalized tissues or associated with prolonged use of intravenous or urinary catheters increases the risk for septicemia with *P. aeruginosa*, a major problem in burned patients (see Chapter 75).

**Cystic Fibrosis**

*P. aeruginosa* is common in children with cystic fibrosis, with a prevalence that increases with increasing age and severity of pulmonary disease (see Chapter 403). Initial infection is caused by nonmucoid environmental strains of *P. aeruginosa*, but after a variable period of time, mucoid strains of *P. aeruginosa* that produce the antiphagocytic exopolysaccharide alginate, which are rarely encountered in other conditions, predominate. Repeated isolation of mucoid *P. aeruginosa* from the sputum is associated with increased morbidity and mortality. The infection begins insidiously or even asymptptomatically, and the progression has a highly variable pace. In children with cystic fibrosis, antibody does not eradicate the organism and antibiotics are only partially effective; thus, after infection becomes chronic, it cannot be completely eradicated. Repeated courses of antibiotics select for *P. aeruginosa* strains that are resistant to multiple antibiotics.

**Immunocompromised Persons**

Children with leukemia or other malignancies, particularly those who are receiving immunosuppressive therapy and who are neutropenic, typically with intravascular catheters, are extremely susceptible to septicemia caused by invasion of the bloodstream by *P. aeruginosa* that is colonizing the respiratory or gastrointestinal tract. Signs of sepsis are often accompanied by a generalized vasculitis, and hemorrhagic necrotic lesions may be found in all organs, including the skin (ecthyma gangrenosum) (see Fig. 205-1). Hemorrhagic or gangrenous perirectal cellulitis or abscesses may occur, associated with ileus and profound hypotension.

**Nosocomial Pneumonia**

Although not a frequent cause of community-acquired pneumonia in children, *P. aeruginosa* is an increasingly important cause of community-acquired pneumonia in adults and of nosocomial pneumonia, especially ventilator-associated pneumonia, in patients of all ages. *P. aeruginosa* has historically been found to contaminate ventilators, tubing, and humidifiers. Such contamination is uncommon because of disinfection practices and routine changing of equipment. Nevertheless, colonization of the upper respiratory tract and the gastrointestinal tract may be followed by aspiration of *P. aeruginosa*-contaminated secretions, resulting in severe pneumonia. Prior use of broad-spectrum antibiotics is a risk factor for colonization with antibiotic-resistant strains of *P. aeruginosa*. One of the most challenging situations is distinguishing between colonization and pneumonia in intubated patients. This distinction can often only be resolved by using invasive culture techniques such as quantitative bronchoalveolar lavage.

**Infants**

*P. aeruginosa* is an occasional cause of nosocomial bacteremia in newborns and accounts for 2-5% of positive blood culture results in neonatal intensive care units. A frequent focus preceding bacteremia is conjunctivitis. Older infants may occasionally present with community-acquired sepsis due to *P. aeruginosa*, but this circumstance is uncommon. In the few reports describing community-acquired sepsis, preceding conditions included ecthyma-like skin lesions, virus-associated transient neutropenia, and prolonged contact with contaminated bath water or a hot tub.

**DIAGNOSIS**

*P. aeruginosa* infection is rarely clinically distinctive. Diagnosis depends on recovery of the organism from the blood, cerebrospinal fluid, urine, or needle aspirate of the lung, or from purulent material obtained by aspiration of subcutaneous abscesses or areas of cellulitis. In the appropriate clinical setting the recovery of *P. aeruginosa* from a coughed or suctioned sputum may represent infection; but it also may only represent colonization and clinical judgment is required. Rarely, skin lesions that resemble *P. aeruginosa* infection may follow septicemia caused by *Aeromonas hydrophila*, other Gram-negative bacilli, and *Aspergillus*. When *P. aeruginosa* is recovered from nonsterile sites such as skin, mucous membranes, voided urine, quantitative cultures may be useful to differentiate colonization from invasive infection. In general, ≥100,000 colony forming units/mL of fluid or gram of tissue is evidence suggestive of invasive infection. Quantitative cultures of tissue and skin are not routine and may require consultation with the clinical microbiology laboratory.

**TREATMENT**

Systemic infections with *P. aeruginosa* should be treated promptly with an antibiotic to which the organism is susceptible in vitro. Response to treatment may be limited, and prolonged treatment may be necessary for systemic infection in immunocompromised hosts.
Septicemia and other aggressive infections should be treated with either 1 or 2 bactericidal agents. Although the number of agents required is controversial, the evidence continues to suggest that the benefit of adding a second agent is questionable, even when studies have included immunosuppressed patients. Whether the use of 2 agents delays the development of resistance is also controversial, with evidence both for and against. Appropriate antibiotics for single-agent therapy include ceftazidime, cefepime, ticarcillin-clavulanate, and piperacillin-tazobactam. Gentamicin or another aminoglycoside may be used concomitantly for synergistic effect.

Ceftazidime has proved to be extremely effective in patients with cystic fibrosis (150-250 mg/kg/day divided every 6-8 hr IV to a maximum of 6 g/day). Piperacillin or piperacillin-tazobactam (300-450 mg/kg/day divided every 6-8 hr IV to a maximum of 12 g/day) also has proven to be effective therapy for susceptible strains of *P. aeruginosa* when combined with an aminoglycoside. Additional effective antibiotics include imipenem-cilastatin, meropenem, and aztreonam. Ciprofloxacin is an effective outpatient therapy and while commonly used in children with cystic fibrosis, it is not approved in the United States for persons younger than 18 yr of age except for oral treatment of urinary tract infections or when there are no other agents to which the organism is susceptible. Inhaled therapy with either tobramycin or aztreonam is also used for chronic pulmonary infection with inhaled colistin reserved for the treatment of resistant pseudomonads.

It is important to base continued treatment on the results of susceptibility tests because antibiotic resistance of *P. aeruginosa* to 1 or more antibiotics is increasing. Macrolide therapy decreases pulmonary exacerbations in patients with chronic lung disease and *P. aeruginosa* infection. Although the mechanism is not entirely clear, it likely relates to altering the virulence properties of *P. aeruginosa* rather than direct bacterial killing.

*P. aeruginosa* displays intrinsic and acquired resistance to antibiotics. It has many mechanisms for resistance to multiple classes of antibiotics, including but not limited to genetic mutation, production of β-lactamases, and drug efflux pumps. Critical care units throughout the United States have documented a rising rate of resistance of *P. aeruginosa* to all of the major classes of antibiotics.

Meningitis can occur from spread from a contiguous focus, as a secondary focus when there is bacteremia, or after invasive procedures. *P. aeruginosa* meningitis is best treated with ceftazidime in combination with an aminoglycoside such as gentamicin, both given intravenously. Concomitant intraventricular or intrathecal treatment with gentamicin may be required when intravenous therapy fails but is not recommended for routine use.

**SUPPORTIVE CARE**

*P. aeruginosa* infections vary in severity from superficial to intense septic presentations. With severe infections there is often multisystem involvement and a systemic inflammatory response. Supportive care is similar to care for severe sepsis caused by other Gram-negative bacilli and requires support of blood pressure, oxygenation, and appropriate fluid management.

**PROGNOSIS**

The prognosis is dependent primarily on the nature of the underlying factors that predisposed the patient to *P. aeruginosa* infection. In severely immunocompromised patients, the prognosis for patients with *P. aeruginosa* sepsis is poor unless susceptibility factors such as neutropenia or hypogammaglobulinemia can be reversed. The overall mortality rate was 12.3% in 1 series of 232 children with *P. aeruginosa* bacteremia, with 3% dying within 48 hr of admission. Resistance of the organism to first-line antibiotics also decreases the chance of survival.

The outcome may be improved when there is a urinary tract portal of entry, absence of neutropenia or recovery from neutropenia, and drainage of local sites of infection.

*P. aeruginosa* is recovered from the lungs of most children who die of cystic fibrosis and adds to the slow deterioration of these patients. The prognosis for normal development is poor in the few infants who survive *P. aeruginosa* meningitis.

**PREVENTION**

Prevention of infections is dependent on limiting contamination of the healthcare environment and preventing transmission to patients. Effective hospital infection control programs are necessary to identify and eradicate sources of the organism as quickly as possible. In hospitals, infection can be transmitted to children by the hands of personnel, from washbasin surfaces, from catheters and other hospital equipment, and from solutions used to rinse suction catheters.

Strict attention to hand hygiene before and between contacts with patients may prevent or interdict epidemic disease. Meticulous care and sterile procedures in suctioning of endotracheal tubes, insertion and maintenance of indwelling catheters, and removal of catheters as soon as medically reasonable greatly reduce the hazard of extrinsic contamination by *P. aeruginosa* and other Gram-negative organisms.

Prevention of follicular dermatitis caused by *P. aeruginosa* contamination of whirlpools or hot tubs is possible by maintaining pool water at a pH of 7.2-7.8.

Infections in burned patients may be minimized by protective isolation, debridement of devitalized tissue, and topical applications of bactericidal cream. Administration of intravenous immunoglobulin may be used. Approaches under investigation to prevent infection include development of a *P. aeruginosa* vaccine. No vaccine is currently licensed in the United States.

Bibliography is available at Expert Consult.

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**205.2 Burkholderia cepacia Complex**

*Burkholderia cepacia* is a filamentous Gram-negative rod now recognized to be a group of related species or genomovars. It is ubiquitous in the environment but may be difficult to isolate from respiratory specimens in the laboratory, requiring an enriched, selective media oxidation fermentation base supplemented with polymyxin B–bacitracin-lactose agar (OFPBL) and as long as 3 days of incubation.

*B. cepacia* is a classic opportunistic that rarely infects normal tissue but can be a pathogen for individuals with preexisting damage to respiratory epithelium, especially persons with cystic fibrosis or with immune dysfunction such as chronic granulomatous disease. *B. cepacia* has multiple virulence factors, including lipopolysaccharide and a type III secretion system that promotes invasion of respiratory epithelial cells. Resistance to many antibiotics and disinfectants appears to be a factor in the emergence of *B. cepacia* as a nosocomial pathogen. In critical care units it may colonize the tubing used to ventilate patients with respiratory failure. In some patients this colonization may lead to invasive pneumonia and septic shock. Although *B. cepacia* is found throughout the environment, human-to-human spread among patients with cystic fibrosis occurs either directly by inhalation of aerosols or indirectly from contaminated equipment or surfaces, accounting for the practice of cohorting patients with cystic fibrosis in some clinics, hospital wards, and social gatherings on the basis of *B. cepacia* colonization. *B. cepacia* infections in persons with cystic fibrosis may represent chronic infection in some patients but others, especially those with *Burkholderia cenocepacia*, genomovar III, can develop an acute respiratory syndrome of fever, leukocytosis, and progressive respiratory failure, and more rapid decline in pulmonary function and lower survival rate.

Treatment in hospitals should include standard precautions and avoidance of placing colonized and uncolonized patients in the same room. Patients with cystic fibrosis who are colonized with *B. cepacia* are asked not to attend events where other persons with cystic fibrosis will be present. The use of antibiotics is guided by susceptibility studies of a patient’s isolates, because the susceptibility pattern of this species is quite variable and multiply resistant strains are common. Trimethoprim-sulfamethoxazole and doxycycline or minocycline are potential oral therapies for *B. cepacia complex*. For intravenous therapy meropenem along with a second agent such as trimethoprim-sulfamethoxazole, doxycycline, minocycline, cefazidime, or amikacin...
Bibliography


are potential options. Even though there is primary resistance to aminoglycosides, these agents may be useful in combination with other antibiotics. Treatment with 2 or more agents may be necessary to control the infection and avoid the development of resistance. No vaccine is currently available.

**BURKHOLDERIA MALLEI (GLANDERS)**

Glanders is a severe infectious disease of horses and other domestic and farm animals that is caused by *Burkholderia mallei*, a nonmotile Gram-negative bacillus that is occasionally transmitted to humans. It is acquired by inoculation into the skin, usually at the site of a previous abrasion, or by inhalation of aerosols. Laboratory workers may acquire it from clinical specimens. The disease is relatively common in Asia, Africa, and the Middle East. The clinical manifestations include septicemia, acute or chronic pneumonia, and hemorrhagic necrotic lesions of the skin, nasal mucous membranes, and lymph nodes. The diagnosis is usually made by recovery of the organism in cultures of affected tissue. Glanders is treated with sulfadiazine, tetracyclines, or chloramphenicol and streptomycin over a period of many months. The disease has been eliminated from the United States, but interest in this organism has increased because of the possibility of its use as a bioterrorism agent (see Chapter 723). Although standard precautions are appropriate when caring for hospitalized infected patients, biosafety level 3 precautions are required for laboratory staff working with *B. mallei*. No vaccine is available.

**BURKHOLDERIA PSEUDOMALLEI (MELOIDOSIS)**

Meliodosis is an important disease of Southeast Asia and northern Australia and occurs in the United States mainly in persons returning from endemic areas. The causative agent is *Burkholderia pseudomallei*, an inhabitant of soil and water in the tropics. It is ubiquitous in endemic areas, and infection follows inhalation of dust, ingestion, or direct contamination of abrasions or wounds. Human-to-human transmission has only rarely been reported. Serologic surveys demonstrate that asymptomatic infection occurs in endemic areas. The disease may remain latent and appear when host resistance is reduced, sometimes years after the initial exposure. Diabetes mellitus is a risk factor for severe meliodosis.

Meliodosis may present as a single primary skin lesion (vesicle, bulla, or urticaria). Pulmonary infection may be subacute and mimic tuberculosis or may present as an acute necrotizing pneumonia. Occasionally, septicemia occurs and numerous abscesses are noted in various organs of the body. Myocarditis, pericarditis, endocarditis, intestinal abscess, cholecystitis, acute gastroenteritis, urinary tract infections, septic arthritis, paraspinal abscess, osteomyelitis, mycotic aneurysm, and generalized lymphadenopathy all have been observed. Meliodosis may also present as an encephalitic illness with fever and seizures. It is also an agent of severe wound infections following contact with contaminated water following a tsunami.

Diagnosis is based on visualization of characteristic small Gram-negative rods in exudates or growth on laboratory media such as eosin–methylene blue or MacConkey agar. Serologic tests are available, and diagnosis can be established by a 4-fold or greater increase in antibody titer in an individual with an appropriate syndrome. It has been recognized as a possible agent of bioterrorism (see Chapter 723).

*B. pseudomallei* is susceptible to many antimicrobial agents, and the Centers for Disease Control and Prevention (CDC) recommends meropenem or ceftazidime as intravenous therapies and trimethoprim-sulfamethoxazole or doxycycline as oral therapy. Other choices include aminoglycosides, tetracycline, chloramphenicol, and amoxicillin-clavulanate. Therapy should be guided by antimicrobial susceptibility tests; 2 or 3 agents such as ceftazidime or meropenem plus either trimethoprim-sulfamethoxazole, sulfisoxazole, or an aminoglycoside are usually chosen for severe or septicemic disease. For severe disease, prolonged treatment for 2-6 mo is recommended to prevent relapses. Appropriate antibiotic therapy generally results in recovery.

**205.3 Stenotrophomonas**

*Stenotrophomonas maltophilia* (formerly *Xanthomonas maltophilia* or *P. maltophilia*) is a short to medium-sized straight Gram-negative bacillus. It is ubiquitous in nature and can be found in the hospital environment, especially in tap water or standing water, and may contaminate sinks and hospital equipment such as nebulizers. Strains isolated in the laboratory may be contaminants, may be a commensal from the colonized surface of a patient, or may represent an invasive pathogen. The species is an opportunist and is often recovered from immunosuppressed patients and patients with cystic fibrosis after multiple courses of antimicrobial therapy. Serious infections usually occur among those requiring intensive care, including neonatal intensive care, typically patients with ventilator-associated pneumonia or catheter-associated infections. Prolonged antibiotic exposure appears to be a frequent factor in nosocomial *S. maltophilia* infections, probably because of its endogenous antibiotic resistance pattern. Common types of infection include pneumonia following airway colonization and aspiration, bacteremia, soft-tissue infections, endocarditis, and osteomyelitis. *S. maltophilia* bacteremia is a nosocomial infection associated with the presence of a central venous catheter.

Strains vary as to antibiotic susceptibility, and the treatment of *S. maltophilia* can be difficult because of inherent antimicrobial resistance. Data are lacking on whether there is clinical benefit to treat *S. maltophilia* recovered from the respiratory tract of a patient with cystic fibrosis. For invasive infections, trimethoprim-sulfamethoxazole is the treatment of choice and is the only antimicrobial for which susceptibility is routinely reported. Mean inhibitory concentration testing is available for other antibiotics, such as ticarcillin-clavulanate, and reserved for trimethoprim-sulfamethoxazole resistant isolates. For resistant organisms or for patients who cannot tolerate sulfa drugs, other options based on clinical outcome include ciprofloxacin, and ceftazidime alone, or in combination with other agents such as aminoglycosides. Tigecycline is a newer agent reported to have efficacy for treating a highly resistant isolate.

Bibliography is available at Expert Consult.
Bibliography

**Burkholderia cepacia Complex**

Cystic Fibrosis Foundation: CF Foundation updates infection prevention and control policy for all foundation events and meetings. Available at: http://www.cff.org/aboutCFFoundation/InfectionPreventionControlPolicy/.


**Burkholderia mallei**


**Burkholderia pseudomallei**


Bibliography

Tularemia is a zoonotic infection caused by the Gram-negative bacterium *Francisella tularensis*. Tularemia is primarily a disease of wild animals; human disease is incidental and usually results from contact with blood-sucking insects or live or dead wild animals. The illness caused by *F. tularensis* is manifested by different clinical syndromes, the most common consisting of an ulcerative lesion at the site of inoculation with regional lymphadenopathy or lymphadenitis. *F. tularensis* is also a potential agent of bioterrorism (see Chapter 723).

**ETIOLOGY**

*F. tularensis* is a small, nonmotile, pleomorphic, Gram-negative coc-cobacillus that can be classified into 4 main subspecies, namely

- *F. tularensis tularensis* [type A],
- *F. tularensis holarctica* [type B],
- *F. tularensis streblonis* [type C],
- *F. tularensis novomexicana* (type D).
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F. tularensis mediaisatica, and F. tularensis novicida. Type A can be further subdivided into 4 distinct genotypes designated A1a, A1b, A2a, and A2b, with A1b appearing to produce more serious disease in humans. Type A is found exclusively in North America and is associated with wild rabbits, ticks, and tabanid flies (e.g., deer flies), whereas type B is found in North America, Europe, and Asia and is associated with semiaquatic rodents, hares, mosquitoes, ticks, tabanid flies, water (e.g., ponds, rivers), and marine animals. Human infections with type B are usually milder and have lower mortality rates compared to infections with type A.

EPIDEMIOLOGY
During 2001-2010, a total of 1,208 cases of tularemia were reported in the United States from 47 states, averaging 126.5 cases (range: 90-154) per year (Fig. 206-1). Six states accounted for 59% of all reported cases: Missouri, 231 cases (19%); Arkansas, 162 cases (13%); Oklahoma, 108 cases (9%); Massachusetts, 84 cases (7%); South Dakota, 65 cases (5%); and Kansas, 59 cases (5%).

Transmission
Of all the zoonotic diseases, tularemia is unusual because of the different modes of transmission of disease. A large number of animals serve as a reservoir for this organism, which can penetrate both intact skin and mucous membranes. Transmission can occur through the bite of infected ticks or other biting insects, by contact with infected animals or their carcasses, by consumption of contaminated foods or water, or through inhalation, as might occur in a laboratory setting. However, this organism is not transmitted from person to person. In the United States, rabbits and ticks are the principal reservoirs. Most disease caused by rabbit exposure occurs in the winter, and disease from tick exposure occurs in the warmer months (April-September). Amblyomma americanum (Lone Star tick), Dermacentor variabilis (dog tick), and Dermacentor andersoni (wood tick) are the most common tick vectors. These ticks usually feed on infected small rodents and later feed on humans. Taking that blood meal through a fecally contaminated field transmits the infection.

PATHOGENESIS
The most common portal of entry for human infection is through the skin or mucous membrane. Entry may occur through the bite of an infected insect or by way of unapparent abrasions. Inhalation or ingestion of F. tularensis can also result in infection. Usually >10^8 organisms are required to produce infection if they are ingested, but as few as 10 organisms may cause disease if they are inhaled or injected into the skin. Within 48-72 hr after injection into the skin, an erythematous, tender, or pruritic papule may appear at the portal of entry. This papule may enlarge and form an ulcer with a black base, followed by regional lymphadenopathy. Once F. tularensis reaches the lymph nodes, the

* One dot is placed randomly within county of residence for each reported case.

organism may multiply and form granulomas. Bacteremia may also be present and is most commonly associated with involvement of the reticuloendothelial system, although any organ of the body may be involved.

Conjunctival inoculation may result in infection of the eye with preauricular lymphadenopathy. Inhalation or hematogenous spread of the organisms can result in pneumonia. Chest roentgenograms of such patients may reveal patchy infiltrates rather than areas of consolidation. Pleural effusions may also be present and may contain blood. In pulmonary infections, mediastinal adenopathy may be present; in oropharyngeal disease, patients may develop cervical lymphadenopathy. Typhoidal tularemia is a term used to describe severe bacteremic disease, regardless of the mode of transmission or portal of entry.

Infection with *F. tularensis* stimulates the host to produce antibodies, which have only recently been recognized as important in the immune response to this organism. The body is most dependent on cell-mediated immunity to contain and eradicate *F. tularensis*. Tularemia is usually followed by specific protection; thus, chronic infection or reinfection is unlikely.

**CLINICAL MANIFESTATIONS**

Although it may vary, the average incubation period from infection until clinical symptoms is 3 days (range: 1-21 days). A sudden onset of fever with other associated symptoms is common (Table 206-1). Physical examination may include lymphadenopathy, hepatosplenomegaly, or skin lesions. Various skin lesions have been described, including erythema multiforme and erythema nodosum. Approximately 20% of patients may develop a generalized maculopapular rash that occasionally becomes pustular. These clinical manifestations of infection are unlikely.

**TABLE 206-1**

<table>
<thead>
<tr>
<th>SIGN OR SYMPTOM</th>
<th>FREQUENCY (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphadenopathy</td>
<td>96</td>
</tr>
<tr>
<td>Fever (≥38.9°C [101.0°F])</td>
<td>87</td>
</tr>
<tr>
<td>Ulcer/eschar/papule</td>
<td>45</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>43</td>
</tr>
<tr>
<td>Myalgias/arthritis</td>
<td>39</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>35</td>
</tr>
<tr>
<td>Hepatosplenomegaly</td>
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</tr>
</tbody>
</table>

**Table 206-2**

<table>
<thead>
<tr>
<th>CLINICAL SYNDROME</th>
<th>FREQUENCY (%)</th>
</tr>
</thead>
<tbody>
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<td>Ulceroglandular</td>
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</tr>
<tr>
<td>Glandular</td>
<td>25</td>
</tr>
<tr>
<td>Pneumonia</td>
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<tr>
<td>Oropharyngeal</td>
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</tr>
<tr>
<td>Oculoglandular</td>
<td>2</td>
</tr>
<tr>
<td>Typhoidal</td>
<td>2</td>
</tr>
<tr>
<td>Other*</td>
<td>6</td>
</tr>
</tbody>
</table>

*Includes meningitis, pericarditis, hepatitis, peritonitis, endocarditis, and osteomyelitis.

**Ulceroaglandular and glandular disease** are the 2 most common forms of tularemia diagnosed in children. The most common glands involved are the cervical or posterior auricular nodes owing to a tick bite on the head or neck. If an ulcer is present, it is erythematous and painful and may last from 1-3 wk. The ulcer is located at the portal of entry. After the ulcer develops, regional lymphadenopathy ensues. These nodes may vary in size from 0.5-10 cm and may appear singly or in clusters. These affected nodes may become fluctuant and drain spontaneously, but usually resolve with treatment. Late suppuration of the involved nodes has been described in 25-30% of patients despite effective therapy. Examination of this material from such lymph nodes usually reveals sterile necrotic material.

**Pneumonia** caused by *F. tularensis* usually presents as variable parenchymal infiltrates that are unresponsive to β-lactam antimicrobial agents. Inhalation-related infection has been described in laboratory workers who are working with the organism and results in a relatively high mortality rate. Aerosols from farming activities involving rodent contamination (haying, threshing) or animal carcass destruction with lawn mowers have been reported to cause pneumonia as well. Patchy parenchymal infiltrates can also be demonstrated in other forms of tularemia. Patchy segmental infiltrates, hilar adenopathy, and pleural effusions are the most common abnormalities demonstrated on chest roentgenograms. Patients may also complain of a nonproductive cough, dyspnea, or pleuritic chest pain.

**Oropharyngeal tularemia** results from consumption of poorly cooked meats or contaminated water. This syndrome is characterized by acute pharyngitis, with or without tonsillitis, and cervical lymphadenitis. Infected tonsils may become large and develop a yellowish-white membrane that may resemble the membranes associated with diphtheria. Gastrointestinal disease may also occur and usually presents with mild, unexplained diarrhea but may progress to rapidly fulminant and fatal disease.

**Oculoglandular tularemia** is uncommon, but when it does occur, the portal of entry is the conjunctiva. Contact with contaminated fingers or debris from crushed insects is the most common way of applying the organisms to the conjunctiva. The conjunctiva is painful and inflamed, with yellowish nodules and pinpoint ulcerations. Purulent conjunctivitis with ipsilateral preauricular or submandibular lymphadenopathy is referred to as **Parinaud oculoglandular syndrome**.

**Typhoidal tularemia** is usually associated with a large inoculum of organisms and usually presents with fever, headaches, and signs or symptoms of endotoxemia. Patients typically are critically ill, and symptoms mimic those with other forms of sepsis. Clinicians practicing in tularemia-endemic regions must always consider this diagnosis in critically ill children.

**DIAGNOSIS**

The history and physical examination of the patient may suggest the diagnosis of tularemia, especially if the patient lives in or has visited an endemic region. A history of animal or tick exposure may be especially helpful. Hematologic blood tests are nondiagnostic. Results of routine cultures and smears are positive in only approximately 10% of cases. *F. tularensis* can be cultured in the microbiology laboratory on cysteine–glucose–blood agar, but care should be taken to alert the personnel in the laboratory if this is attempted so that they can take the proper precautions to protect themselves from acquiring infection.

The diagnosis of tularemia is most commonly established through the use of a standard and highly reliable serum agglutination test. In the standard tube agglutination test, a single titer of ≥1:160 in a patient with a compatible history and physical findings can establish the diagnosis. A 4-fold increase in titer from paired serum samples collected 2-3 wk apart is also diagnostic. False-negative serologic responses can be obtained early in the infection, and as many as 30% of individuals require longer than 3 wk before testing positive. Once infected, patients may have a positive agglutination test result (1:20 to 1:80) that may persist for life.

Other testing techniques available include a microagglutination test, enzyme-linked immunosorbent assay, analysis of urine for tularemia...
antigen, and polymerase chain reaction. These techniques may become more popular in the future but at this time have a limited role in establishing the diagnosis of tularemia.

**Differential Diagnosis**

The differential diagnosis of ulceroglandular or glandular tularemia includes cat scratch disease (*Bartonella henselae*); infectious mononucleosis; Kawasaki syndrome; lymphadenopathy caused by *Staphylococcus aureus*, group A streptococcus, *Mycobacterium tuberculosis*, *Toxoplasma gondii*, nontuberculous mycobacteria, or *Sporothrix schenckii*; plague; anthrax; melioidosis; and rat-bite fever. Oculoglandular disease may also occur with other infectious agents, such as *B. henselae*, *Treponema pallidum*, *Coccidioides immitis*, herpes simplex virus, adenoviruses, and the bacterial agents responsible for purulent conjunctivitis. Oropharyngeal tularemia must be differentiated from the same diseases that cause ulceroglandular/glandular disease and from cytomegalovirus, herpes simplex, adenovirus, and other viral or bacterial etiologies. Pneumonic tularemia must be differentiated from the other non-β-lactam-responsive organisms such as *Mycoplasma*, *Chlamydia*, mycobacteria, fungi, and rickettsia. Typhoidal tularemia must be differentiated from other forms of sepsis as well as from enteric fever (typhoid and paratyphoid fever) and brucellosis.

**TREATMENT**

All strains of *F. tularensis* are susceptible to gentamicin and streptomycin. Gentamicin (5 mg/kg/day divided bid or tid IV or IM) is the drug of choice for the treatment of tularemia in children because of the limited availability of streptomycin (30–40 mg/kg/day divided bid IM) and the fewer adverse effects of gentamicin. Therapy is typically continued for 7–10 days, but in mild cases, 5–7 days may be sufficient. Chloramphenicol and tetracyclines have been used, but the high relapse rate has limited their use in children. Early data suggested that *F. tularensis* is susceptible to the third-generation cephalosporins (ceftaxime, ceftriaxone), but clinical case reports demonstrate a nearly universal failure rate with these agents. Fluoroquinolones have been used with success in cases of illness caused by the subspecies *holarctica*. Ciprofloxacin (15–20 mg/kg/day in 2 divided doses for 10–14 days) has been used in children, but the lack of treatment data for the subspecies *tularensis* and the issues related to the use of fluoroquinolones in patients younger than 18 yr of age limit the use of this group of medications in North American children at this time.

Patients typically have defervescence within 24–48 hr after starting therapy, and relapses are uncommon if gentamicin or streptomycin is used. Patients who have not started on appropriate therapy early may respond more slowly to antimicrobial therapy. Late suppuration of involved lymph nodes may occur despite adequate therapy.

**PROGNOSIS**

Poor outcomes are associated with a delay in recognition and treatment, but with rapid recognition and treatment, fatalities are exceedingly rare. The mortality rate for severe untreated disease (e.g., pneumonia, typhoidal disease) can be as high as 30% in these situations, but in general, the overall mortality rate is <1%.

**PREVENTION**

Prevention of tularemia is based on avoiding exposure. Children living in tick-endemic regions should be taught to avoid tick-infested areas, and families should have a tick control plan for their immediate environment and for their pets. Protective clothing should be worn when entering a tick-infested area. Insect repellents for use on the skin (e.g., DEET [N,N-diethyl-3-methylbenzamide] or picaridin) can be used safely in infants and children. If skin repellents are used, they should be used sparingly on the exposed skin, avoiding the hands and face on children younger than 1 yr of age. The repellent should be washed off completely after leaving the high-risk region. Clothing repellents that use permethrin have been demonstrated to be an effective addition to the use of protective clothing. Infants and young children should not be allowed to chew or suck on permethrin impregnated clothing.
Bibliography
Human brucellosis is caused by organisms of the genus *Brucella* and continues to be a major public health problem worldwide. Humans are accidental hosts and acquire this zoonotic disease from direct contact with an infected animal or consumption of products of an infected animal. Although brucellosis is widely recognized as an occupational risk among adults working with livestock, much of the brucellosis in children is foodborne and is associated with consumption of unpasteurized milk products. *Brucella* spp. are also potential agents of bioterrorism (see Chapter 723).

**ETIOLOGY**

*Brucella abortus* (cattle), *Brucella melitensis* (goat/sheep), *Brucella suis* (swine), and *Brucella canis* (dog) are the most common organisms responsible for human disease. These organisms are small, aerobic, non–spore-forming, nonmotile, Gram-negative coccobacillary bacteria that are fastidious in their growth but can be grown on various laboratory media, including blood and chocolate agars.

**EPIDEMIOLOGY**

Because of improved sanitation, brucellosis has become rare in industrialized countries. Brucellosis exists worldwide and is especially prevalent in the Mediterranean basin, Persian Gulf, Indian subcontinent, and parts of Mexico and Central and South America. In industrialized countries, recreational or occupational exposure to infected animals is a major risk factor for the development of disease. In the United States, more than 50% of cases occur in California, Florida, and Texas, and hunting feral swine in these states is a recently recognized risk factor. Among children, geographic locations that are endemic for *B. melitensis* remain areas of increased risk for the development of infection. In such locations, unpasteurized milk from goats or camels may be used to feed children, thus leading to the development of brucellosis. A history of travel to endemic regions or consumption of exotic food or unpasteurized dairy or dairy products may be an important clue to the diagnosis of human brucellosis.

**PATHOGENESIS**

Routes of infection for these organisms include inoculation through cuts or abrasions in the skin, inoculation of the conjunctival sac of the eye, inhalation of infectious aerosols, or ingestion of contaminated meat or dairy products. The risk for infection depends on the nutritional and immune status of the host, the route of inoculum, and the species of *Brucella*. For reasons that remain unclear, it has been suggested that *B. melitensis* and *B. suis* are more virulent than *B. abortus* or *B. canis*. 
The major virulence factor for Brucella appears to be its cell wall lipopolysaccharide. Strains containing smooth lipopolysaccharide have been demonstrated to have greater virulence and are more resistant to killing by polymorphonuclear leukocytes. These organisms are facultative intracellular pathogens that can survive and replicate within the mononuclear phagocytic cells (monocytes, macrophages) of the reticuloendothelial system. Even though Brucella are chemotactic for entry of leukocytes into the body, the leukocytes are less efficient at killing these organisms than other bacteria despite the assistance of serum factors such as complement.

Organisms that are not phagocytosed by the leukocytes are ingested by the macrophages and become localized within the reticuloendothelial system. Specifically, they reside within the liver, spleen, lymph nodes, and bone marrow and result in granuloma formation. Antibodies are produced against the lipopolysaccharide and other cell wall antigens, providing a means of diagnosis and probably playing a role in long-term immunity. The major factor in recovery from infection appears to be development of a cell-mediated response resulting in macrophage activation and enhanced intracellular killing. Specifically, sensitized T lymphocytes release cytokines (e.g., interferon-γ and tumor necrosis factor-α), which activate the macrophages and enhance their intracellular killing capacity.

**CLINICAL MANIFESTATIONS**

Brucellosis is a systemic illness that can be very difficult to diagnose in children without a history of animal or food exposure. Symptoms can be acute or insidious in nature and are usually nonspecific, beginning 2-4 wk after inoculation. Although the clinical manifestations vary, the classic triad of fever, arthralgia/arthritis, and hepatosplenomegaly can be demonstrated in most patients. Some present as a fever of unknown origin. Other associated symptoms include abdominal pain, headache, diarrhea, rash, night sweats, weakness/fatigue, vomiting, cough, and pharyngitis. A common constellation of symptoms in children is refusal to eat, lassitude, refusal to bear weight, and failure to thrive. Besides hepatosplenomegaly, the physical findings on examination are usually few, with the exception of arthritis. The fever pattern can vary widely, and virtually any organ or tissue can be involved.

If abnormalities are demonstrated on physical examination, mononuclear arthritis of the knees and hips in children and of the sacroiliac joint in adolescents and adults can be found. Although headache, mental inattention, and depression may be demonstrated in patients with brucellosis, invasion of the nervous system occurs in only approximately 1% of cases. Neonatal and congenital infections with these organisms have also been described, resulting from transmission transplacentally, from breast milk, and through blood transfusions. The signs and symptoms associated with brucellosis are vague and not pathognomonic.

**DIAGNOSIS**

Routine laboratory examinations of the blood are not helpful; thrombocytopenia, neutropenia, anemia, or pancytopenia may occur. A history of exposure to animals or ingestion of unpasteurized dairy products may be more helpful. A definitive diagnosis is established by recovering the organisms in the blood, bone marrow, or other tissues. Although automated culture systems and the use of the lysis-centrifugation method have shortened the isolation time from weeks to days, it is prudent to alert the clinical microbiology laboratory that brucellosis is suspected. Isolation of the organism still may require as long as 4 wk from a blood culture sample unless the laboratory is using an automated culture system such as the lysis centrifugation method where the organism can be recovered in <5 days. Bone marrow cultures may be superior to blood cultures when evaluating patients with previous antimicrobial therapy. Caution is advised when using automated bacterial identification systems, because isolates have been misidentified as other Gram-negative organisms (Haemophilus influenzae type b).

In the absence of positive culture results, various serologic tests have been applied to the diagnosis of brucellosis. The serum agglutination test is the most widely used and detects antibodies against B. abortus, B. melitensis, and B. suis. This method does not detect antibodies against B. canis because this organism lacks the smooth lipopolysaccharide. No single titer is ever diagnostic, but most patients with acute infections have titers of ≥1:160. Low titers may be found early in the course of the illness, requiring the use of acute and convalescent sera testing to confirm the diagnosis. Because patients with active infection have both an immunoglobulin (Ig) M and an IgG response and the serum agglutination test measures the total quantity of agglutinating antibodies, the total quantity of IgG is measured by treatment of the serum with 2-mercaptoethanol. This fractionation is important in determining the significance of the antibody titer because low levels of IgM can remain in the serum for weeks to months after the infection has been treated. It is important to remember that all titers must be interpreted in light of a patient's history and physical examination. False-positive results resulting from crossreacting antibodies to other Gram-negative organisms, such as Yersinia enterocolitica, Francisella tularense, and Vibrio cholerae, can occur. In addition, the prozone effect can give false-negative results in the presence of high titers of antibody. To avoid this issue, serum that is being tested should be diluted to ≥1:320.

Among newer tests, the enzyme immunoassay should only be used for suspected cases with negative serum agglutination tests or for the evaluation of patients in the following situations: (1) complicated cases; (2) suspected chronic brucellosis; (3) reinfection. Polymerase chain reaction assays have been developed but are not available in most clinical laboratories.

**Differential Diagnosis**

Brucellosis may be confused with other infections such as tularemia, cat scratch disease, typhoid fever, histoplasmosis, blastomycosis, and coccidioidomycosis. Infections caused by Mycobacterium tuberculosis, atypical mycobacteria, rickettsiae, and Yersinia can present in a similar fashion to brucellosis.

**TREATMENT**

Many antimicrobial agents are active in vitro against the Brucella species, but the clinical effectiveness does not always correlate with these results. Doxycycline is the most useful antimicrobial agent and, when combined with an aminoglycoside, is associated with the fewest relapses (Table 207-1). Treatment failures with β-lactam antimicrobial agents, including the third-generation cephalosporins, may be because of the intracellular nature of the organism. Agents that provide intracellular killing are required for eradication of this infection. Similarly, it is apparent that prolonged treatment is the key to preventing disease relapse. Relapse is confirmed by isolation of Brucella within weeks to months after therapy has ended and is usually not associated with antimicrobial resistance. The onset of initial antimicrobial therapy may precipitate a Jarisch-Herxheimer-like reaction, presumably because of a large antigen load. It is rarely severe enough to require corticosteroid therapy.

**PROGNOSIS**

Before the use of antimicrobial agents, the course of brucellosis was often prolonged and may have led to death. Since the institution of specific therapy, most deaths are a result of specific organ system involvement (e.g., endocarditis) in complicated cases. The prognosis after specific therapy is excellent if patients are compliant with the prolonged therapy (see Table 207-1).

**PREVENTION**

Prevention of brucellosis is dependent on effective eradication of the organism from cattle, goats, and swineherds, as well as from other animals. Pasteurization of milk and dairy products for human consumption remains an important aspect of prevention. It should be noted that certification of raw milk does not eliminate the risk of brucellosis acquisition. No vaccine currently exists for use in children and, therefore, education of the public continues to have a prominent role in prevention of this disease.

*Bibliography is available at Expert Consult.*
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Legionellosis comprises Legionnaires disease (Legionella pneumonia), other invasive extrapulmonary Legionella infections, and an acute flu-like illness known as Pontiac fever. In contrast to the syndromes associated with invasive disease, Pontiac fever is a self-limited illness that develops after aerosol exposure and may represent a toxic or hypersensitivity response to Legionella.

ETIOLOGY
Legionellaceae are aerobic, non-spore-forming, unencapsulated Gram-negative bacilli that stain poorly with Gram stain when performed on smears from clinical specimens. Microorganisms in tissue can be better visualized with the Gimenez or silver stains (Dieterle or Warthin-Starry). Stained smears of Legionella pneumophila taken from colonial growth resemble Pseudomonas. Unlike other Legionella species, Legionella micdadei stains acid fast. Although more than 30 species of the genus have now been identified, the majority (90%) of clinical infections are caused by L. pneumophila, and most of the remainder are caused by L. micdadei, Legionella bozemanii, Legionella dumoffii, and Legionella longbeachae. The organisms are fastidious and require L-cysteine, ferric ion, and α-keto acids for growth. Colonies develop within 3-5 days on buffered charcoal yeast extract agar, which may contain selected antibiotics to inhibit overgrowth by other microorganisms; Legionella rarely grows on routine laboratory media.

EPIDEMIOLOGY
The environmental reservoir of Legionella in nature is fresh water (lakes, streams, thermally polluted waters, potable water), and invasive pneumonia (Legionnaires disease) is related to exposure to potable water or to aerosols containing the bacteria. Growth of Legionella occurs more readily in warm water, and exposure to warm water sources is an important risk factor for disease. Legionella organisms are facultative intracellular parasites and grow inside protozoans present in biofilms consisting of organic and inorganic material found in plumbing and water storage tanks and various other bacterial species. Epidemic and sporadic cases of community-acquired Legionnaires disease can be attributed to potable water in the local environment of the patient. Risk factors for acquisition of sporadic community-acquired pneumonia include exposure to cooling towers, nonmunicipal water supply, residential plumbing repairs, and lower water heater temperatures, which facilitate growth of bacteria or lead to release of a bolus of biofilm containing Legionella into potable water. The mode of transmission may be by way of inhalation of aerosols or by microaspiration. Outbreaks of Legionnaires disease have been associated with protozoans in the implicated water source; replication within these eukaryotic cells presumably amplifies and maintains Legionella within the potable water distribution system or in cooling towers. Outbreaks of community-acquired pneumonia and some nosocomial outbreaks have been linked to common sources, including potable hot water heaters, evaporative condensers, cooling towers, whirlpool baths, humidifiers, and nebulizers. Travel-associated Legionnaires disease and Pontiac fever are increasingly recognized in major outbreaks.

Hospital-acquired infections are most often linked to potable water. Exposure may occur through 3 general mechanisms: (1) inhalation of contaminated water vapor through artificial ventilation; (2) aspiration of ingested microorganisms, including those in gastric feedings that are mixed with contaminated tap water; and (3) inhalation of aerosols from showers, sinks and fountains. Extrapulmonary legionellosis may occur through topical application of contaminated tap water into surgical or traumatic wounds. In contrast to Legionnaires disease, Pontiac fever outbreaks have occurred through exposure to aerosols from whirlpool baths and ventilation systems.

The incidence of legionellosis in the United States increased from 1,100 cases in 2000 to 3,522 cases in 2009 for a national incidence rate of 1.15 per 100,000 persons based on passive reporting to the Centers for Disease Control and Prevention (CDC) through the National Notifiable Disease Surveillance System. Legionellosis demonstrates geographic differences, and the vast majority of cases are classified as Legionnaires disease (99.5%) vs a small fraction as Pontiac fever (0.5%). Legionella infections are reported most frequently in fall and summer, and recent studies show an association with total monthly rainfall and humidity. Approximately 0.5-5.0% of those exposed to a common source develop pneumonia, whereas the attack rate in Pontiac fever outbreaks is very high (85-100%). Although Legionella is associated with 2-9% of pneumonia cases in adults, it is a rare cause of disease in pediatric populations, accounting for fewer than 1% of cases. Taken together, Mycoplasma pneumoniae, Chlamydia pneumoniae, and L. pneumophila have been identified in 3-23% of children studied with atypical pneumonia. These pathogens show a specific age distribution, with M. pneumoniae more commonly isolated in older children and C. pneumoniae more frequently recovered from infants. Legionella remains a rare cause of community-acquired pneumonia in those younger than 19 yr of age. Acquisition of antibodies to L. pneumophila
in healthy children occurs progressively over time, although these antibodies presumably reflect subclinical infection or mild respiratory disease or antibodies that crossreact with other bacterial species. Community-acquired Legionnaires disease in children is increasingly reported (1.7% of reported cases), and most cases occur in children ages 15-19 yr, followed by infants age younger than 1 yr. The incidence in infants is reported to be 0.11 per 100,000. It is likely that legionellosis is significantly underreported, both in children and adults.

As estimated by seroconversion to L. pneumophila among children hospitalized with pneumonia, the Legionnaires disease rate is quite low. Most nosocomial infections have been reported as case reports; consequently, the true incidence of disease in children is unknown. Nosocomial infection rates in adults are difficult to determine, because many hospital laboratories do not attempt to isolate Legionella by culture. Hospital-acquired legionellosis in children is associated with clinical risk factors and with environmental exposure.

**PATHOGENESIS**

Although Legionella can be grown on artificial media, the intracellular environment of eukaryotic cells provides the definitive site of growth. Legionella organisms are facultative intracellular parasites of eukaryotic cells. In nature, Legionella replicate within protozoans found in fresh water. In humans, the main target cell for Legionella is the alveolar macrophage, although other cell types may also be invaded. After entry, virulent strains of L. pneumophila stimulate the formation of a special phagosome that permits bacterial replication to proceed. The phagosome consists of components of the endoplasmic reticulum and escapes the degradative lysosomal pathway. Growth in macrophages occurs to the point of cell death, followed by reinfection of new cells, until these cells are activated and can subsequently kill intracellular microorganisms. Acute, severe infection of the lung provokes an acute inflammatory response and necrosis; early on, more bacteria are found in extracellular spaces as a result of intracellular replication, lysis, and release of bacteria. Subsequently, macrophage activation and other immune responses produce intense infiltration of tissue by macrophages that contain intracellular bacteria, ultimately leading to control of bacterial replication and killing. Corticosteroid therapy poses a high risk for infection by interfering with T-cell and macrophage function. Although community-acquired Legionnaires disease may occur in healthy, immunocompetent patients without other comorbid conditions, those who have defects in cellular-mediated immunity are at high risk for infection. As in other diseases caused by facultative intracellular microorganisms, the outcome is critically dependent on the specific and nonspecific immune responses of the host, particularly macrophage and T-cell responses.

**CLINICAL MANIFESTATIONS**

Legionnaires disease was originally believed to cause atypical pneumonia associated with extrapulmonary signs and symptoms, including diarrhea, confusion, hyponatremia, hypophosphatemia, abnormal results of liver function tests, and renal dysfunction. Although a subset of patients may exhibit these classic manifestations, Legionella infection typically causes pneumonia that is indistinguishable from disease produced by other infectious agents. Fever, cough, and chest pain are common presenting symptoms; the cough may be productive of purulent sputum or may be nonproductive. Although the classic chest radiographic appearance demonstrates rapidly progressive alveolar filling infiltrates, in usual cases of pneumonia the chest radiographic appearance is widely variable, appearing as tumor-like shadows, evidence of nodular infiltrates, unilateral or bilateral infiltrates, or cavitation, although cavitation is rarely seen in immunocompetent patients. This picture overlaps substantially with disease caused by Streptococcus pneumoniae. Although pleural effusion is less commonly associated with Legionnaires disease, its frequency varies so widely that neither the presence nor absence of effusion is helpful in differential diagnosis. If present, pleural fluid should be obtained for culture.

A few clinical features may help to differentiate Legionella pneumonia from other causes. Legionella pneumonia produces an acute-onset febrile illness and radiographic evidence of alveolar filling infiltrates, and usually there is no clinical response to broad-spectrum β-lactam (penicillins and cephalosporins) or aminoglycoside antibiotics.

Concomitant infection with other pathogens, including M. pneumonias and C. pneumoniae, occurs in 5-10% of cases of Legionnaires disease; therefore, detection of another potential pulmonary pathogen does not preclude the diagnosis of legionellosis.

Most reports of nosocomial Legionella pneumonia in children demonstrate the following clinical features: rapid onset, temperature greater than 38.5°C (101.3°F), cough, pleuritic chest pain, tachypnea, and dyspnea. Abdominal pain, headache, and diarrhea are also common. Chest radiographs reveal lobar consolidations or diffuse bilateral infiltrates, and pleural effusions may be noted. Risk factors for Legionnaires disease in adults include chronic diseases of the lung (smoking, bronchitis), older age, diabetes and renal failure, immunosuppression associated with organ transplantation, corticosteroid therapy; and episodes of aspiration. In surveys of community-acquired infection, a significant number of adults have no identified risk factors. The number of reported cases of community-acquired Legionnaires disease in children is small. Among these, immunocompromised status, especially corticosteroid treatment, coupled with exposure to contaminated potable water is the major risk factor. Infection in a few children with chronic pulmonary disease without immune deficiency has also been reported, but infection in children lacking any risk factors is very uncommon. The modes of transmission of community-acquired disease in children include exposure to mists, fresh water, water coolers, and other aerosol-generating apparatuses. Nosocomial Legionella infection occurs more frequently than community-acquired disease in children and occurs most commonly in those who are immunocompromised, although Legionnaires disease has been seen in immunocompetent children who are postoperative receiving artificial ventilation or exposed to other aerosols. The modes of acquisition include macroaspiration, frequently associated with nasogastric tubes, and aerosol inhalation. Bronchopulmonary Legionella infections are reported in patients with cystic fibrosis and have been associated with aerosol therapy or mist tents. Legionnaires disease is also reported in pediatric patients with asthma and tracheal stenosis. Chronic corticosteroid therapy for asthma is a reported risk factor for Legionnaires infections in children. Molecular fingerprinting of strains has demonstrated that potable water serves as the major reservoir and source of nosocomial infection.

Pontiac fever in adults and children is characterized by high fever, myalgia, headache, and extreme debilitation, lasting for a few days. Cough, breathlessness, diarrhea, confusion, and chest pain may occur, but there is no evidence for invasive infection. The disease is self-limited without sequelae. Virtually all exposed individuals seroconvert to Legionella antigens. A very large outbreak in Scotland that affected 35 children was attributed to L. micdadei, which was isolated from a whirlpool spa. The onset of illness was 1-7 days (median: 3 days), and all exposed children developed significant titers of specific antibodies to L. micdadei. The pathogenesis of Pontiac fever is not known. In the absence of evidence of true infection, the most likely hypothesis is that this syndrome is caused by a toxic or hypersensitivity reaction to microbial, or protozoan, antigens.

**DIAGNOSIS**

Culture of Legionella from sputum, other respiratory tract specimens, blood, or tissue is the gold standard against which indirect methods of detection should be compared. Specimens obtained from the respiratory tract that are contaminated with oral flora must be treated and processed to reduce contaminants and plated onto selective media. Because these are costly and time-consuming methods, many laboratories do not process specimens for culture. The urinary antigen assay that detects L. pneumophila serogroup I has revolutionized the diagnosis of Legionella infection and has 80% sensitivity and 99% specificity. The assay is a useful method in the prompt diagnosis of Legionnaires disease caused by this serogroup, which accounts for the majority of symptomatic infections. In the United States, this test is frequently used because it is widely available in reference laboratories. Where available, polymerase chain reaction is used to identify L. pneumophila from bronchoscopic lavage and other clinical specimens to the exclusion of other respiratory pathogens. Other methods, including direct immunofluorescence, have low sensitivity and are generally not employed. Retrospective diagnosis can be made serologically using the enzyme-linked
immunosorbent assay or enzyme immunoassay to detect specific antibody production. Seroconversion may not occur for several weeks after onset of infection, and the available serologic assays do not detect all strains of *L. pneumophila* or all species. In view of the low sensitivity of direct detection and the slow growth of the microorganism in culture, the diagnosis of legionellosis should be pursued actively when there is suggestive clinical evidence, including the lack of response to usual antibiotics, even when results of other laboratory studies are negative.

**TREATMENT**

In community-acquired pneumonia in adults who are hospitalized, guidelines recommend empirical treatment with a broad-spectrum cephalosporin plus a macrolide or quinolone so as to treat atypical microorganisms (*Legionella, Chlamydia pneumoniae, M. pneumoniae*). Evidence-based guidelines for management of community-acquired pneumonia in children do not yet include *Legionella* in the differential diagnosis or empiric treatment recommendations. Effective treatment of Legionnaires disease is based in part on the intracellular concentration of antibiotics. Erythromycin (40 mg/kg/day PO or IV) with or without rifampin (15 mg/kg/day) was considered effective therapy many years ago. Azithromycin (10 mg/kg on day 1, not to exceed 500 mg/day, and then 5 mg/kg daily for 4 days PO) and clarithromycin (15 mg/kg/day PO) and the quinolones (ciprofloxacin and levofloxacin) have generally replaced erythromycin as therapy for patients with diagnosed *Legionella* infection. Quinolones are not approved for children younger than 18 yr of age and should be avoided in those who have not achieved growth maturity. In serious infections or in high-risk patients, parenteral therapy is recommended initially; a switch to oral therapy can be made when a patient has had a clinical response. The duration of oral azithromycin therapy for Legionnaires disease in adults is 4 days, although therapy is usually continued for 10-14 days in more seriously ill or immunocompromised patients. Acute reversible hearing loss is associated with high-dose parenteral macrolide therapy. Treatment of extrapulmonary infections, including prosthetic valve endocarditis and sternal wound infections, may require prolonged therapy. Trimethoprim-sulfamethoxazole (TMP-SMZ; 15 mg TMP/kg/day and 75 mg SMZ/kg/day) is used as an alternative.

**PROGNOSIS**

The mortality rate for community-acquired Legionnaires disease in adults who are hospitalized is approximately 15% but may exceed 50% in immunocompromised patients. The prognosis depends on underlying host factors and possibly on the duration of illness before initiation of appropriate therapy. Despite appropriate antibiotic therapy, patients may succumb to respiratory complications, such as acute respiratory distress syndrome, associated with artificial ventilation and intubation. A high mortality rate is noted in case reports of premature infants and children, virtually all of whom have been immunocompromised. Delay in diagnosis is also associated with increased mortality. Consequently, *Legionella* should be considered in the differential diagnosis of both community-acquired and nosocomial pneumonia in children, especially in those refractory to empiric therapy or with epidemiologic risk factors for legionellosis.

*Bibliography is available at Expert Consult.*
Bibliography


Chapter 209  Bartonella  1423

The spectrum of disease resulting from human infection with Bartonella species includes the association of bacillary angiomatosis and cat-scratch disease (CSD) with Bartonella henselae. There are more than 30 validated species of Bartonella; however, 6 major species are pathogenic for humans: Bartonella henselae, Bartonella quintana, Bartonella bacilliformis, Bartonella elizabethae, Bartonella vinsonii, and Bartonella clarridgeiae (Table 209-1). Several other Bartonella species have been found in animals, particularly rodents and moles.

Members of the genus Bartonella are Gram-negative, oxidase-negative, fastidious aerobic rods that ferment no carbohydrates. B. bacilliformis is the only species that is motile, achieving motility by means of polar flagella. Optimal growth is obtained on fresh media containing 5% or more sheep or horse blood in the presence of 5% carbon dioxide. The use of lysis centrifugation for specimens from blood on chocolate agar for extended periods (2–6 wk) enhances recovery.

Bibliography is available at Expert Consult.

209.1 Cat-Scratch Disease (Bartonella henselae)
Barbara W. Stechenberg

The most common presentation of Bartonella infection is CSD, which is a subacute, regional lymphadenitis caused by B. henselae. It is the most common cause of chronic lymphadenitis that persists for longer than 3 wk.

ETIOLOGY
B. henselae can be cultured from the blood of healthy cats. B. henselae organisms are the small pleomorphic Gram-negative bacilli visualized with Warthin-Starry stain in affected lymph nodes from patients with CSD. Development of serologic tests that showed prevalence of antibodies in 84–100% of cases of CSD, culturing of B. henselae from CSD nodes, and detection of B. henselae by polymerase chain reaction in the majority of lymph node samples and pus from patients with CSD, confirmed the organism as the cause of CSD. Occasional cases of CSD may be caused by other organisms; 1 report described a veterinarian with CSD caused by B. clarridgeiae.

EPIDEMIOLOGY
CSD is common, with more than 24,000 estimated cases per year in the United States. It is transmitted by cutaneous inoculation. Most (87–99%) patients have had contact with cats, many of which are kittens younger than 6 mo of age, and more than 50% of patients have a definite history of a cat scratch or bite. Cats have high-level Bartonella bacteremia for months without any clinical symptoms; kittens are more frequently bacteremic than adult cats. Transmission between cats occurs via the cat flea, Ctenocephalides felis. In temperate zones, the majority of cases occur between September and March, perhaps in relation to the seasonal breeding of domestic cats or to the close proximity of family pets in the fall and winter. In tropical zones, there is no seasonal prevalence. Distribution is worldwide, and infection occurs in all races.

Cat scratches appear to be more common among children, and boys are affected more often than girls. CSD is a sporadic illness; usually only 1 family member is affected, even though many siblings play with the same kitten. However, clusters do occur, with family cases within weeks of one another. Anecdotal reports have implicated other sources, such as dog scratches, wood splinters, fishhooks, cactus spines, and porcupine quills.

PATHOGENESIS
The pathologic findings in the primary inoculation papule and affected lymph nodes are similar. Both show a central avascular necrotic area with surrounding lymphocytes, giant cells, and histiocytes. Three stages of involvement occur in affected nodes, sometimes simultaneously in the same node. The 1st stage consists of generalized enlargement with thickening of the cortex and hypertrophy of the germinal center and with a predominance of lymphocytes. Epitheloid granulomas with Langhans giant cells are scattered throughout the node. The middle stage is characterized by granulomas that increase in density, fuse, and become infiltrated with polymorphonuclear leukocytes, with
Bibliography

beginning central necrosis. In the final stage, necrosis progresses with formation of large pus-filled sinuses. This purulent material may rupture into surrounding tissue. Similar granulomas have been found in the liver, spleen, and osteolytic lesions of bone when those organs are involved.

**CLINICAL MANIFESTATIONS**

After an incubation period of 7-12 days (range: 3-30 days), 1 or more 3-5 mm red papules develop at the site of cutaneous inoculation, often reflecting a linear cat scratch. These lesions are often overlooked because of their small size but are found in at least 65% of patients when careful examination is performed (Fig. 209-1). Lymphadenopathy is generally evident within a period of 1-4 wk (Fig. 209-2). Chronic regional lymphadenitis is the hallmark, affecting the 1st or 2nd set of nodes draining the entry site. Affected lymph nodes in order of frequency include the axillary, cervical, submandibular, preauricular, epi- trochlear, femoral, and inguinal nodes. Involvement of more than 1 group of nodes occurs in 10-20% of patients, although at a given site, half the cases involve several nodes.

Nodes involved are usually tender and have overlying erythema but without cellulitis. They usually range between 1 and 5 cm in size, although they can become much larger. Between 10% and 40% eventually suppurate. The duration of enlargement is usually 1-2 mo, with persistence up to 1 yr in rare cases. Fever occurs in approximately 30% of patients, usually 38-39°C (100.4-102.2°F). Other nonspecific symptoms, including malaise, anorexia, fatigue, and headache, affect less than one-third of patients. Transient rashes, which may occur in approximately 5% of patients, are mainly truncal maculopapular rashes. Erythema nodosum, erythema multiforme, and erythema annulare are also reported.

CSD is usually a self-limited infection that spontaneous resolves within a few weeks to months. The most common atypical presentation is Parinaud oculoglandular syndrome, which is unilateral conjunctivitis followed by preauricular lymphadenopathy and occurs in 2-17% of patients with CSD (Fig. 209-3). Direct eye inoculation as a result of rubbing with the hands after cat contact is the presumed mode of spread. A conjunctival granuloma may be found at the inoculation site. The involved eye is usually not painful and has little or no discharge but may be quite red and swollen. Submandibular or cervical lymphadenopathy may also occur.

More severe, disseminated illness occurs in a small percentage of patients and is characterized by presentation with high fever, often persisting for several weeks. Other prominent symptoms include significant abdominal pain and weight loss. Hepatosplenomegaly may occur, although hepatic dysfunction is rare (Fig. 209-4). Granulomatous changes may be seen in the liver and spleen. Another common site of dissemination is bone, with the development of granulomatous osteolytic lesions, associated with localized pain but without erythema, tenderness, or swelling. Other uncommon manifestations are neuroretinitis with papilledema and stellate macular exudates, encephalitis, fever of unknown origin, and atypical pneumonia.

**DIAGNOSIS**

In most cases, the diagnosis can be strongly suspected on clinical grounds in a patient with history of exposure to a cat. The U.S. Centers for Disease Control and Prevention (CDC) has developed

| Table 209-1 Bartonella Species Causing Human Disease |
|--------------|--------------|----------|----------------------------------|
| **DISEASE**  | **ORGANISM**   | **VECTOR** | **PRIMARY RISK FACTOR**             |
| Bartonellosis| *B. bacilliformis* | Sandfly (Lutzomyia verrucarum) | Living in endemic areas (Andes Mountains) |
| Cat-scratch disease | *B. henselae* | Cat | Cat scratch or bite |
| Trench fever | *B. quintana* | Human body louse | Body louse infestation during outbreak |
| Bacteremia, endocarditis | *B. henselae* | Cat for *B. henselae* | Severe immunosuppression |
|                | *B. quintana* | Human body louse for *B. quintana* |
|                | *B. elizabethae* | | |
|                | *B. vinsonii* | | |
| Bacillary angiomatosis | *B. henselae* | Cat for *B. henselae* | Severe immunosuppression |
|                | *B. quintana* | Human body louse for *B. quintana* |
| Peliosis hepatis | *B. henselae* | Cat for *B. henselae* | Severe immunosuppression |
|                | *B. quintana* | Human body louse for *B. quintana* |
Bartonella


Figure 209-3  The granulomatous conjunctivitis of Parinaud oculo-glandular syndrome is associated with ipsilateral local lymphadenopathy, usually preauricular and less commonly submandibular. (From Mandell GL, Bennett JE, Dolin R, editors: Principles and practice of infectious diseases, ed 6. Philadelphia, 2006, Elsevier, p. 2739.}

Figure 209-4  In this CT scan of a patient with hepatic involvement of cat-scratch disease, the absence of enhancement of the multiple lesions after contrast infusion is consistent with the granulomatous inflammation of this entity. Treated empirically with various antibiotics without improvement before establishment of this diagnosis, the patient subsequently recovered fully with no further antimicrobial therapy. (Courtesy of Dr. V.H. San Joaquin, University of Oklahoma Health Sciences Center, Oklahoma City.)

an indirect immunofluorescent assay that shows good correlation with disease. Other immunofluorescent assay and enzyme-linked immunosassay tests are commercially available, although little comparative data are available. Most patients have elevated antibody titers at presentation; however, the timing of immunoglobulin G and immunoglobulin M response to *B. henselae* can be quite variable. There is crossreactivity among *Bartonella* species, particularly *B. henselae* and *B. quintana*.

If tissue specimens are obtained, bacilli may be visualized with Warthin-Starry and Brown-Hopps tissue stains. *Bartonella* DNA can be identified through polymerase chain reaction analysis of tissue specimens. Culturing of the organism is not generally practical for clinical diagnosis.

**Differential Diagnosis**

The differential diagnosis of CSD includes virtually all causes of lymphadenopathy (see Chapter 490). The more-common entities include pyogenic (suppurative) lymphadenitis, primarily from staphylococcal infections, atypical mycobacterial infections, and malignancy. Less-common entities are tularemia, brucellosis, and sporotrichosis. Epstein-Barr virus, cytomegalovirus, and *Toxoplasma gondii* infections usually cause more generalized lymphadenopathy.

**LABORATORY FINDINGS**

Routine laboratory tests are not helpful. The erythrocyte sedimentation rate is often elevated. The white blood cell count may be normal or mildly elevated. Hepatic transaminases are often normal, but may be elevated in systemic disease. Ultrasonography or CT may reveal many granulomatous nodules in the liver and spleen; the nodules appear as hypodense round irregular lesions.

**TREATMENT**

Antibiotic treatment of CSD is not always needed and is not clearly beneficial. For most patients, treatment consists of conservative symptomatic care and observation. Studies show a significant discordance between in vitro activity of antibiotics and clinical effectiveness. For many patients, diagnosis is considered in the context of failure to respond to β-lactam antibiotic treatment of presumed staphylococcal lymphadenitis.

A small prospective study of oral azithromycin (500 mg on day 1, and then 250 mg on days 2-5; for smaller children, 10 mg/kg/24 hr on day 1 and 5 mg/kg/24 hr on days 2-5) showed a decrease in initial lymph node volume in 50% of patients during the 1st 30 days, but after 30 days there was no difference in lymph node volume. No other clinical benefit was found. For the majority of patients, CSD is self-limited, and resolution occurs over weeks to months without antibiotic treatment. Azithromycin, clarithromycin, trimethoprim-sulfamethoxazole, rifampin, ciprofloxacin, and gentamicin appear to be the best agents if treatment is considered.

Suppurative lymph nodes that become tense and extremely painful should be drained by needle aspiration, which may need to be repeated. Incision and drainage of nonsuppurative nodes should be avoided because chronic draining sinuses may result. Surgical excision of the node is rarely necessary.

Children with hepatosplenic CSD appear to respond well to rifampin at a dose of 20 mg/kg for 14 days, either alone or in combination with trimethoprim-sulfamethoxazole.

**COMPLICATIONS**

**Encephalopathy,** which can occur in as many as 5% of patients with CSD, typically manifests 1-3 wk after the onset of lymphadenitis as the sudden onset of neurologic symptoms, which often include seizures, combative or bizarre behavior, and altered level of consciousness. Imaging studies are generally normal. The cerebrospinal fluid is normal or shows minimal pleocytosis and protein elevation. Recovery occurs without sequelae in nearly all patients but may take place slowly over many months.

Other neurologic manifestations include peripheral facial nerve paralysis, myelitis, radiculitis, compression neuropathy, and cerebellar ataxia. One patient has been reported to have encephalopathy with persistent cognitive impairment and memory loss.

**Stellate macular retinopathy** is associated with several infections, including CSD. Children and young adults present with unilateral or rarely bilateral loss of vision with central scotoma, optic disc swelling, and macular star formation from exudates radiating out from the macula. The findings usually resolve completely, with recovery of vision, generally within 2-3 mo. The optimal treatment for the neuro-retinopathy is unknown, although treatment of adults with doxycycline and rifampin for 4-6 wk has had good results.

**Hematologic manifestations** include hemolytic anemia, thrombocytopenic purpura, nonthrombocytopenic purpura, and eosinophilia. *Leukocytoclastic vasculitis,* similar to Henoch-Schönlein purpura, has been reported in association with CSD in 1 child. A systemic presentation of CSD with pleurisy, arthralgia or arthritis, mediastinal masses, enlarged nodes at the head of the pancreas, and atypical pneumonia also has been reported.
PROGNOSIS
The prognosis for CSD in a normal host is generally excellent, with resolution of clinical findings over weeks to months. Recovery is occasionally slower and may take as long as a year.

PREVENTION
Person-to-person spread of Bartonella infections is not known. Isolation of the affected patient is not necessary. Prevention would require elimination of cats from households, which is not practical or necessarily desirable. Awareness of the risk of cat (and particularly kitten) scratches should be emphasized to parents. Cat scratches or bites should be washed immediately. Cat flea control is helpful.

Bibliography is available at Expert Consult.

209.2 Bartonellosis (Bartonella bacilliformis)
Barbara W. Stechenberg

The first human Bartonella infection described was bartonellosis, a geographically distinct disease caused by B. bacilliformis. There are 2 predominant forms of illness caused by B. bacilliformis: Oroya fever, a severe, febrile hemolytic anemia, and verruca peruana (verruca peruana), an eruption of hemangioma-like lesions. B. bacilliformis also causes asymptomatic infection. Bartonellosis is also called Carrión disease.

ETIOLOGY
B. bacilliformis is a small, motile, Gram-negative organism with a brush of 10 or more unipolar flagella, which appear to be important components for invasiveness. An obligate aerobe, it grows best at 28°C (82.4°F) in semisolid nutrient agar containing rabbit serum and hemoglobin.

EPIDEMIOLOGY
Bartonellosis is a zoonosis found only in mountain valleys of the Andes Mountains in Peru, Ecuador, Colombia, Chile, and Bolivia at altitudes and environmental conditions favorable for the vector, which is the sandfly, Lutzomyia verrucarum.

PATHOGENESIS
After the sandfly bite, Bartonella organisms enter the endothelial cells of blood vessels, where they proliferate. Found throughout the reticuloendothelial system, they then re-enter the bloodstream and parasitize erythrocytes. They bind on the cells, deform the membranes, and then enter intracellular vacuoles. The resultant hemolytic anemia may involve as many as 90% of circulating erythrocytes. Patients who survive this acute phase may or may not experience the cutaneous manifestations, which are nodular hemangiomatous lesions or verrucae ranging in size from a few millimeters to several centimeters.

CLINICAL MANIFESTATIONS
The incubation period is 2-14 wk. Patients may be totally asymptomatic or may have nonspecific symptoms such as headache and malaise without anemia.

Oroya fever is characterized by fever with rapid development of anemia. Clouding of the sensorium and delirium are common symptoms and may progress to overt psychosis. Physical examination demonstrates signs of severe hemolytic anemia, including icterus and pallor, sometimes in association with generalized lymphadenopathy.

In the preeruptive stage of verruca peruana (Fig. 209-5), patients may complain of arthralgias, myalgias, and paresthesias. Inflammatory reactions such as phlebitis, pleuritis, erythema nodosum, and encephalitis may develop. The appearance of verrucae is pathognomonic of the eruptive phase. Lesions vary greatly in size and number.

DIAGNOSIS
The diagnosis is established on clinical grounds in conjunction with a blood smear demonstrating organisms or with blood culture. The anemia is macrocytic and hypochromic, with reticulocyte counts as high as 50%. B. bacilliformis may be seen on Giemsa stain preparation as red-violet rods in the erythrocytes. In the recovery phase, organisms change to a more coccoid form and disappear from the blood. In the absence of anemia, the diagnosis depends on blood cultures. In the eruptive phase, the typical verruca confirms the diagnosis. Antibody testing has been used to document infection.

TREATMENT
B. bacilliformis is sensitive to many antibiotics, including rifampin, tetracycline, and chloramphenicol. Treatment is very effective in rapidly diminishing fever and eradicating the organism from the blood. Chloramphenicol (50-75 mg/kg/day) is considered the drug of choice, because it is also useful in the treatment of concomitant infections such as Salmonella. Fluoroquinolones are used successfully as well. Blood transfusions and supportive care are critical in patients with severe anemia. Antimicrobial treatment for verruca peruana is considered when there are more than 10 cutaneous lesions, if the lesions are erythematous or violaceous, or if the onset of the lesions was <1 mo before presentation. Oral rifampin is effective in the healing of lesions. Surgical excision may be needed for lesions that are large and disfiguring or that interfere with function.

PREVENTION
Prevention depends on avoidance of the vector, particularly at night, by the use of protective clothing and insect repellents (see Chapter 175).

Bibliography is available at Expert Consult.

209.3 Trench Fever (Bartonella quintana)
Barbara W. Stechenberg

ETIOLOGY
The causative agent of trench fever was first designated Rickettsia quintana, was then assigned to the genus Rochalimaea, and now has been reassigned as B. quintana.
Bibliography


Bibliography
EPIDEMIOLOGY

Trench fever was first recognized as a distinct clinical entity during World War I, when more than a million troops in the trenches were infected. The disease became quiescent until World War II, when it again was epidemic. It is extremely rare in the United States.

Humans are the only known reservoir. No other animal is naturally infected, and usual laboratory animals are not susceptible. The human body louse, Pediculus humanus var. corporis, is the vector and is capable of transmission to a new host 5–6 days after feeding on an infected person. Lice excrete the organism for life; transovarian passage does not occur. Humans may have prolonged asymptomatic bacteremia for years.

CLINICAL MANIFESTATIONS

The incubation period for trench fever averages about 22 days (range: 4–35 days). The clinical presentation is highly variable. Symptoms can be very mild and brief. About half of infected persons have a single febrile illness with abrupt onset lasting 3–6 days. In other patients, prolonged, sustained fever may occur. More commonly, patients have periodic febrile illness with 3–8 episodes lasting 4–5 days each, sometimes occurring over a period of a year or more. This form is reminiscent of malaria or relapsing fever (Borrelia recurrentis). Afebrile bacteremia can occur.

Clinical findings usually consist of fever (typically with a temperature of 38.5–40°C [101.3–104°F]), malaise, chills, sweats, anorexia, and severe headache. Common findings include marked conjunctival injection, tachycardia, myalgias, arthralgias, and severe pain in the neck, back, and legs. Crops of erythematous macules or papules may occur on the trunk on as many as 80% of patients. Splenomegaly and mild liver enlargement may be noted.

DIAGNOSIS

In nonepidemic situations, it is impossible to establish a diagnosis of trench fever on clinical grounds, because the findings are not distinctive. A history of body louse infection or having been in an area of epidemic disease should heighten suspicions. B. quintana can be cultured from the blood with modification to include culture on epithelial cells. Serologic tests for B. quintana are available, but there is cross reaction with B. henselae.

TREATMENT

There are no controlled trials of treatment, but patients with trench fever typically show dramatic response to tetracycline or chloramphenicol, with rapid defervescence.

209.4 Bacillary Angiomatosis and Bacillary Peliosis Hepatitis (Bartonella henselae and Bartonella quintana)

Barbara W. Stechenberg

Both B. henselae and B. quintana cause vascular proliferative disease called bacillary angiomatosis and bacillary peliosis in severely immunocompromised persons, primarily adult patients with AIDS or cancer and organ transplant recipients. Subcutaneous and lytic bone lesions are strongly associated with B. quintana, whereas peliosis hepatitis is associated exclusively with B. henselae.

BACILLARY ANGIOMATOSIS

Lesions of cutaneous bacillary angiomatosis, also known as epithelioid angiomatosis, are the most easily identified and recognized form of Bartonella infection in immunocompromised hosts. They are found primarily in patients with AIDS who have very low CD4 counts. The clinical appearance can be quite diverse. The vasoproliferative lesions of bacillary angiomatosis may be cutaneous or subcutaneous and may resemble the vascular lesions (verruca peruana) of B. bacilliformis in immunocompetent persons, characterized by erythematous papules on an erythematous base with a collarette of scale. They may enlarge to form large pedunculated lesions and may ulcerate. Trauma may result in profuse bleeding.

Bacillary angiomatosis may be clinically indistinguishable from Kaposi sarcoma. Other considerations in the differential diagnosis are pyogenic granuloma and verruca peruana (B. bacilliformis). Deep soft-tissue masses caused by bacillary angiomatosis may mimic a malignancy.

Osseous bacillary angiomatosis lesions commonly involve the long bones. These lytic lesions are very painful and highly vascular and are occasionally associated with an overlying erythematous plaque. The high degree of vascularity produces a very positive result on a technetium-Tc 99m methylene diphosphonate bone scan, resembling that of a malignant lesion.

Lesions can be found in virtually any organ, producing similar vascular proliferative lesions. They may appear raised, nodular, or ulcerative when seen on endoscopy or bronchoscopy. They may be associated with enlarged lymph nodes with or without an obvious local cutaneous lesion. Brain parenchymal lesions have been described.

BACILLARY PELIOSIS

Bacillary peliosis affects the reticuloendothelial system, primarily the liver (peliosis hepatitis) and less frequently the spleen and lymph nodes. It is a vasoproliferative disorder characterized by random proliferation of venous lakes surrounded by fibromyxoid stroma harboring numerous bacillary organisms. Clinical findings include fever and abdominal pain in association with abnormal results of liver function tests, particularly a markedly increased alkaline phosphatase level. Cutaneous bacillary angiomatosis with splenomegaly may be associated with thrombocytopenia or pancytopenia. The vascular proliferative lesions in the liver and spleen appear on CT scan as hypodense lesions scattered throughout the parenchyma. The differential diagnosis includes hepatic Kaposi sarcoma, lymphoma, and disseminated infection with Pneumocystis carinii or Mycobacterium avium complex.

BACTEREMIA AND ENDOCARDITIS

B. henselae, B. quintana, B. vinsonii, and B. elizabethae all are reported to cause bacteremia or endocarditis. They are associated with symptoms such as prolonged fevers, night sweats, and profound weight loss. A cluster of cases in Seattle in 1993 occurred in a homeless population with chronic alcoholism. These patients with high fever or hypothermia were thought to represent “urban trench fever,” but no body louse infestation was associated. Some cases of culture-negative endocarditis may represent Bartonella endocarditis. One report described central nervous system involvement with B. quintana infection in 2 children.

DIAGNOSIS

Diagnosis of bacillary angiomatosis is made initially by biopsy. The characteristic small vessel proliferation with mixed inflammatory response and the staining of bacilli by Warthin-Starry silver staining distinguish bacillary angiomatosis from pyogenic granuloma or Kaposi sarcoma (see Chapter 257). Travel history can usually preclude verruca peruana.

Culture is impractical for CSD but is the diagnostic procedure for suspected bacteremia or endocarditis. Use of the lysis centrifugation technique or fresh chocolate or heart infusion agar with 5% rabbit blood with prolonged incubation may increase the yield of culture. Polymerase chain reaction can also be a useful tool.

TREATMENT

Bartonella infections in immunocompromised hosts caused by both B. henselae and B. quintana have been treated successfully with antimicrobial agents. Bacillary angiomatosis responds rapidly to erythromycin, azithromycin, and clarithromycin, which are the drugs of choice. Alternative choices are doxycycline or tetracycline. Severely ill patients with peliosis hepatitis, endocarditis, or osteomyelitis may be treated initially with intravenous erythromycin or doxycycline and the addition of rifampin or gentamicin. The use of an aminoglycoside for a minimum of 2 wk is associated with improved prognosis in
endocarditis. A Jarisch-Herxheimer reaction may occur. Relapses may follow, and prolonged treatment for several months may be necessary.

PREVENTION
Immunocompromised persons should consider the potential risks of cat ownership because of the risks for Bartonella infections as well as toxoplasmosis and enteric infections. Those who elect to obtain a cat should adopt or purchase a cat >1 yr of age and in good health. Prompt washing of any wounds from cat bites or scratches is essential.

Bibliography is available at Expert Consult.
Bibliography
Three naturally occurring forms of human botulism are known: infant (intestinal toxemia) botulism (the most common in the United States), foodborne (classic) botulism, and wound botulism. Two other forms, both human-made, also occur: inhalational botulism from inhaling accidentally aerosolized toxin and iatrogenic botulism from overdosage of therapeutic or cosmetic use of botulinum toxin.

ETIOLOGY

Botulism is the acute, flaccid paralysis caused by the neurotoxin produced by Clostridium botulinum or, infrequently, an equivalent neurotoxin produced by rare strains of Clostridium butyricum and Clostridium baratii. C. botulinum is a Gram-positive, spore-forming, obligate anaerobe whose natural habitat worldwide is soil, dust, and marine sediments. The organism is found in a wide variety of fresh and cooked agricultural products. Spores of some C. botulinum strains endure boiling for several hours, enabling the organism to survive efforts at food preservation. In contrast, botulinum toxin is heat labile and easily destroyed by heating at ≥85°C (185°F) for 5 min. Neurotoxicogenic C. butyricum has been isolated from a soybean food and from soils near Lake Weishan in China, the site of foodborne botulism outbreaks associated with this organism. Little is known about the ecology of neurotoxicogenic C. baratii.

Botulinum toxin is a simple dichain protein consisting of a 100 kDa heavy chain that contains the neuronal attachment sites and a 50 kDa light chain that is taken into the cell after binding. Botulinum toxin is the most poisonous substance known, the parenteral human lethal dose being estimated at 10⁻⁶ mg/kg. The toxin blocks neuromuscular transmission and causes death through airway and respiratory muscle paralysis. Eight antigenic toxin types, designated by letters A–H, are distinguished by the inability of neutralizing antibody against 1 toxin type to protect against a different toxin type. Toxin types are further differentiated into subtypes by differences in the nucleotide sequences of their toxin genes. Like the gene for tetanus toxin, the gene for botulinum toxin for some toxin types and subtypes resides on a plasmid.

The 8 toxin types serve as convenient clinical and epidemiologic markers. Toxin types A, B, E, and F are well-established causes of human botulism, whereas types C and D cause illness in other animals. Neurotoxicogenic C. butyricum strains produce a type E toxin, whereas neurotoxicogenic C. baratii strains produce a type F toxin. Type G toxin has not been established as a cause of either human or animal disease. Type H toxin is a novel toxin that was discovered in 2013 and sickened an infant patient. The phenomenal potency of the botulinum toxins occurs because their 8 light chains are zinc endopeptidases whose substrates are 1 or 2 proteins of the docking complex by which synaptic vesicles fuse with the terminal neuronal cell membrane and release acetylcholine into the synaptic cleft.

EPIDEMIOLOGY

Infant botulism has been reported from all inhabited continents except Africa. Notably, the infant is the only family member who is ill. The most striking epidemiologic feature of infant botulism is its age distribution, with 95% of cases involving infants between 3 wk and 6 mo of age, with a broad peak from 2-4 mo of age. Cases have been recognized in infants as young as 1.5 days or as old as 382 days at onset. The male:female ratio of hospitalized cases is approximately 1:1, and cases have occurred in most racial and ethnic groups.

Although infant botulism is an uncommon and often unrecognized illness, it is the most common form of human botulism in the United States, with 80-120 hospitalized cases diagnosed annually. The full clinical spectrum of infant botulism includes mild outpatient cases and fulminant sudden death cases. Approximately 40% of U.S. hospitalized cases have been reported from California. Consistent with the known asymmetric soil distribution of C. botulinum toxin types, most cases west of the Mississippi River have been caused by type A strains, whereas most cases east of the Mississippi River have been caused by type B strains. One case each in New Mexico, Washington, Ohio, California, Iowa, and Colorado has been caused by C. baratii and type F toxin. Four cases in Italy have resulted from C. butyricum and type E toxin. Identified risk factors for the illness include breastfeeding, the ingestion of honey, a slow intestinal transit time (<1 stool/day), and ingestion of untreated well-water. Breastfeeding may provide protection against fulminant sudden death from infant botulism. Under rare circumstances of altered intestinal anatomy, physiology, and microflora, older children and adults may contract infant-type botulism.

Foodborne botulism results from the ingestion of a food in which C. botulinum has multiplied and produced its toxin. Outbreaks in North America have been associated with baked potatoes, sautéed onions, and chopped garlic served in restaurants, revising the traditional view of foodborne botulism as resulting mainly from home-canned foods. Other outbreaks in the United States have occurred from commercial foods sealed in plastic pouches that relied solely on refrigeration to prevent outgrowth of C. botulinum spores. Uncanned foods responsible for foodborne botulism cases include poyte tea, the hazelnut flavoring added to yogurt, sweet cream cheese, sautéed onions in "patty melt" sandwiches, potato salad, and fresh and dried fish. A trend toward a single case per outbreak or of cases manifesting separately in different cities or hospitals portends that physicians cannot rely on the temporal and geographic clustering of cases to suggest the diagnosis.

Most types of preserved foods have been implicated in foodborne botulism, but the usual offenders in the United States are the "low-acid" (pH ≥ 6.0) home-canned foods such as jalapeño peppers, asparagus, olives, and beans. The potential for foodborne botulism exists throughout the world, but outbreaks occur most commonly in the temperate zones rather than the tropics, where preservation of fruits, vegetables, and other foods is less common.

Approximately 5-10 outbreaks and 15-25 cases of foodborne botulism occur annually in the United States. Most of the continental U.S. outbreaks resulted from proteolytic type A or type B strains, which produce a strongly putrefactive odor in the food that some people find necessary to verify by tasting. In contrast, in Alaska and Canada, most foodborne outbreaks have resulted from nonproteolytic type E strains.
in Native American foods, such as fermented salmon eggs and seal flippers, which do not exhibit signs of spoilage. A further hazard of type E strains is their ability to grow at the temperatures maintained by household refrigerators (5°C [41°F]).

**Wound botulism** is an exceptionally rare disease, with fewer than 400 cases reported worldwide, but it is important to pediatrics because adolescents and children may be affected. Although many cases have occurred in young, physically active males who are at greatest risk for traumatic injury, wound botulism also occurs with crush injuries in which no break in the skin is evident. In the past 15 yr, wound botulism from injection has become increasingly common in adult heroin abusers in the western United States and in Europe, not always with evident abscess formation or cellulitis. A single outbreak of **inhaled botulism** was reported in 1962 in which 3 laboratory workers in Germany were exposed unintentionally to aerosolized botulinum toxin. Some patients in the United States have been hospitalized by accidental overdose of therapeutic or cosmetic botulinum toxin.

**PATHOGENESIS**

All forms of botulism produce disease through a final common pathway. Botulinum toxin is carried by the bloodstream to peripheral cholinergic synapses, where it binds irreversibly, blocking acetylcholine release and causing impaired neuromuscular and autonomic transmission. **Infant botulism** is an infectious disease that results from ingesting the spores of any of the 3 botulinum toxin-producing clostridial strains, with subsequent spore germination, multiplication, and production of botulinum toxin in the large intestine. **Foodborne botulism** is an intoxication that results when preformed botulinum toxin contained in an improperly preserved or inadequately cooked food is swallowed. **Wound botulism** results from spore germination and colonization of traumatized tissue by *C. botulinum*; it is the analog of tetanus. **Inhalational botulism** occurs when aerosolized botulinum toxin is inhaled. A bioterrorist attack could result in large or small outbreaks of inhalational or foodborne botulism (see Chapter 723).

Botulinum toxin is not a cytotoxin and does not cause overt macroscopic or microscopic pathology. Secondary pathologic changes (pneumonia, petechiae on intrathoracic organs) may be found at autopsy. No diagnostic technique is available to identify botulinum toxin bound at the neuromuscular junction. The healing process in botulism consists of sprouting of new terminal unmyelinated motor neurons. Movement resumes when these new twigs locate noncontracting muscle fibers and reinnervate them by inducing formation of a new motor end plate. In experimental animals, this process takes about 4 wk.

**CLINICAL MANIFESTATIONS**

Botulinum toxin is distributed hematogenously. Because relative blood flow and density of innervation are greatest in the bulbar musculature, all forms of botulism manifest neurologically as a symmetric, descending, flaccid paralysis beginning with the cranial nerve musculature. It is not possible to have botulism without having multiple bulbar palsies, yet in infants, such symptoms as poor feeding, weak suck, feeble cry, drooling, and even obstructive apnea are often not recognized as bulbar in origin (Fig. 210-1). Patients with evolving illness may already have generalized weakness and hypotonia in addition to bulbar palsies when first examined. In contrast to botulism caused by *C. botulinum*, a majority of the rare cases caused by intestinal colonization with *C. butyricum* are associated with a Meckel diverticulum accompanying abdominal distention, often leading to misdiagnosis as an acute abdomen. The also rare *C. barati* type F infant botulism cases have been characterized by very young age at onset, rapidity of onset, and greater severity but shorter duration of paralysis.

In older children with **foodborne or wound botulism**, the onset of neurologic symptoms follows a characteristic pattern of diplopia, blurred vision, ptosis, dry mouth, dysphagia, dysphonia, and dysarthria, with decreased gag and corneal reflexes. Importantly, because the toxin acts only on motor nerves, paresthesias are not seen in botulism, except when a patient hyperventilates from anxiety. The sensorium remains clear, but this fact may be difficult to ascertain because of the slurred speech.

**Foodborne botulism** begins with gastrointestinal symptoms of nausea, vomiting, or diarrhea in approximately 30% of cases. These symptoms are thought to result from metabolic by-products of growth of *C. botulinum* or from the presence of other toxic contaminants in the food, because gastrointestinal distress is rarely observed in wound botulism. Constipation may occur in foodborne botulism once flaccid paralysis becomes evident. Illness usually begins 12-36 hr after ingestion of the contaminated food but can range from as little as 2 hr to as long as 8 days. The incubation period in wound botulism is 4-14 days. Fever may be present in wound botulism but is absent in foodborne botulism unless a secondary infection (often pneumonia) is present. All forms of botulism display a wide spectrum of clinical severity, from the very mild, with minimal ptosis, flattened facial expression, minor dysphagia, and dysphonia, to the fulminant, with rapid onset of extensive paralysis, frank apnea, and fixed, dilated pupils. Fatigability with repetitive muscle activity is the clinical hallmark of botulism.

**Infant botulism** differs in apparent initial symptoms of illness only because the infant cannot verbalize them. Usually, the first indication of illness is a decreased frequency or even absence of defecation, although this sign is frequently overlooked. Parents typically notice inability to feed, lethargy, weak cry, and diminished spontaneous movement. Dysphagia may be evident as secretions drooling from the mouth. Gag, suck, and corneal reflexes diminish as the paralysis advances. Oculomotor palsies may be evident only with sustained observation. Paradoxically, the pupillary light reflex may be unaffected until the child is severely paralyzed, or it may be initially sluggish. Loss of head control is typically a prominent sign. Respiratory arrest may occur suddenly from airway occlusion by unswallowed secretions or...
from obstructive flaccid pharyngeal musculature. Occasionally, the diagnosis of infant botulism is suggested by a respiratory arrest that occurs after the infant is curled into position for lumbar puncture.

In mild cases or in the early stages of illness, the physical signs of infant botulism may be subtle and easily missed. Eliciting cranial nerve palsies and fatigueability of muscular function requires careful examination. Ptosis may not be seen unless the head of the child is kept erect.

**DIAGNOSIS**

Clinical diagnosis of botulism is confirmed by specialized laboratory testing that requires hours to days to complete. Therefore, clinical diagnosis is the foundation for early recognition of and response to all forms of botulism. Routine laboratory studies, including those of the cerebrospinal fluid, are normal in botulism unless dehydration, undernourishment (metabolic acidosis and ketosis), or secondary infection is present.

The classic triad of botulism is the acute onset of a symmetric flaccid descending paralysis with clear sensorium, no fever, and no paresthesias. Suspected botulism represents a medical and public health emergency that is immediately reportable by telephone in most U.S. health jurisdictions. State health departments (first call) and the U.S. Centers for Disease Control and Prevention (CDC; telephone 770-488-7100 at any time) can arrange for diagnostic testing, epidemiologic investigation, and provision of equine antitoxin.

The diagnosis of botulism is unequivocally established by demonstration of the presence of botulinum toxin in serum or of the organism in wound material, enema fluid, or feces. C. botulinum is not part of the normal resident intestinal flora of humans, and its presence in the setting of acute flaccid paralysis is diagnostic. An epidemiologic diagnosis of food-borne botulism can be established when C. botulinum organisms and toxin are found in food eaten by patients.

Electromyography can sometimes distinguish between causes of acute flaccid paralysis, although results may be variable, including normal, in patients with botulism. The distinctive electromyography finding in botulism is facilitation (potentiation) of the evoked muscle action potential at high-frequency (50 Hz) stimulation. In infant botulism, a characteristic pattern, known by the acronym BSAP (brief, small, abundant motor unit action potentials), is present only in clinically weak muscles. Nerve conduction velocity and sensory nerve function are normal in botulism.

Infant botulism requires a high index of suspicion for early diagnosis (Table 210-1). “Rule out sepsis” remains the most common admission diagnosis. If a previously healthy infant (commonly 2-4 mo of age) demonstrates weakness with difficulty in sucking, swallowing, crying, or breathing, infant botulism should be considered a likely diagnosis. A careful cranial nerve examination is then very helpful. Rare instances of coinfection with *Clostridium difficile*, respiratory syncytial virus, or influenza virus have occurred.

**Additional diagnostic procedures** may be useful in rapidly excluding botulism as the cause of paralysis. The cerebrospinal fluid is unchanged in botulism but is abnormal in many central nervous system diseases. Although the cerebrospinal fluid protein concentration is eventually elevated in Guillain–Barré syndrome, it may be normal early in illness. Imaging of the brain, spine, and chest may reveal hemorrhage, inflammation, or neoplasm. A test dose of edrophonium chloride briefly reverses paralytic symptoms in many patients with myasthenia gravis and, reportedly, in some with botulism. A close inspection of the skin, especially the scalp, may reveal an attached tick that is causing paralysis. Possible organophosphate intoxication should be pursued aggressively because specific antidotes (oximes) are available and because the patient may be part of a commonly exposed group, some of whom have yet to demonstrate illness. Other tests that require days for results include stool culture for *Campylobacter jejuni* as a precipitant of Guillain–Barré syndrome, spinal muscular atrophy and other genetic (including mitochondrial) disorders, and assays for the autoantibodies that cause myasthenia gravis, Lambert–Eaton syndrome, and Guillain–Barré syndrome.

**TREATMENT**

Human botulism immune globulin, given intravenously (BIG-IV), is licensed for the treatment of infant botulism caused by type A or B botulinum toxin. Treatment with BIG-IV consists of a single intravenous infusion of 50-100 mg/kg (see package insert) that should be given as soon as possible after infant botulism is suspected so as to

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**Table 210-1**

<table>
<thead>
<tr>
<th>ADMISSION DIAGNOSIS</th>
<th>SUBSEQUENTLY CONSIDERED DIAGNOSES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suspected sepsis, meningitis</td>
<td>Guillain-Barré syndrome</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>Myasthenia gravis</td>
</tr>
<tr>
<td>Dehydration</td>
<td>Disorders of amino acid metabolism</td>
</tr>
<tr>
<td>Viral syndrome</td>
<td>Hypothyroidism</td>
</tr>
<tr>
<td>Hypotonia of unknown etiology</td>
<td>Drug ingestion</td>
</tr>
<tr>
<td>Constipation</td>
<td>Brainstem encephalitis</td>
</tr>
<tr>
<td>Failure to thrive</td>
<td>Heavy metal poisoning (Pb, Mg, As)</td>
</tr>
<tr>
<td>Spinal muscular atrophy type 1</td>
<td>Poliomyelitis</td>
</tr>
<tr>
<td>(Werdnig-Hoffmann disease)</td>
<td>Viral polyneuritis</td>
</tr>
<tr>
<td></td>
<td>Hirschsprung disease</td>
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<tr>
<td></td>
<td>Metabolic encephalopathy</td>
</tr>
<tr>
<td></td>
<td>Medium chain acetyl–coenzyme A</td>
</tr>
<tr>
<td></td>
<td>Dehydrogenase deficiency</td>
</tr>
</tbody>
</table>

**Table 210-2**

<table>
<thead>
<tr>
<th>Diagnoses Considered in Foodborne and Wound Botulism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute gastroenteritis</td>
</tr>
<tr>
<td>Myasthenia gravis</td>
</tr>
<tr>
<td>Guillain-Barré syndrome</td>
</tr>
<tr>
<td>Organophosphate poisoning</td>
</tr>
<tr>
<td>Meningitis</td>
</tr>
<tr>
<td>Encephalitis</td>
</tr>
<tr>
<td>Psychiatric illness</td>
</tr>
<tr>
<td>Cerebrovascular accident</td>
</tr>
<tr>
<td>Poliomyelitis</td>
</tr>
<tr>
<td>Hypothyroidism</td>
</tr>
<tr>
<td>Aminoglycoside-associated paralysis</td>
</tr>
<tr>
<td>Tick paralysis</td>
</tr>
<tr>
<td>Hypocalcaemia</td>
</tr>
<tr>
<td>Hypermagnesemia</td>
</tr>
<tr>
<td>Carbon monoxide poisoning</td>
</tr>
<tr>
<td>Hypersarcinosis gravidarum</td>
</tr>
<tr>
<td>Laryngeal trauma</td>
</tr>
<tr>
<td>Diabetic complications</td>
</tr>
<tr>
<td>Inflammatory complications</td>
</tr>
<tr>
<td>Myopathic complications</td>
</tr>
<tr>
<td>Overexertion</td>
</tr>
</tbody>
</table>
Complications of Infant Botulism

**Supportive Care**

Management of botulism rests on the following 3 principles: (1) fatigability with repetitive muscle activity is the clinical hallmark of the disease; (2) complications are best avoided by anticipating them; and (3) meticulous supportive care is a necessity. The first principle applies mainly to feeding and breathing. Correct positioning is imperative to protect the airway and improve respiratory mechanics. The patient is placed face up on a rigid-bottomed crib (or bed), the head of which is tilted at 30 degrees. A small cloth roll is placed under the cervical vertebrae to tilt the head back so that secretions drain to the posterior pharynx and away from the airway. In this tilted position, the abdominal viscera pull the diaphragm down, thereby improving respiratory mechanics. The patient’s head and torso should not be elevated by bending the middle of the bed; in such a position, the hypotonic thorax would slump into the abdomen and breathing would be compromised.

About half of patients with infant botulism require endotracheal intubation, which is best done prophylactically. The indications include diminished gag and cough reflexes and progressive airway obstruction by secretions. With meticulous management techniques (especially proper tube diameter), monitoring, and positioning, patients have tolerated months of intubation without subglottic stenosis or need for tracheostomy.

Feeding should be done by a nasogastric or nasojejunal tube until sufficient oropharyngeal strength and coordination enable feeding by breast or bottle. Expressed breast milk is the most desirable food for infants, in part because of its immunologic components (e.g., secretory immunoglobulin A, lactoferrin, leukocytes). Tube feeding also assists in the restoration of peristalsis, a nonspecific but probably essential part of eliminating *C. botulinum* from the intestinal flora. Intravenous feeding (hyperalimentation) is discouraged because of the potential for infection and the advantages of tube feeding.

Because sensation remains intact, providing auditory, tactile, and visual stimuli is beneficial. Maintaining strong central respiratory drive is essential, so sedatives and central nervous system depressants are best avoided. Full hydration and stool softeners such as lactulose may mitigate the protracted constipation. Cathartics are not recommended. Patients with foodborne and infant botulism excrete *C. botulinum* toxin and organisms in their feces, often for many weeks, and care should be taken in handling their excreta. When bladder palsy occurs in severe cases, gentle suprapubic pressure with the patient in the sitting position with the head supported may help attain complete voiding and reduce the risk for urinary tract infection. Families of affected patients may require emotional and financial support, especially when the paralysis of botulism is prolonged.

**Complications**

Almost all of the complications of botulism are nosocomial, and a few are iatrogenic (Table 210-3). Some critically ill, toxin-paralyzed patients who must spend weeks or months on ventilators in intensive care units inevitably experience some of these complications. Suspected “relapses” of infant botulism usually reflect premature hospital discharge or an inapparent underlying complication such as pneumonia, urinary tract infection, or otitis media.

**Prognosis**

When the regenerating nerve endings have induced formation of a new motor end plate, neuromuscular transmission is restored. In the absence of complications, particularly those related to hypoxia, the prognosis in infant botulism is for full and complete recovery. Hospital stay in untreated infant botulism averages 5.7 wk but differs significantly by toxin type, with patients with untreated type B disease being hospitalized a mean of 4.2 wk and those with untreated type A disease being hospitalized a mean of 6.7 wk.

In the United States, the case fatality ratio for hospitalized cases of infant botulism is <1%. After recovery, patients with untreated infant botulism appear to have an increased incidence of strabismus that requires timely screening and treatment.

The case fatality ratio in foodborne and wound botulism varies by age, with younger patients having the best prognosis. Some adults with botulism have reported chronic weakness and fatigue for more than 1 yr as sequelae.

**Prevention**

Foodborne botulism is best prevented by adherence to safe methods of home canning (pressure cooker and acidification), by avoiding suspicious foods, and by heating all home canned foods to 85°C (185°F) for 25 min. Wound botulism is best prevented by not using illicit drugs and by treatment of contaminated wounds with thorough cleansing, surgical debridement, and provision of appropriate antibiotics.

Most patients with infant botulism probably inhaled and then swallowed airborne clostridial spores; these cases cannot be prevented. The 1 identified, avoidable source of botulinum spores for infants is honey. Honey is an unsafe food for any child younger than 1 yr. Corn syrups were once thought to be a possible source of botulinum spores, but evidence indicates otherwise. Breastfeeding appears to slow the onset of infant botulism and to diminish the risk for sudden death in infants in whom the disease develops.

**Bibliography is available at Expert Consult.**

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**Table 210-3 Complications of Infant Botulism**

<table>
<thead>
<tr>
<th>Complication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute respiratory distress syndrome</td>
</tr>
<tr>
<td>Aspiration</td>
</tr>
<tr>
<td><em>Clostridium difficile</em> enterocolitis</td>
</tr>
<tr>
<td>Hypotension</td>
</tr>
<tr>
<td>Inappropriate antidiuretic hormone secretion</td>
</tr>
<tr>
<td>Long bone fractures</td>
</tr>
<tr>
<td>Misplaced or plugged endotracheal tube</td>
</tr>
<tr>
<td>Nosocomial anemia</td>
</tr>
<tr>
<td>Otitis media</td>
</tr>
<tr>
<td>Pneumonia</td>
</tr>
<tr>
<td>Pneumothorax</td>
</tr>
<tr>
<td>Recurrent atelectasis</td>
</tr>
<tr>
<td>Seizures secondary to hyponatremia</td>
</tr>
<tr>
<td>Sepsis</td>
</tr>
<tr>
<td>Subglottic stenosis</td>
</tr>
<tr>
<td>Tracheal granuloma</td>
</tr>
<tr>
<td>Tracheitis</td>
</tr>
<tr>
<td>Transfusion reaction</td>
</tr>
<tr>
<td>Urinary tract infection</td>
</tr>
</tbody>
</table>

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in the United States, BIG-IV may be obtained from the California Department of Public Health (24-hr telephone 510-231-7600; [http://www.infantbotulism.org](http://www.infantbotulism.org)). The use of BIG-IV shortens mean hospital stay from approximately 6 wks to 2 wks. Most of the decrease in length of hospital stay results from the reduced time that the patient requires ventilation and intensive care. Hospital costs are reduced by more than $100,000 per case (in 2012 dollars).

Older patients with suspected food, wound, or inhalational botulism may be treated with 1 vial of licensed equine heptavalent (A-G) botulinum antitoxin, available in the United States through the Centers for Disease Control and Prevention (CDC) by way of state and local health departments.

Antibiotic therapy is not part of the treatment of uncomplicated infant or foodborne botulism, because the toxin is primarily an intracellular molecule that is released into the intestinal lumen with vegetative bacterial cell death and lysis. Antibiotics are reserved for the treatment of secondary infections, and in the absence of antitoxin therapy, a nonclostridiocidal antibiotic such as trimethoprim–sulfamethoxazole is preferred. Aminoglycoside antibiotics should be avoided because they may potentiate the blocking action of botulinum toxin at the neuromuscular junction. Wound botulism requires aggressive treatment with antibiotics and antitoxin in a manner analogous to that for tetanus (see Chapter 211).
Bibliography
ETIOLOGY
Tetanus is an acute, spastic paralytic illness historically called lockjaw that is caused by the neurotoxin produced by Clostridium tetani, a motile, Gram-positive, spore-forming obligate anaerobe whose natural habitat worldwide is soil, dust, and the alimentary tracts of various animals. C. tetani forms spores terminally, producing a drumstick or tennis racket appearance microscopically. Tetanus spores can survive boiling but not autoclaving, whereas the vegetative cells are killed by antibiotics, heat, and standard disinfectants. Unlike many clostridia, C. tetani is not a tissue-invasive organism and instead causes illness through the effects of a single toxin, tetanospsasmin, more commonly referred to as tetanus toxin. Tetanospsasmin is the second most poisonous substance known, surpassed in potency only by botulinum toxin. The human lethal dose of tetanus toxin is estimated to be $10^{-7}$ mg/kg.

EPIDEMIOLOGY
Tetanus occurs worldwide and is endemic in approximately 90 developing countries, although its incidence varies considerably. The most common form, neonatal (or umbilical) tetanus, kills approximately 300,000 infants each year, with approximately 80% of deaths in just 12 tropical Asian and African countries. It occurs in infants whose mothers are not immunized. In addition, an estimated 15,000-30,000 unimmunized women worldwide die each year of maternal tetanus, which results from postpartum, postabortal, or postpartum wound infection with C. tetani. Approximately 50 cases of tetanus are reported each year in the United States, mostly in persons older than 60 yr of age, although cases also occur in toddlers and neonates. Approximately 20% of children in the United States 10-16 yr of age lack a protective antibody level. The majority of childhood cases of tetanus in the United States have occurred in unimmunized children whose parents objected to vaccination.

Most nonneonatal cases of tetanus are associated with a traumatic injury, often a penetrating wound inflicted by a dirty object such as a nail, splinter, fragment of glass, or unsterile injection. Tetanus occurring after illicit drug injection is becoming more common. The disease also occurs after the use of contaminated suture material and after intramuscular injection of medicines, most notably quinine for chloroquine-resistant falciparum malaria. The disease may also occur in association with animal bites, abscesses (including dental abscesses), ear and other body piercing, chronic skin ulceration, burns, compound fractures, frostbite, gangrene, intestinal surgery, ritual scarification, infected insect bites, and female circumcision. Rare cases have no history of trauma.

PATHOGENESIS
Tetanus occurs after introduced spores germinate, multiply, and produce tetanus toxin in the low oxidation-reduction potential of an infected injury site. A plasmid carries the toxin gene. Toxin is released after vegetative bacterial cell death and lysis. Tetanus toxin (and the botulinum toxins) is a 150 kDa simple protein consisting of a heavy chain (100 kDa) and a light (50 kDa) chain joined by a single disulfide bond. Tetanus toxin binds at the neuromuscular junction and enters the motor nerve by endocytosis, after which it undergoes retrograde axonal transport to the cytoplasm of the α-motoneuron. In the sciatic nerve, the transport rate was found to be 3.4 mm/hr. The toxin exits the motoneuron in the spinal cord and next enters adjacent spinal inhibitory interneurons, where it prevents release of the neurotransmitters glycine and γ-aminobutyric acid. Tetanus toxin thus blocks the normal inhibition of antagonistic muscles on which voluntary coordinated movement depends; as a consequence, affected muscles sustain maximal contraction and cannot relax. The autonomic nervous system is also rendered unstable in tetanus.

The phenomenal potency of tetanus toxin is enzymatic. The light chain of tetanus toxin (and of several botulinum toxins) is a zinc-containing endoprotease whose substrate is synaptobrevin, a constituent protein of the docking complex that enables the synaptic vesicle to fuse with the terminal neuronal cell membrane. The heavy chain of the toxin contains its binding and internalization domains.

Because C. tetani is not an invasive organism, its toxin-producing vegetative cells remain where introduced into the wound, which may display local inflammatory changes and a mixed bacterial flora.

CLINICAL MANIFESTATIONS
Tetanus is most often generalized but may also be localized. The incubation period typically is 2-14 days but may be as long as months after the injury. In generalized tetanus, the presenting symptom in about half of cases is trismus (masseter muscle spasm, or lockjaw). Headache, restlessness, and irritability are early symptoms, often followed by stiffness, difficulty chewing, dysphagia, and neck muscle spasm. The so-called sardonic smile of tetanus (risus sardonicus) results from intractable spasms of facial and buccal muscles. When the paralysis extends to abdominal, lumbar, hip, and thigh muscles, the patient may assume an arched posture of extreme hyperextension of the body, or opisthotonos, with the head and the heels bent backward and the body bowed forward with only the back of the head and the heels touching the supporting surface. Opisthotonos is an equilibrium position that results from unrelenting total contraction of opposing muscles, all of which display the typical board-like rigidity of tetanus. Laryngeal and respiratory muscle spasm can lead to airway obstruction and asphyxiation. Because tetanus toxin does not affect sensory nerves or cortical function, the patient unfortunately remains conscious, in extreme pain, and in fearful anticipation of the next tetanic seizure. The seizures are characterized by sudden, severe tonic contractions of the muscles, with fist clenching, flexion, and adduction of the arms and hyperextension of the legs. Without treatment, the seizures range from a few seconds to a few minutes in length with intervening respite periods, but as the illness progresses, the spasms become sustained and exhausting. The smallest disturbance by sight, sound, or touch may trigger a tetanic spasm. Dysuria and urinary retention result from bladder sphincter spasm; forced defecation may occur. Fever, occasionally as high as 40°C (104°F), is common because of the substantial metabolic energy consumed by spastic muscles. Notable autonomic effects include tachycardia, dysrhythmias, labile hypertension, diaphoresis, and cutaneous vasoconstriction. The tetanic paralysis usually becomes more severe in the 1st wk after onset, stabilizes in the 2nd wk, and ameliorates gradually over the ensuing 1-4 wk.

Neonatal tetanus, the infantile form of generalized tetanus, typically manifests within 3-12 days of birth as progressive difficulty in feeding (sucking and swallowing), associated hunger, and crying. Paralysis or diminished movement, stiffness and rigidity to the touch, and spasms, with or without opisthotonos, are characteristic. The umbilical stump may hold remnants of dirt, dung, clotted blood, or serum, or it may appear relatively benign.

Localized tetanus results in painful spasms of the muscles adjacent to the wound site and may precede generalized tetanus. Cephalic tetanus is a rare form of localized tetanus involving the bulbar musculature that occurs with wounds or foreign bodies in the head, nostrils, or face. It also occurs in association with chronic otitis media. Cephalic tetanus is characterized by retracted eyelids, deviated gaze, trismus, risus sardonicus, and spastic paralysis of the tongue and pharyngeal musculature.

DIAGNOSIS
The picture of tetanus is one of the most dramatic in medicine, and the diagnosis may be established clinically. The typical setting is an...
unimmunized patient (and/or mother) who was injured or born within the preceding 2 wk, who presents with trismus, other rigid muscles, and a clear sensorium.

Results of routine laboratory studies are usually normal. A peripheral leukocytosis may result from a secondary bacterial infection of the wound or may be stress induced from the sustained tetanic spasms. The cerebrospinal fluid is normal, although the intense muscle contractions may raise intracranial pressure. Neither the electroencephalogram nor the electromyogram shows a characteristic pattern. C. tetani is not always visible on Gram stain of wound material and is isolated in only approximately 30% of cases.

**DIFFERENTIAL DIAGNOSIS**

Fully developed, generalized tetanus cannot be mistaken for any other disease. However, trismus may result from parapharyngeal, retropharyngeal, or dental abscesses or, rarely, from acute encephalitis involving the brainstem. Either rhabdies or tetanus may follow an animal bite, and rhabdies may manifest as trismus with seizures. Rabies may be distinguished from tetanus by hydrophobia, marked dysphagia, predominantly clonic seizures, and pleocytosis (see Chapter 274). Although strychnine poisoning may result in tonic muscle spasms and generalized seizure activity, it seldom produces trismus, and unlike in tetanus, general relaxation usually occurs between spasms. Hypocalcemia may produce tetany that is characterized by laryngeal and carpopedal spasms, but trismus is absent. Occasionally, epileptic seizures, narcotic withdrawal, or other drug reactions may suggest tetanus.

**TREATMENT**

Management of tetanus requires eradication of C. tetani and the wound environment conducive to its anaerobic multiplication, neutralization of all accessible tetanus toxin, control of seizures and respiration, palliation, provision of meticulous supportive care, and, finally, prevention of recurrences.

Surgical wound excision and debridement are often needed to remove the foreign body or devitalized tissue that created anaerobic growth conditions. Surgery should be performed promptly after administration of human tetanus immunoglobulin (TIG) and antibiotics. Excision of the umbilical stump in the neonate with tetanus is no longer recommended.

Tetanus toxin cannot be neutralized by TIG after it has begun its axonal ascent to the spinal cord. TIG should be given as soon as possible so as to neutralize toxin that diffuses from the wound into the circulation before the toxin can bind at distant muscle groups. The optimal dose of TIG has not been determined. A single intramuscular injection of 500 units of TIG is sufficient to neutralize systemic tetanus toxin, but total doses as high as 3,000-6,000 units are also recommended. Infiltration of TIG into the wound is now considered unnecessary. If TIG is unavailable, use of human intravenous immunoglobulin may be necessary. Intravenous immunoglobulin contains 4-90 units/mL of TIG; the optimal dosage of intravenous immunoglobulin for treating tetanus is not known, and its use is not approved for this indication. Another alternative is equine- or bovine-derived tetanus antitoxin (TAT). The usual dose of TAT is 50,000-100,000 units, with half given intramuscularly and half intravenously, but as little as 10,000 units may be sufficient. TAT is not available in the United States. Approximately 15% of patients given the usual dose of TAT experience serum sickness. When TAT is used, it is essential to check for possible sensitivity to horse serum; desensitization may be needed. The human-derived immunoglobulins are much preferred because of their longer half-lives (30 days) and the virtual absence of allergic and serum sickness adverse effects. Intrathecal TIG, given to neutralize tetanus toxin in the spinal cord, is not effective.

Penicillin G (100,000 units/kg/day divided every 4-6 hr IV for 10-14 days) remains the antibiotic of choice because of its effective clostridial action and its diffusibility, which is an important consideration because blood flow to injured tissue may be compromised. Metronidazole (500 mg every 8 hr IV for adults) appears to be equally effective. Erythromycin and tetracycline (for persons >8 yr of age) are alternatives for penicillin-allergic patients.

**Supportive Care**

Meticulous supportive care in a quiet, dark, secluded setting is most desirable. Because tetanic spasms may be triggered by minor stimuli, the patient should be sedated and protected from all unnecessary sounds, sights, and touch, and all therapeutic and other manipulations must be carefully scheduled and coordinated. Endotracheal intubation may not be required, but it should be done to prevent aspiration of secretions before laryngospasm develops. A tracheostomy kit should be immediately at hand for intuinated patients. Endotracheal intubation and suctioning easily provoke reflex tetanic seizures and spasms, so early tracheostomy should be considered in severe cases not managed by pharmacologically induced flaccid paralysis. Therapeutic botulinum toxin has been used for this purpose, that is, to overcome trismus.

Cardiorespiratory monitoring, frequent suctioning, and maintenance of the patient's substantial fluid, electrolyte, and caloric needs are fundamental. Careful nursing attention to mouth, skin, bladder, and bowel function is needed to avoid ulceration, infection, and obstruction. Prophylactic subcutaneous heparin may be of value but must be balanced with the risk for hemorrhage.

**Complications**

The seizures and the severe, sustained rigid paralysis of tetanus predispose the patient to many complications. Aspiration of secretions and pneumonia may have begun before the first medical attention was received. Maintaining airway patency often mandates endotracheal intubation and mechanical ventilation with their attendant hazards, including pneumothorax and mediastinal emphysema. The seizures may result in lacerations of the mouth or tongue, in intramuscular hematomas or rhabdomyolysis with myoglobinuria and renal failure, or in long bone or spinal fractures. Venous thrombosis, pulmonary embolism, gastric ulceration with or without hemorrhage, paralytic ileus, and decubitus ulceration are constant hazards. Excessive use of muscle relaxants, which are an integral part of care, may produce iatrogenic apnea. Cardiac arrhythmias, including asystole, unstable blood pressure, and labile temperature regulation reflect disordered autonomic nervous system control that may be aggravated by inattention to maintenance of intravascular volume needs.

**Prognosis**

Recovery in tetanus occurs through regeneration of synapses within the spinal cord and thereby the restoration of muscle relaxation. However, because an episode of tetanus does not result in the production of toxin-neutralizing antibodies, active immunization with tetanus toxoid at discharge with provision for completion of the primary series is mandatory.

The most important factor that influences outcome is the quality of supportive care. Mortality is highest in the very young and the very old. A favorable prognosis is associated with a long incubation period, absence of fever, and localized disease. An unfavorable prognosis is associated with onset of trismus <7 days after injury and with onset of generalized tetanic spasms <3 days after onset of trismus. Sequelae of hypoxic brain injury, especially in infants, include cerebral palsy.
diminished mental abilities, and behavioral difficulties. Most fatalities occur within the first week of illness. Reported case fatality rates for generalized tetanus are 5-35%, and for neonatal tetanus they extend from <10% with intensive care treatment to >75% without it. Cephalic tetanus has an especially poor prognosis because of breathing and feeding difficulties.

**PREVENTION**

Tetanus is an entirely preventable disease. A serum antibody titer of ≥0.01 units/mL is considered protective. Active immunization should begin in early infancy with combined diphtheria toxoid–tetanus toxoid–acellular pertussis (DTaP) vaccine at 2, 4, 6, and 15-18 months of age, with boosters at 4-6 yr (DTaP) and 11-12 yr (Tdap) of age and at 10 yr intervals thereafter throughout adult life with tetanus and reduced diptheria toxoid (Td). Immunization of women with tetanus toxoid prevents neonatal tetanus, and pregnant women should receive 1 dose of reduced diptheria and pertussis toxoids (Tdap) during each pregnancy, preferably at 27-36 wk gestation. Recommended immunization schedules are regularly updated; the most current versions may be found at http://www.cdc.gov/vaccines/schedules.

Arthus reactions (type III hypersensitivity reactions), a localized vasculitis associated with deposition of immune complexes and activation of complement, are reported rarely after tetanus vaccination. Mass immunization campaigns in developing countries have occasionally provoked a widespread hysterical reaction.

**Wound Management**

Tetanus prevention measures after trauma consist of inducing active immunity to tetanus toxin and of passively providing antitoxic antibody (Table 211-1). Tetanus prophylaxis is an essential part of all wound management, but specific measures depend on the nature of the injury and the immunization status of the patient. Regrettably, prevention of tetanus must now be included in planning for the consequences of bombings and other possible civilian mass-casualty events.

Tetanus toxoid should always be given after a dog or other animal bite, even though *C. tetani* is infrequently found in canine mouth flora.

All nonminor wounds require human TIG except those in a fully immunized patient. In any other circumstance (e.g., patients with an unknown or incomplete immunization history; crush, puncture, or projectile wounds; wounds contaminated with saliva, soil, or feces; avulsion injuries; compound fractures; or frostbite), TIG 250 units should be given intramuscularly, with 500 units for highly tetanus-prone wounds (i.e., unable to be debrided, with substantial bacterial contamination, or longer than 24 hr since injury). If TIG is unavailable, use of human intravenous immunoglobulin may be considered. If neither of these products is available, then 3,000-5,000 units of equine- or bovine-derived TAT may be given intramuscularly after testing for hypersensitivity. Even at this dose, serum sickness may occur.

The wound should undergo immediate, thorough surgical cleansing and debridement to remove foreign bodies and any necrotic tissue in which anaerobic conditions might develop. Tetanus toxoid should be given to stimulate active immunity and may be administered concurrently with TIG (or TAT) if given in separate syringes at widely separated sites. A tetanus toxoid booster (preferably Td or Tdap) is administered to all persons with any wound if the tetanus immunization status is unknown or incomplete. A booster is administered to injured persons who have completed the primary immunization series if (1) the wound is clean and minor but 10 or more years have passed since the last booster or (2) the wound is more serious and 5 or more years have passed since the last booster. Persons who experienced an Arthus reaction after a dose of tetanus toxoid–containing vaccine should not receive Td more frequently than every 10 yr, even for tetanus prophylaxis as part of wound management. In a situation of delayed wound care, active immunization should be started at once. Although fluid tetanus toxoid produces a more rapid immune response than the absorbed or precipitated toxoids, the absorbed toxoid results in a more durable titer.

Bibliography is available at Expert Consult.

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**Table 211-1** Tetanus Prophylaxis in Routine Wound Management

<table>
<thead>
<tr>
<th>HISTORY OF ABSORBED TETANUS TOXOID</th>
<th>Clean, Minor Wounds</th>
<th>All Other Wounds*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Tdap OR Td† TIG‡</td>
<td>Tdap OR Td† TIG‡</td>
</tr>
<tr>
<td>Uncertain or &lt;3 doses</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>3 or more doses</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

*Such as, but not limited to, wounds contaminated with dirt, feces, and saliva; puncture wounds, avulsions; wounds resulting from missiles, crushing, burns, and frostbite.

†For children younger than 7 yr of age, DTaP is preferred to tetanus toxoid alone if <3 doses of DTaP have been previously given. If pertussis vaccine is contraindicated, DT is given. For persons 7 yr of age or older, Td (or Tdap for adolescents 11-18 yr of age) is preferred to tetanus toxoid alone. Tdap is preferred to Td for adolescents 11-18 yr of age who have never received Tdap. Td is preferred to tetanus toxoid for adolescents who received Tdap previously or when Tdap is not available.

‡TIG should be administered for tetanus-prone wounds in HIV-infected patients regardless of the history of tetanus immunizations.

§Yes, if 10 yr or longer since the last toxoid–containing vaccine dose.

*Yes, if 5 yr or longer since the last toxoid–containing vaccine dose. (More frequent boosters are not needed and can accentuate adverse events.)

DT, diphtheria and tetanus toxoid vaccine; DTaP, combined diphtheria toxoid–tetanus toxoid–acellular pertussis vaccine; Td, tetanus toxoid and reduced diptheria toxoid vaccine; Tdap, tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine; TIG, tetanus immune globulin.

Bibliography


**Clostridium difficile infection** (CDI), also known as *pseudomembranous colitis* or *C. difficile*-associated diarrhea, refers to gastrointestinal colonization with *C. difficile* resulting in a diarrheal illness. An increase in inpatient and outpatient acquisition of CDI has been observed and new risk factors identified, fueling the development of new therapeutic options.

**ETIOLOGY**
*C. difficile* is a Gram-positive, anaerobic bacillus capable of forming a spore that is resistant to killing by alcohol. Organisms causing symptomatic disease produce 1 or both of the following: toxin A and toxin B. These toxins affect intracellular signaling pathways, resulting in inflammation and cell death. The cytotoxic binary toxin, an AB toxin, is not present in the majority of strains but has been detected in epidemic strains.

**EPIDEMIOLOGY**
Once thought to be an infrequent infection of chronically ill and hospitalized patients, the incidence of CDI is increasing and the setting of acquisition is changing. The incidence in pediatric patients increased 48%, from 2.5 to 3.7 cases per 1,000 admissions between 2001 and 2006. A population-based cohort study over a similar time period found that 75% of cases were community-acquired and 16% had no
preceeding hospitalization or antibiotic exposure. In addition to an overall increase in all strains, a hypervirulent strain, denoted NAP1/BI/027 (also called BI), has emerged and is estimated to cause approximately 10-20% of pediatric infections. This strain produces binary toxin and exhibits 16- and 23-fold increases in the production of toxins A and B, respectively. The specific role of this hypervirulent strain in the changing epidemiology of CDI is not completely understood.

Asymptomatic carriage occurs with potentially pathogenic strains; this is common in neonates and infants 1 year of age and younger. A carrier frequency rate of 50% may occur in children younger than age 1 yr, but the rate declines by age 3 yr. Carriers can infect other susceptible individuals.

Risk factors for CDI include the use of broad-spectrum antibiotics, hospitalization (particularly if the prior room occupant was infected), gastrointestinal surgery, inflammatory bowel disease, chemotherapy, enteral tube feeding, proton pump–inhibitor use, and chronic illness.

PATHOGENESIS

Disease is caused by gastrointestinal infection with a toxin-producing strain. Any process that disrupts normal flora, impairs the acid barrier defense, alters the normal gastrointestinal immune response (e.g., inflammatory bowel disease), or inhibits intestinal motility may lead to infection. Normal bowel flora appears to be protective, conferring “colonization resistance.”

By affecting intracellular signaling pathways and cytoskeletal organization, toxins induce an inflammatory response and cell death, leading to diarrhea and pseudomembrane formation. Antibodies against toxin A have been shown to confer protection against symptomatic disease, and failure of antibody production has been shown to occur in patients with recurrent disease.

CLINICAL MANIFESTATIONS

Infection with toxin-producing strains of *C. difficile* leads to a spectrum of disease ranging from mild, self-limited diarrhea to explosive, watery diarrhea with occult blood or mucus, to pseudomembranous colitis, and even death. *Pseudomembranous colitis* describes a bloody diarrhea with accompanying fever, abdominal pain/cramps, nausea, and vomiting. Rarely, small gut involvement, bacteremia, abscess formation, toxic megacolon, and even death can occur.

Symptoms of CDI generally begin less than a week after colonization and may develop during or weeks after antibiotic exposure. They are generally more severe in certain populations, including patients receiving chemotherapy, patients with chronic gastrointestinal disease (e.g., inflammatory bowel disease), and some patients with cystic fibrosis.

DIAGNOSIS

CDI is diagnosed by the detection of a *C. difficile* toxin in the stool of a symptomatic patient. Most patients present with a history of recent antibiotic use, but the absence of antibiotic exposure should not dissuade the astute clinician from considering this diagnosis and ordering the appropriate test. Conversely, high carriage rates among infants should prompt careful consideration when testing and treating children younger than the age of 3 yr.

The cell culture cytotoxicity assay was replaced as the standard test for toxin detection by the enzyme immunoassay, a same-day test for 1 or both toxins with sufficient specificity (94-100%) but less-than-ideal sensitivity (88-93%). Nucleic acid amplification tests are used by some laboratories to supplement or supplant the immunoassay with the goal of improving sensitivity.

Culture for organism isolation is a sensitive test but is labor intensive, taking several days. Culture alone is not specific, as it does not differentiate between toxin-producing and non–toxin-producing strains. Pseudomembranous nodules and characteristic plaques may be seen on colonoscopy or sigmoidoscopy.

TREATMENT

Initial treatment of CDI involves discontinuation of any nonvital antibiotic therapy and administration of fluid/electrolyte replacement. For mild cases, this treatment may be curative. Persistent symptoms or moderate to severe disease warrants antimicrobial therapy directed against *C. difficile*.

Oral metronidazole (20–40 mg/kg/day PO divided every 6-8 hr for 7-10 days) works well in mild to moderate infection. Orally administered vancomycin (40 mg/kg/day PO divided every 6 hr for 7-10 days) is approved by the U.S. Food and Drug Administration for use against infection with *C. difficile*. Vancomycin exhibits ideal pharmacologic properties for treatment of this enteric pathogen, as it is not absorbed in the gut. This agent is suggested as a first-line agent for severe disease as manifested by hypotension, peripheral leukocytosis, or severe pseudomembranous colitis. Concern for the emergence of vancomycin-resistant enterococci and cost limit its use as first-line therapy in mild to moderate disease. Fidaxomicin, a second-line agent not yet approved for pediatric use, is a narrow spectrum macrolide antibiotic with non-inferior efficacy to vancomycin but superior recurrence prevention. The cost of a course of fidaxomicin can be twice that of vancomycin and 125-fold higher than that of metronidazole. Reports have demonstrated a high success treatment efficacy for donor (unaffected) fecal therapy (transplant) (see below for recurrences).

PROGNOSIS

The response rate to initial treatment of CDI is greater than 95%; however, both the treatment failure rate and the recurrence rate have increased since the late 1990s. Additionally, the risk of subsequent reappearance increases with each recurrence.

Initial recurrence rates are between 5% and 20%, are diagnosed clinically and generally occur within 4 wk of treatment. Some recurrences are a result of incomplete eradication of the original strain and others are because of reinfection with a different strain. Treatment for the initial recurrence involves retreatment with the original antibiotic course.

Recurrences of CDI may be a consequence of a suboptimal immune response, failure to kill organisms that have sporulated, or failure of delivery of antibiotic to the site of infection in the case of ileus or toxic megacolon. In the case of the 1st 2 causes, treatment with pulsed or tapered vancomycin decreases recurrence rates. In addition to this approach, other antibiotics (rifaximin or nitazoxanide), toxin-binding polymers (Tolerase), and probiotics (Saccharomyces boulardii or Lactobacillus GG) have been used as adjunctive therapy. Although not well studied in children, *S. boulardii* significantly decreases recurrence rates when used as an adjunct to vancomycin therapy in adults. Because failure to manifest an adequate antitoxin immune response is associated with a higher frequency of recurrent CDI, intravenous immune globulin has been used to treat recurrent disease. In the case of ileus or toxic megacolon, an enema of vancomycin may be used to directly place the antibiotic at the site of infection, although most often intravenous therapy is first attempted in this circumstance.

Fecal microbial transplantation has been used to address the disruption in normal gut flora felt to allow colonization with *C. difficile*. Transplantation involves the instillation of fecal material from a healthy donor into the patient's gastrointestinal tract by nasoenteric tube, enema, capsules, or colonoscopy. Initial reports indicate an overall success rate of approximately 90% in patients with recurrent CDI.

It is important to recognize that postinfectious diarrhea may be from other causes. Examples are postinfectious irritable bowel syndrome, microscopic colitis, and inflammatory bowel disease. A test of cure is not useful until at least 4 wk after the initial test.

PREVENTION

Strategies for prevention of CDI include recognition of common sites of acquisition (hospitals, childcare settings, extended care facilities); effective environmental cleaning (i.e., use of chlorinated cleaning solutions); appropriate antibiotic and proton-pump inhibitor prescription practices; cohorting of infected patients; and proper handwashing with soap and water. There is moderate evidence that probiotics may reduce the incidence of *C. difficile*–associated diarrhea.

Bibliography is available at Expert Consult.
Bibliography


Anaerobic bacteria are among the most numerous organisms colonizing humans. Anaerobes are present in soil and are normal inhabitants of all living animals, but infections caused by anaerobes are relatively uncommon. Anaerobes are relatively or entirely intolerant of exposure to oxygen. Most are facultative anaerobes, being able to survive in the presence of oxygen but growing better in reduced oxygen tensions. Obligate anaerobes cannot survive any exposure to oxygen.

Infections with anaerobes frequently occur adjacent to mucosal surfaces, often as mixed infections with aerobes. Conditions of reduced oxygen tension provide the optimal conditions for proliferation of anaerobes. Traumatized areas, devascularized areas, and areas of crush injury are all ideal sites for anaerobic infection. Often both aerobic and anaerobic organisms are inoculated in devitalized areas, with local extension and bacteremia most often caused by the more virulent aerobes. Abscess formation evolves over days to weeks and generally involves both aerobes and anaerobes. Examples of such infections include appendicitis and periappendiceal, pelvic, perirectal, peritonsillar, retropharyngeal, parapharyngeal, and dental abscesses. Septic thrombophlebitis, as a consequence of appendicitis, chronic sinusitis, pharyngitis, and otitis media, provides a route for hematogenous spread of anaerobic infection to parenchymal organs such as the liver, brain, and lungs.

Anaerobic infection is usually caused by endogenous flora. Combinations of impaired physical barriers to infection, compromised tissue viability, alterations in normal flora, impaired host immunity, and anaerobic bacterial virulence factors contribute to infection with normal anaerobic inhabitants of mucous membranes. Virulence factors include capsules, toxins, enzymes, and fatty acids.

**CLINICAL MANIFESTATIONS**

Anaerobic infections occur in a variety of sites throughout the body (Table 213-1). Anaerobes often coexist synergistically with aerobes. Infections with anaerobes are usually polymicrobial and also include aerobes.

**Bacteremia**

Anaerobes account for approximately 1% of bloodstream bacterial isolates in adults, but the rate is lower in children. Isolation of anaerobes from the blood is often an indication of a serious primary anaerobic infection. The most common blood isolates of anaerobic bacteria in children are *Bacteroides fragilis*, *Peptostreptococcus* spp., *Clostridium* spp., and *Fusobacterium* spp. As with aerobes, the cell walls of Gram-negative anaerobes may contain endotoxin and can be associated with the development of hypotension and shock when present in the circulatory system. Clostridia produce hemolysins, and the presence of these organisms in the blood can result in massive hemolysis and cardiovascular collapse.

**Central Nervous System**

Anaerobic meningitis is rare but can occur in neonates and as a complication of infections of the ear and neck or because of anatomic defects of meninges (sinus tracts). Brain abscess and subdural empyema are usually polymicrobial, with anaerobes commonly involved (see Chapter 604). Brain abscess usually occurs as a result of spread from infected sinuses, middle ear, or lung.

**Upper Respiratory Tract**

The respiratory tract is colonized by both aerobes and anaerobes. Anaerobic bacteria are involved in chronic sinusitis, chronic otitis media, peritonsillar infections, parapharyngeal and retropharyngeal abscesses, and periodontal infections. Anaerobic periodontal disease is most common in patients with poor dental hygiene or who are receiving drugs that provide hypertrophy of the gums. *Vincent angina*, also known as acute necrotizing ulcerative gingivitis or trench mouth, is an acute, fulminating, mixed anaerobic bacterial–spirochetal infection of the gingival margin and floor of the mouth. It is characterized by gingival pain, foul breath, and pseudomembrane formation. *Ludwig angina* is an acute, life-threatening cellulitis of dental origin of the sublingual and submandibular spaces. Infection spreads rapidly in the neck and may cause sudden airway obstruction.

*Lemierre syndrome*, or postanginal sepsis, is a suppurative infection of the lateral pharyngeal space, of increasing prevalence, that often begins as pharyngitis (see Chapter 381). It may complicate Epstein-Barr virus or other viral and bacterial infections of the pharynx. It usually manifests as a unilateral septic thrombophlebitis of the jugular venous system with septic pulmonary embolization. Clinical signs include unilateral painful neck swelling, trismus, and dysphagia, culminating with signs of sepsis and respiratory distress. *Fusobacterium necrophorum* is the most commonly isolated organism, although polymicrobial infection may occur. Metastatic infections involving muscles, bones, and solid organs can occur as a complication of Lemierre syndrome.

**Lower Respiratory Tract**

Anaerobic lung abscess, empyema, and anaerobic pneumonia are most common in children who have disordered swallowing or seizures or in whom an inhaled foreign body is occluding a bronchus. Children and adults can aspirate oral contents during sleep, seizure, or periods of unconsciousness. In most cases, lung cilia and phagocytes clear particulate matter and microbes. If the aspiration is of increased volume or frequency or a foreign body blocks normal ciliary clearance, normal pulmonary clearance mechanisms are overcome and infection ensues. In unusual cases, particularly in patients with poor dental hygiene, aspirated mouth contents may contain the anaerobe *Actinomyces israelii*, resulting in pulmonary actinomycosis (see Chapter 189). This anaerobic pneumonitis is remarkable for traversing tissues planes, and affected patients often have fistulas extruding distinctive particulate matter, called sulfur granules, from the chest wall overlying areas of intrathoracic infection.

**Intraabdominal Infection**

The entire digestive tract is heavily colonized by anaerobes. The density of organisms is highest in the colon, where anaerobes outnumber aerobes 1,000:1. Perforation of the gut leads to leakage of gut flora into the peritoneum, resulting in peritonitis involving both aerobes and anaerobes. Secondary sepsis caused by aerobes often occurs early. As the peritoneal infection is walled off, an abscess containing both aerobes and anaerobes often evolves. Secondary hepatic abscesses may then develop as complications of appendicitis, intestinal perforation, inflammatory bowel disease, or biliary tract disease. In children with malignancies who are receiving chemotherapy, the intestinal mucosa is often damaged, leading to translocation of bacteria and focal invasion of bowel flora. *Typhilitis* is a mixed infection of the gut wall usually beginning in the ileocecum and characterized by abdominal pain, diarrhea, fever, and abdominal distention in neutropenic patients. Empiric antimicrobial therapy of fever and neutropenia may not be optimal against the anaerobes involved in typhilitis (see Chapter 178). Similarly, a mixed aerobic–anaerobic infection of the intestinal wall and peritoneum may develop in a small infant as a complication of necrotizing enterocolitis, believed to be a result of the relative vascular insufficiency of the gut and hypoxia (see Chapter 102.2).

**Genital Tract**

Pelvic inflammatory disease and tuboovarian abscesses are frequently caused by mixed aerobic anaerobic infection. Vaginitis can be caused
### Table 213-1  Infections Associated with Anaerobic Bacteria

<table>
<thead>
<tr>
<th>SITE AND INFECTION</th>
<th>MAJOR RISK FACTORS</th>
<th>ANAEROBIC BACTERIA*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CENTRAL NERVOUS SYSTEM</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cerebral abscess</td>
<td>Cyanotic heart disease, Cystic fibrosis, Penetrating trauma</td>
<td>Polymicrobial</td>
</tr>
<tr>
<td>Epidural and subdural empyemas, meningitis</td>
<td>Direct extension from contiguous sinusitis, otitis media, mastoiditis, or anatomic defect involving the dura</td>
<td>Bacteroides fragilis, Fusobacterium, Peptostreptococcus, Veillonella</td>
</tr>
<tr>
<td><strong>UPPER RESPIRATORY TRACT</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dental abscess</td>
<td>Poor periodontal hygiene, Drugs producing gingival hypertrophy</td>
<td>Peptostreptococcus, Fusobacterium</td>
</tr>
<tr>
<td>Ludwig angina (cellulitis of sublingual-submandibular space)</td>
<td>Tymanic perforation, Tymanostomy tubes, Streptococcal pharyngitis</td>
<td>Prevotella melananogenica</td>
</tr>
<tr>
<td>Necrotizing gingivitis (Vincent stomatitis)</td>
<td>Tympanic perforation, Tymanostomy tubes, Streptococcal pharyngitis</td>
<td></td>
</tr>
<tr>
<td>Chronic otitis-mastoiditis-sinusitis</td>
<td>Penetrating injury, Preexisting viral or bacterial pharyngitis</td>
<td>Fusobacterium</td>
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<tr>
<td>Peritonsillar abscess</td>
<td></td>
<td></td>
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<tr>
<td>Retropharyngeal abscess</td>
<td></td>
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<tr>
<td>Lemierre syndrome</td>
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<td></td>
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<tr>
<td><strong>LOWER RESPIRATORY TRACT</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspiration pneumonia</td>
<td>Periodontal disease, Bronchial obstruction, Altered gag or consciousness</td>
<td>Polymicrobial, P. melananogenica, Bacteroides intermedius, Fusobacterium, Peptostreptococcus, Eubacterium, B. fragilis, Veillonella, Fusobacterium</td>
</tr>
<tr>
<td>Necrotizing pneumonitis</td>
<td></td>
<td></td>
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<tr>
<td>Lung abscess</td>
<td></td>
<td></td>
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<tr>
<td>Septic pulmonary emboli</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>INTRAABDOMINAL</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abscess</td>
<td>Appendicitis, Penetrating trauma (especially of the colon)</td>
<td>Polymicrobial, Bacteroides spp., Clostridium, Peptostreptococcus, Eubacterium, Fusobacterium</td>
</tr>
<tr>
<td>Secondary peritonitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>FEMALE GENITAL TRACT</strong></td>
<td></td>
<td></td>
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<tr>
<td>Bartholin abscess</td>
<td>Vaginosis, Intrauterine device</td>
<td>B. fragilis, Bacteroides bivius, Peptostreptococcus, Clostridium, Mobiluncus, Actinomyces, Clostridium</td>
</tr>
<tr>
<td>Tuboovarian abscess</td>
<td></td>
<td></td>
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<tr>
<td>Endometritis</td>
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<tr>
<td>Pelvic thrombophlebitis</td>
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<td>Salpingitis</td>
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<tr>
<td>Chorioamnionitis</td>
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<td></td>
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<tr>
<td>Septic abortion</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>SKIN AND SOFT TISSUE</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cellulitis</td>
<td>Decubitus ulcers</td>
<td>Varies with site and contamination with oral or enteric flora, Clostridium perfringens (myonecrosis), Bacteroides, Clostridia, Fusobacterium, Clostridium tertium, Clostridium septicum, Anaerobic streptococci</td>
</tr>
<tr>
<td>Perirectal cellulitis</td>
<td>Abdominal wounds, Pilonidal sinus</td>
<td></td>
</tr>
<tr>
<td>Myonecrosis (gas gangrene)</td>
<td>Trauma, Human and animal bites, Immunosuppressed or neutropenic patients, Varicella</td>
<td></td>
</tr>
<tr>
<td>Necrotizing fascitis and synergistic gangrene</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>BLOOD</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bacteremia</td>
<td>Intraabdominal infection, abscesses, myonecrosis, necrotizing fascitis</td>
<td>B. fragilis, Clostridium, Peptostreptococcus, Fusobacterium</td>
</tr>
</tbody>
</table>

*Infections may also be from or may involve aerobic bacteria as the sole agent or as part of a mixed infection; brain abscesses may contain microaerophilic streptococci; intraabdominal infections may contain Gram-negative enteric organisms and enterococci; and salpingitis may contain Neisseria gonorrheae and Chlamydia trachomatis.*

†Bacteroides fragilis is usually isolated from infections below the diaphragm except for brain abscesses.

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by overgrowth of anaerobic flora. Anaerobes frequently contribute to chorioamnionitis and premature labor and may result in anaerobic bacteremia of the newborn. Although these bacteremias are often transient, anaerobes occasionally cause invasive disease in the newborn, including central nervous system infection.

### Skin and Soft Tissue

Anaerobic skin infections occur in the setting of bites, foreign bodies, and skin and tissue ulceration because of pressure necrosis or lack of adequate blood supply. Animal bites and human bites inoculate oral and skin flora into damaged and hypoxic cutaneous tissue. The extent
of the infection depends on the depth of the bite and the associated crush injury to the tissues. In immunocompromised patients, unusual oral anaerobes such as Capnocytophaga canimorsus can cause life-threatening infection.

Clostridial myonecrosis, or gas gangrene, is a rapidly progressive infection of deep soft tissues, primarily muscles, associated with Clostridium perfringens. Necrotizing fasciitis is a more superficial, polymicrobial infection of the subcutaneous space with acute onset and rapid progression that has significant morbidity and mortality (see Chapter 665.2). Group A streptococcus, known in the popular press as “the flesh-eating bacteria,” and Staphylococcus aureus are occasionally the causative pathogens. Commonly, necrotizing fasciitis is produced by combined infection of S. aureus or Gram-negative bacilli and anaerobic streptococci, termed synergistic gangrene. This infection is often seen as a complication of varicella following secondary infection of cutaneous vesicles. Diabetic patients may have a particularly aggressive and destructive synergistic gangrene of the inguinal area and adjacent scrotum or vulva known as Fournier gangrene. Early recognition with aggressive surgical debridement and antimicrobial therapy is necessary to limit disfiguring morbidity and mortality.

Other Sites
Occasionally, the bone adjacent to an anaerobic infection becomes infected by direct extension from a contiguous infection or by direct inoculation associated with trauma. Anaerobic infections of the kidneys (renal and perirenal abscesses) and heart (pericarditis) are rare. Enteritis necroticans (pigbel) is a rare but often fatal gastrointestinal infection that most commonly follows ingestion of a large meal in a previously starved child or adult. Anaerobic osteomyelitis, particularly of fingers and toes, can complicate any process capable of producing hypoxic necrosis, including diabetes, neuropathies, vasculopathies, and coagulopathies.

DIAGNOSIS
The diagnosis of anaerobic infection requires a high index of suspicion and the collection of appropriate and adequate specimens for anaerobic culture (Table 213-2). Culture specimens should be obtained in a manner that protects them from contamination with mucosal bacteria and from exposure to ambient oxygen. Swab samples from mucosal surfaces, nasal secretions, respiratory specimens, and stool should not be sent for anaerobic culture, because these sites normally harbor many anaerobes. Aspirates of infected sites, abscess material, and biopsy specimens are appropriate for anaerobic culturing. Specimens must be protected from oxygen and transported to the laboratory immediately. Anaerobic transport medium is used to increase the likelihood of recovery of obligate anaerobes. Gram staining of abscess fluid from suspected anaerobic infections is useful because even if the organisms do not grow in culture, they can be seen on the smear. The use of DNA probe technology in the near future is likely to increase the sensitivity of microbiologic confirmation of an anaerobic infection. Methods for susceptibility testing exist but may not be routinely available. A rapid and simple screening test for antibiotic susceptibility can be used to detect β-lactamase production and presumptive penicillin resistance.

TREATMENT
Treatment of anaerobic infections usually requires adequate drainage and appropriate antimicrobial therapy. Antibiotic therapy varies depending on the suspected or proven anaerobe involved. Many oral anaerobic bacterial species are susceptible to penicillins, although some strains may produce a β-lactamase. Drugs that are active against such strains include metronidazole, penicillins combined with β-lactamase inhibitors (ampicillin-sulbactam, ticarcillin-clavulanate, and pipercillin-tazobactam), carbapenems (imipenem and meropenem), clindamycin, and cefoxitin. Penicillin and vancomycin are active against the Gram-positive anaerobes. Aerobes are usually present with the anaerobes, necessitating broad-spectrum antibiotic combinations for empirical therapy. Specific therapy is based on culture results and clinical course.

For soft-tissue infections, providing adequate perfusion to the area is critical. At times, a muscle flap or skin flap procedure is needed to ensure that nutrients and antimicrobial agents are brought to the affected area and adequate oxygen tension is maintained. Drainage of infected areas is often necessary for cure. Bacteria may survive in abscesses because of high bacterial inoculum, lack of bactericidal activity, and local conditions that facilitate bacterial proliferation. Aspiration is sometimes effective for small collections, whereas incision and drainage may be required for larger abscesses. Extensive debridement and resection of all devitalized tissue are needed to control fasciitis and myonecrosis. The therapeutic benefit of hyperbaric oxygen therapy remains uncertain.

COMMON ANAEROBIC PATHOGENS

**Clostridium**
Strains of Clostridium cause disease by proliferation and often by production of toxins. Of the more than 60 species that have been identified, only a few cause infections in humans. The most frequently implicated species are Clostridium difficile (see Chapter 212), C. perfringens, Clostridium botulinum (see Chapter 210), Clostridium tetani (see Chapter 211), Clostridium butyricum, Clostridium septicum, Clostridium sordellii, Clostridium tertium, and Clostridium histolyticum.

C. perfringens produces a variety of toxins and virulence factors. Strains of C. perfringens are designated A through E. Alpha toxin is a phospholipase that hydrolyzes sphingomyelin and lecithin and is produced by all strains. This toxin causes hemolysis, platelet lysis, increased capillary permeability, and hepatotoxicity. Beta toxin, produced by strains B and C, causes hemorrhagic necrosis of the small bowel. Epsilon toxin is produced by B and D strains and injures vascular endothelial cells, leading to increased vascular permeability, edema, and organ dysfunction. Lota toxin, produced by E strains, causes dermal edema. An enterotoxin is produced by type A and some type
C and D strains. Hemolysins and a variety of enzymes are produced by many *C. perfringens* strains.

*Clostridium* species commonly invade the bloodstream shortly before, during, or just after death, leading to contamination of tissues that may be donated for transplantation. A large outbreak of *Clostridium* infections in tissue graft recipients was reported in 14 patients who received musculoskeletal grafts processed at a single tissue bank. As a result of this outbreak, recommendations for tissue processing now include a processing method that kills bacterial spores.

**Myonecrosis (Gas Gangrene)**
*C. perfringens* is the major etiologic cause of myonecrosis, a rapidly progressive anaerobic soft-tissue infection. In immunocompromised persons, especially patients receiving cancer chemotherapy, *C. septicum* is a classic cause of rapidly fatal gas gangrene. A clue to the diagnosis is pain out of proportion to the clinical appearance of the wound. Infection progresses rapidly with edema, swelling, myonecrosis, and sometimes crepitation of soft tissues. Hypotension, mental confusion, shock, and renal failure are common. A characteristic sweet odor is present in the serosanguineous discharge. Gram staining of the exudate reveals Gram-positive bacilli but few leukocytes. Early and complete debridement with excision of necrotic tissue is key to controlling the infection. Repeated, frequent assessment of tissue viability in the operating room is required. High-dose penicillin (250,000 units/kg/day divided every 4-6 hr IV) or clindamycin (25-40 mg/kg/day divided every 6-8 hr IV) should be started immediately. Amputation of affected limbs is often required. The role of hyperbaric oxygen remains unclear but has been reported to be beneficial in several studies. Unfortunately, the prognosis for patients with myonecrosis is poor, even with early, aggressive therapy.

**Food Poisoning**
*C. perfringens* type A produces an enterotoxin that causes food poisoning (see Chapter 340). This intoxication results in the acute onset of watery diarrhea and crampy abdominal pain. The usual foods containing toxin are improperly prepared or stored meats and gravies. A specific etiologic diagnosis is rarely made in children with food poisoning. Therapy consists of rehydration and electrolyte replacement if necessary. The illness resolves spontaneously within 24 hr of onset. Prevention requires the maintenance of hot food at a temperature ≥74°C (165.2°F).

**Bacteroides and Prevotella**
*B. fragilis* is one of the more virulent anaerobic pathogens and is most frequently recovered from blood cultures and cultures of tissue or pus. The most common *B. fragilis* infection in children occurs as a complication of appendicitis. The organism is part of normal colonic flora but is not common in the mouth or respiratory tract. *B. fragilis* is usually found as part of polymicrobial appendiceal and other intraabdominal abscesses and is often involved in genital tract infections such as pelvic inflammatory disease and tuboovarian abscess. *Prevotella* organisms are normal oral flora, and infection with them typically involves gums, teeth, tonsils, and parapharyngeal spaces. Both *B. fragilis* and *Prevotella* may be involved in aspiration pneumonitis and lung abscess.

Strains of *B. fragilis* and *Prevotella melaninogenica* produce β-lactamase and are resistant to penicillins. Recommended treatment is with ticarcillin-clavulanate, piperacillin-tazobactam, cefoxitin, metronidazole, clindamycin, imipenem, or meropenem. Because infections involving these organisms are usually polymicrobial, therapy should include antimicrobial agents active against likely concomitant aerobic pathogens. Drainage of any abscesses and debridement of necrotic tissue are often required for control of these infections.

**Fusobacterium**
*Fusobacterium* organisms inhabit the intestine, respiratory tract, and female genital tracts. These organisms, which are more virulent than most of the normal anaerobic flora, cause bacteremia and a variety of rapidly progressive infections. *Lemierre syndrome*, bone and joint infections, and abdominal and genital tract infections are most common. Some strains produce a β-lactamase and are resistant to penicillins, requiring therapy with drugs like ampicillin-sulbactam and clindamycin.

**Veillonella**
*Veillonella* organisms are normal flora of the mouth, upper respiratory tract, intestine, and vagina. These anaerobes rarely cause infection. Strains are recovered as part of the polymicrobial flora causing abscess, chronic sinusitis, empyema, peritonitis, and wound infection. *Veillonella* organisms are susceptible to penicillins, cephalosporins, clindamycin, metronidazole, and carbapenems.

**Anaerobic Cocci**
*Peptostreptococcus* species are normal flora of the skin, respiratory tract, and gut. These organisms are often present in brain abscesses, chronic sinusitis, chronic otitis, and lung abscesses. Such infections are often polymicrobial, and therapy is aimed at the accompanying aerobes as well as the anaerobes. Most of the Gram-positive cocci are susceptible to penicillin, cephalosporins, carbapenems, and vancomycin.

**Bibliography is available at Expert Consult.**
Bibliography


The treatment of mycobacterial infection and disease can be challenging. Patients require therapy with multiple agents, the offending pathogens commonly exhibit complex drug resistance patterns, and patients often have underlying conditions that affect drug choice and monitoring. Several of the drugs have not been well studied in children, and current recommendations are extrapolated from the experience in adults.

Single-drug therapy of *Mycobacterium tuberculosis* and nontuberculous mycobacteria is not recommended because of the high likelihood of developing antimicrobial resistance. Susceptibility testing of mycobacterial isolates often can aid in therapeutic decision making.

**AGENTS USED AGAINST MYCOBACTERIUM TUBERCULOSIS**

Commonly Used Agents

**Isoniazid**

Isoniazid (INH) is a hydrazide form of isonicotinic acid and is bactericidal for rapidly growing *M. tuberculosis*. The primary target of INH involves the INH A gene, which encodes the enoyl ACP (acyl carrier
If daily therapy is not possible, DOT twice a week can be used for 9 mo.
If daily therapy is not possible, DOT twice a week can be used for 6 mo. If possible drug resistance is a concern (see text), another drug (ethambutol or an aminoglycoside) is added to the initial 3 drug therapy until drug susceptibilities are determined; DOT is highly desirable. Drugs can be given 2 or 3×/wk under DOT in the initial phase if nonadherence is likely. A 4th drug, such as an aminoglycoside, is given with initial therapy until drug susceptibility is known. For patients who might have acquired tuberculosis in geographic areas where resistance to streptomycin is common, kanamycin, amikacin, or capreomycin can be used instead of streptomycin.

**Table 214-2**  Isoniazid Drug–Drug Interactions

<table>
<thead>
<tr>
<th>DRUG USED WITH ISONIAZID</th>
<th>EFFECTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaminophen, alcohol, rifampin</td>
<td>Increased hepatotoxicity of isoniazid or listed drugs</td>
</tr>
<tr>
<td>Aluminum salts (antacids)</td>
<td>Decreased absorption of isoniazid</td>
</tr>
<tr>
<td>Carbamazepine, phenytoin, theophylline, diazepam, warfarin</td>
<td>Increased level, effect, or toxicity of listed drugs due to decreased metabolism</td>
</tr>
<tr>
<td>Itraconazole, ketoconazole, oral hypoglycemic agents</td>
<td>Decreased level or effect of listed drugs due to increased metabolism</td>
</tr>
<tr>
<td>Cycloserine, ethionamide</td>
<td>Increased central nervous system adverse effects of cycloserine and ethionamide</td>
</tr>
<tr>
<td>Prednisolone</td>
<td>Increased isoniazid metabolism</td>
</tr>
</tbody>
</table>

* Positive TST or IGRA result, no disease.
1. Duration of therapy is longer for human immunodeficiency virus (HIV)-infected people, and additional drugs may be indicated.
2. Medications should be administered daily for the 1st 2 wk to 2 mo of treatment and then can be administered 2-3×/wk by DOT.
3. If initial chest radiograph shows cavitory lesions and sputum after 2 mo of therapy remains positive, duration of therapy is extended to 9 mo.

**Table 214-1**  Recommended Treatment Regimens for Drug-Susceptible Tuberculosis in Infants, Children, and Adolescents

<table>
<thead>
<tr>
<th>INFECTION OR DISEASE CATEGORY</th>
<th>REGIMEN</th>
<th>REMARKS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LATENT TUBERCULOSIS INFECTION</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isoniazid susceptible</td>
<td>9 mo of isoniazid, once a day</td>
<td>If daily therapy is not possible, DOT twice a week can be used for 9 mo</td>
</tr>
<tr>
<td>Isoniazid resistant</td>
<td>6 mo of rifampin, once a day</td>
<td>If daily therapy is not possible, DOT twice a week can be used for 6 mo</td>
</tr>
<tr>
<td>Isoniazid-rifampin resistant†</td>
<td>Consult a tuberculosis specialist</td>
<td></td>
</tr>
<tr>
<td><strong>PULMONARY AND EXTRAPULMONARY INFECTION</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Except meningitis</td>
<td>2 mo of isoniazid, rifampin, pyrazinamide, and ethambutol daily, followed by 4 mo of isoniazid and rifampin† by DOT‡ for drug-susceptible Mycobacterium tuberculosis</td>
<td>If possible drug resistance is a concern (see text), another drug (ethambutol or an aminoglycoside) is added to the initial 3 drug therapy until drug susceptibilities are determined; DOT is highly desirable. Drugs can be given 2 or 3×/wk under DOT in the initial phase if nonadherence is likely. A 4th drug, such as an aminoglycoside, is given with initial therapy until drug susceptibility is known. For patients who might have acquired tuberculosis in geographic areas where resistance to streptomycin is common, kanamycin, amikacin, or capreomycin can be used instead of streptomycin</td>
</tr>
<tr>
<td>Meningitis</td>
<td>2 mo of isoniazid, rifampin, pyrazinamide, and an aminoglycoside or ethambutol or ethionamide, once a day, followed by 7-10 mo of isoniazid and rifampin, once a day or twice a week (9-12 mo total) for drug-susceptible M. tuberculosis</td>
<td></td>
</tr>
</tbody>
</table>
Resistance is from a mutation in the DNA-dependent RNA polymerase gene (RpoB) that is often induced by previous incomplete therapy. Cross-resistance between rifampin and rifabutin has been demonstrated.

Rifampin is active against *M. tuberculosis*, *Mycobacterium leprae*, *M. kansasi*, and *Mycobacterium avium* complex. Rifampin is an integral drug in standard combination treatment of active *M. tuberculosis* disease and can be used as an alternative to INH in the treatment of latent tuberculosis infection in children who cannot tolerate INH. Rifabutin has a similar spectrum, with increased activity against *M. avium* complex. Rifapentine is undergoing pediatric clinical trials and appears to have activity similar to the activity of rifampin. The pediatric dosage of rifampin is 10-15 mg/kg/day PO in a single dose, not to exceed 600 mg/day. The adult dosage of rifampin is 5-10 mg/kg/day PO in a single dose, not to exceed 600 mg/day. Commonly used rifampin preparations include 150 and 300 mg capsules and a suspension that is usually formulated at a concentration of 10 mg/mL. The shelf life of rifampin suspension is short (approximately 4 wk), so it should not be compounded with other antimycobacterial agents. An intravenous form of rifampin is also available for initial treatment of patients who cannot take oral preparations. Dosage adjustment is needed for patients with liver failure. Other rifamycins (rifabutin and rifapentine) have been poorly studied in children and are not recommended for use in children.

Rifampin can be associated with **adverse events** such as transient elevations of liver enzymes; gastrointestinal (GI) upset with cramps, nausea, vomiting, and anorexia; headache; dizziness; and immunologically mediated fever and flu-like symptoms. Thrombocytopenia and hemolytic anemias can also occur. Rifabutin has a similar spectrum of toxicities, except for an increased incidence of rash (4%) and neutropenia (2%). Rifapentine has fewer adverse effects but is associated with hyperuricemia and cytopenias, especially lymphopenia and neutropenia. All rifamycins can turn urine and other secretions (tears, saliva, stool, sputum) orange, which can stain contact lenses. Patients and families should be warned about this common but otherwise innocuous adverse effect.

Rifamycins induce the hepatic cytochrome P450 isozyme system and are associated with the increased metabolism and decreased level of several drugs when administered concomitantly. These drugs include digoxin, corticosteroids such as prednisone and dexamethasone, dapsone, fluconazole, phenytoin, oral contraceptives, warfarin, and many antiretroviral agents, especially protease inhibitors and non-nucleoside reverse transcriptase inhibitors. Rifabutin has less of an effect on lowering protease inhibitor levels.

The use of pyrazinamide in combination with rifampin for short-course latent tuberculosis therapy has been associated with serious liver dysfunction and death. This combination has never been well studied or recommended for pediatric patients and should not be used.

No routine laboratory monitoring for rifamycins is indicated unless the patient is symptomatic. In patients with signs of toxicity, complete blood count (CBC) and kidney and liver function tests are indicated.

**Pyrazinamide**

Pyrazinamide (PZA) is a synthetic pyrazide analog of nicotinamide that is bactericidal against intracellular *M. tuberculosis* organisms in acidic environments, such as within macrophages or inflammatory lesions. A bacteria-specific enzyme (pyrazinamidase) converts PZA to pyrazinoic acid, which leads to low pH levels not tolerated by *M. tuberculosis*. Resistance is poorly understood but can arise from bacterial pyrazinamidase alterations.

PZA is indicated for the initial treatment phase of active tuberculosis in combination with other antimycobacterial agents. The pediatric dosage is 15-30 mg/kg/day PO in a single dose, not to exceed 2,000 mg/day. Twice weekly dosing with directly observed therapy only is with 50 mg/kg/day PO in a single dose, not to exceed 4,000 mg/day. It is available in a 500 mg tablet and can be made into a suspension of 100 mg/mL.

**Adverse events** include GI upset (e.g., nausea, vomiting, poor appetite) in approximately 4% of children, dosage-dependent hepatotoxicity, and elevated serum uric acid levels that can precipitate gout in susceptible adults. Approximately 10% of pediatric patients have elevated uric acid levels but with no associated clinical sequelae. Minor reactions include arthralgias, fatigue, and, rarely, fever.

Use of PZA in combination with rifampin for short-course treatment of latent tuberculosis is associated with serious liver dysfunction and death, and this combination should be avoided.

No routine laboratory monitoring for PZA is required, but monthly visits to reinforce the importance of therapy are desirable.

**Ethambutol**

Ethambutol is a synthetic form of ethylenedi-imino-di-1-butanol dihydrochloride that inhibits RNA synthesis needed for cell wall formation. At standard dosages it is bacteriostatic, but at dosages of >25 mg/kg ethambutol has bactericidal activity. The mechanism of resistance to ethambutol is unknown, but resistance develops rapidly when ethambutol is used as a single agent against *M. tuberculosis*.

Ethambutol is indicated for the treatment of infections caused by *M. tuberculosis*, *M. kansasi*, *M. bovis*, and *M. avium* complex. Ethambutol should only be used as part of a combination treatment regimen for *M. tuberculosis*. Daily dosage is 15-20 mg/kg PO in a single dose, not to exceed 2,500 mg/day. Twice-weekly dosing is with 50 mg/kg PO in a single dose, not to exceed 2,500 mg/day. Dosage adjustment is needed in renal insufficiency. Ethambutol is available in 100 and 400 mg tablets.

The major adverse effect with ethambutol is optic neuritis, and thus ethambutol should generally be reserved for children old enough to have visual acuity and color discrimination reliably monitored. Visual changes are usually dosage dependent and reversible. Other adverse events include headache, dizziness, confusion, hyperuricemia, GI upset, peripheral neuropathy, hepatotoxicity, and cytopenias, especially neutropenia and thrombocytopenia.

Routine laboratory monitoring includes baseline and periodic visual acuity and color discrimination testing, CBC, serum uric acid levels, and kidney and liver function tests.

**Less Commonly Used Agents**

**Aminoglycosides**

The aminoglycosides used for mycobacterial infections include streptomycin, amikacin, kanamycin, and capreomycin. Streptomycin is isolated from *Streptomyces griseus* and was the first drug used to treat *M. tuberculosis*. Capreomycin, a cyclic polypeptide from *Streptomyces capreolus*, and amikacin, a semisynthetic derivative of kanamycin, are newer agents that are recommended when streptomycin is unavailable. Aminoglycosides act by binding irreversibly to the 30S subunit of ribosomes and inhibiting subsequent protein synthesis. Streptomycin exhibits concentration-dependent bactericidal activity, and capreomycin is bacteriostatic. Resistance results from mutation in the binding site of the 30S ribosome, by decreased transport into cells, or by inactivation by bacterial enzymes. Cross-resistance between aminoglycosides has been demonstrated.

The aminoglycosides are indicated for the treatment of *M. tuberculosis* and *M. avium* complex. All are considered second-line drugs in the treatment of *M. tuberculosis* and should be used only when resistance patterns are known. Aminoglycosides are poorly absorbed orally and are administered by IM injection. Pediatric dosing ranges for streptomycin are 20 mg/kg/day if given daily and 20-40 mg/kg/day if given twice weekly; dosing is IM in a single daily dose. Capreomycin, amikacin, and kanamycin dosages are 15-30 mg/kg/day IM in a single dose, not to exceed 1 g/day. Dosage adjustment is necessary in renal insufficiency.

Aminoglycosides have **adverse effects** on proximal renal tubules, the cochlea, and the vestibular apparatus of the ear. Nephrotoxicity and ototoxicity account for most of the significant adverse events. Rarely, patients exhibit fever or rash with the administration of aminoglycosides. Concomitant use of other nephrotoxic or ototoxic agents should be avoided, because adverse effects may be additive. An infrequent but
serious, synergistic, dosage-dependent, aminoglycoside effect with nondepolarizing neuromuscular blockade agents can result in respiratory depression or paralysis.

Hearing and kidney function should be monitored at baseline and periodically. Early signs of ototoxicity include tinnitus, vertigo, and hearing loss. Ototoxicity appears to be irreversible, but early kidney damage may be reversible. As with other aminoglycosides, peak and trough drug levels are helpful in dosing and managing early toxicities.

**Cycloserine**

Cycloserine, derived from *Streptomyces orchidaceus* or *Streptomyces garyphalus*, is a synthetic analog of the amino acid D-alanine that interferes with bacterial cell wall synthesis via competitive inhibition of D-alanine components to be incorporated into the cell wall. It is bacteriostatic, and the mechanism of resistance is unknown.

Cycloserine is used to treat *M. tuberculosis* and *M. bovis*. The dosage is 10-20 mg/kg/day PO divided into 2 doses, not to exceed 1g/day. It is available in a 250 mg capsule.

The major adverse event is neurotoxicity with significant psychologic disturbance, including seizures, acute psychosis, headache, confusion, depression, and personality changes. The neurotoxic effects are additive with ethionamide and INH. It has also been associated with megaloblastic anemia. Cycloserine must be dosage adjusted with kidney impairment. It should be used with caution in patients with underlying psychiatric illness.

Routine laboratory monitoring includes kidney and hepatic function, CBC, and cycloserine levels. Psychiatric symptoms are less common at blood levels of <30 µg/mL.

**Ethionamide**

Ethionamide is structurally related to INH and is an ethyl derivative of thioisonicotinamide that inhibits peptide synthesis by an unclear mechanism thought to involve nicotinamide adenine dinucleotide and nicotinamide adenine dinucleotide phosphate dehydrogenase disruptions. Ethionamide is bacteriostatic at most therapeutic levels. Resistance develops quickly if ethionamide used as a single-agent therapy, although the mechanism is unknown.

Ethionamide is used as an alternative to streptomycin or ethambutol in the treatment of *M. tuberculosis* and has some activity against *M. kansasii* and *M. avium* complex. A metabolite, ethionamide sulfoxide, is bactericidal against *M. leprae*. Ethionamide has been shown to have good central nervous system (CNS) penetration and has been used as a 4th drug in combination with rifampin, INH, and PZA. The pediatric dosage is 15-20 mg/kg/day PO in 2 divided doses, not to exceed 1 g/day. It is available as a 250 mg tablet.

GI upset is common, and other adverse effects include neurologic disturbances (anxiety, dizziness, peripheral neuropathy, seizures, acute psychosis), hepatic enzyme elevations, hypothyroidism, hypoglycemia, and hypersensitivity reaction with rash and fever. It should be used with caution in patients with underlying psychiatric or thyroid disease. The psychiatric adverse effects can be potentiated with concomitant use of cycloserine.

In addition to close assessment of mood, routine monitoring includes thyroid and liver function tests. In diabetic patients, blood glucose levels should be monitored.

**Fluoroquinolones**

The fluoroquinolones are fluorinated derivatives of the quinolone class of antibiotics. Ciprofloxacin is a first-generation fluoroquinolone, and levofloxacin is the more active l-isomer of ofloxacin. Moxifloxacin and gatifloxacin are agents with emerging use in pediatric mycobacterial disease. Fluoroquinolones are not indicated for use in children younger than 18 yr of age, but studies of their use in pediatric patients continue to indicate that they may be used in special circumstances. Fluoroquinolones are bactericidal and exert their effect via inhibition of DNA gyrase. The alterations in DNA gyrase result in relaxation of supercoiled DNA and breaks in double-stranded DNA. The mechanism of resistance is not well defined but likely involves mutations in the DNA gyrase.

Levofloxacin is an important second-line drug in the treatment of multidrug-resistant *M. tuberculosis*. Ciprofloxacin has activity against *Mycobacterium fortuitum* complex and against *M. tuberculosis*. The pediatric dosage of ciprofloxacin is 20-30 mg/kg/day PO or IV, not to exceed 1.5 mg/day PO or 800 mg/day IV. The adult dosage of ciprofloxacin is 500-750 mg/dose PO divided into 2 doses or 200-400 mg/dose IV every 12 hr. Ciprofloxacin is available in 100, 250, 500, and 750 mg tablets and can be made in 5% (50 mg/mL) or 10% (100 mg/mL) suspensions. The dosage of levofloxacin for children is 5-10 mg/kg/day given once daily either PO or IV, not to exceed 1,000 mg/day, and for adults it is 500-1,000 mg/day PO or IV, not to exceed 1,000 mg/day. Levofloxacin is available in 250, 500, and 750 mg tablets, and a 50 mg/mL suspension can be extemporaneously compounded. The suspension has a shelf life of only 8 wk.

The most common adverse effect of fluoroquinolones is GI upset, with nausea, vomiting, abdominal pain, and diarrhea, including pseudomembranous colitis. Other less-common adverse effects include bone marrow depression, CNS effects (e.g., lowered seizure threshold, confusion, tremor, dizziness, headache), elevated liver transaminases, photosensitivity, and arthropathies. The potential for arthropathies (e.g., tendon ruptures, arthralgias, tendinitis) is the predominant reason that fluoroquinolones are not recommended for pediatric use. The mechanism of injury appears to involve the disruption of extracellular matrix of cartilage and depletion of collagen, a particular concern related to the bone and joint development of children.

Fluoroquinolones induce the cytochrome P450 isoenzymes that can increase the concentrations of dually administered theophylline and warfarin. Nonsteroidal antiinflammatories can potentiate the CNS effects of fluoroquinolones and should be avoided while taking a fluoroquinolone. Both ciprofloxacin and levofloxacin should be dosage adjusted in patients with significant renal dysfunction.

While taking fluoroquinolones, patients should be monitored for hepatic and renal dysfunction, arthropathies, and hematologic abnormalities.

**Linezolid**

Linezolid is a synthetic oxazolidinone derivative. This drug is not currently approved for use against mycobacterial infection in pediatric or adult patients but has activity against some mycobacterial species. Studies on efficacy of treatment of mycobacterial infections are under way. Linezolid inhibits translation by binding to the 23S ribosomal component of the 50S ribosome subunit, preventing coupling with the 70S subunit. Resistance is thought to be from a point mutation at the binding site but is poorly studied because only a few cases of resistance have been reported.

The approved indications for linezolid are for bacterial infections other than mycobacteria, but studies reveal in vitro activity against rapidly growing mycobacteria (*M. fortuitum* complex, *Mycobacterium chelonae, Mycobacterium abscessus*), *M. tuberculosis*, and *M. avium* complex. The dosage for 0-11 yr old children is 10 mg/kg/day PO or IV in divided doses every 8-12 hr. For persons older than 12 yr of age, the dosage is 600 mg PO or IV every 12 hr. Linezolid is available in 400 and 600 mg tablets and as a 20 mg/mL suspension.

Adverse effects of linezolid include GI upset (e.g., nausea, vomiting, diarrhea), CNS disturbances (e.g., dizziness, headache, insomnia, peripheral neuropathy), lactic acidosis, fever, myelosuppression, and pseudomembranous colitis. Linezolid is a weak inhibitor of monoamine oxidase A, and patients are advised to avoid foods with high tyramine content. Linezolid should be used cautiously in patients with preexisting myelosuppression.

In addition to monitoring for GI upset and CNS perturbations, routine laboratory monitoring includes CBC at least weekly.

**Paraaminosalicylic Acid**

Paraaminosalicylic acid (PAS) is a structural analog of paraaminobenzoic acid (PABA). It is bacteriostatic and acts by competitively inhibiting the synthesis of folic acid similar to the action of sulfonamides. Resistance mechanisms are poorly understood.
PAS acts against *M. tuberculosis*. The dosage is 150 mg/kg/day PO in 2 or 3 divided doses. PAS is dispensed in 4 g packets, and the granules should be mixed with liquid and swallowed whole.

Common adverse events include GI upset, and less-common events include hypokalemia, hematuria, albuminuria, crystalluria, and elevations of hepatic transaminases. PAS can decrease the absorption of rifampin, and coadministration with ethionamide potentiates the adverse effects of PAS.

In addition to monitoring for weight loss, routine laboratory monitoring includes liver and kidney function tests.

**Bedaquiline Fumarate**
This oral diarylquinoline has been recommended for the treatment of multidrug resistant tuberculosis. It should be used as part of combination therapy and administered by direct observation. Although approved for patients 18 yr of age and older, it may be considered for children on a case-by-case basis. Serious side effects include hepatotoxicity and a prolonged Qt interval.

### AGENTS USED AGAINST MYCOBACTERIUM LEPRAE

#### Dapsone
Dapsone is a sulfone antibiotic with characteristics similar to sulfonamides. Similar to other sulfonamides, dapsone acts as a competitive antagonist of PABA, which is needed for the bacterial synthesis of folic acid. Dapsone is bacteriostatic against *M. leprae*. Resistance is not well understood but is thought to occur after alterations at the PABA-binding site.

Dapsone is used in the treatment of *M. leprae* in combination with other antileprosy agents (rifampin, clofazimine, ethionamide). The pediatric dosage is 1-2 mg/kg/day PO as a single dose, not to exceed 100 mg/day for a duration of 3-10 yr. The adult dosage is 100 mg/day PO as a single dose. Dapsone is available in 25 and 100 mg scored tablets and as an oral suspension of 2 mg/mL. The dosage should be adjusted in renal insufficiency.

Dapsone has many reported adverse events, including dosage-related hemolytic anemia, especially in patients with glucose-6-phosphate dehydrogenase deficiency, pancreatitis, renal complications (acute tubular necrosis, acute renal failure, albuminuria), increased liver enzymes, psychosis, tinnitus, peripheral neuropathy, photosensitivity, and a hypersensitivity syndrome with fever, rash, hepatic damage, and malaise. A *lepra reaction* may occur with treatment, which is a nontoxic, paradoxical worsening of lepromatous leprosy with the initiation of therapy. This hypersensitivity reaction is not an indication to discontinue therapy. Dapsone should be used with caution in patients with glucose-6-phosphate dehydrogenase deficiency or taking other folic acid antagonists. Dapsone levels can decrease with concomitant rifampin and can increase with concomitant clotrimazole.

Routine laboratory monitoring includes CBC weekly during the 1st mo of therapy, weekly through 6 mo of therapy, and then every 6 mo thereafter. Other periodic assessments include kidney function with creatine levels and urinalysis and liver function tests.

#### Clofazimine
Clofazimine is a synthetic phenidmetrazine tartrate derivative that acts by binding to the mycobacterial DNA at guanine sites. It has a slow bactericidal activity against *M. leprae*. Mechanisms of resistance are not well studied. No cross-resistance between clofazimine and dapsone or rifampin has been shown.

Clofazimine is indicated as part of a combination therapy for the treatment of *M. leprae*. It appears there may be some activity against other mycobacteria such as *M. avium* complex, although treatment failures are common. Safety and efficacy of clofazimine are poorly studied in children. The pediatric dosage is 1 mg/kg/day PO as a single dose, not to exceed 100 mg/day in combination with dapsone and rifampin for 2 yr and then additionally as a single agent for longer than 1 yr. The adult dosage is 100 mg/day PO. It should be taken with food to increase absorption.

The most common adverse effect is a dosage-related, reversible pink to tan-brown discoloration of the skin and conjunctiva. Other adverse effects include a dry, itchy skin rash, headache, dizziness, abdominal pain, diarrhea, vomiting, peripheral neuropathy, and elevated hepatic transaminases.

Routine laboratory monitoring includes periodic liver function tests.

### AGENTS USED AGAINST NONTUBERCULOUS MYCOBACTERIA

#### Cefoxitin
Cefoxitin, a cephamycin derivative, is a second-generation cephalosporin that, like other cephalosporins, inhibits cell wall synthesis by linking with penicillin-binding proteins to create an unstable bacterial cell wall. Resistance develops by alterations in penicillin-binding proteins.

Cefoxitin is often used in combination therapy for mycobacterial disease (Table 214-3). Pediatric dosing is based on disease severity, with a range of 80-160 mg/kg/day divided every 4-8 hr, not to exceed 12 g/day. Adult dosages are 1-2 g/day, not to exceed 12 g/day. Cefoxitin is available in IV or IM formulations. Increased dosing intervals are needed with renal insufficiency.

Adverse effects are primarily hematologic (eosinophilia, granulocytopenia, thrombocytopenia, hemolytic anemia), GI (nausea, vomiting, diarrhea with possible pseudomembranous colitis), and CNS-related (dizziness, vertigo). Potential additive adverse effects can occur when cefoxitin is used with aminoglycosides.

Routine laboratory monitoring with long-term use includes CBC and liver and renal function tests.

#### Doxycycline
Doxycycline is in the tetracycline family of antibiotics and has limited use in pediatrics. Like other tetracyclines, doxycycline acts to decrease protein synthesis by binding to the 30S ribosome and to transfer RNA. It can also cause alterations to the cytoplasmic membrane of susceptible bacteria.

Doxycycline is used to treat *M. fortuitum* (see Table 214-3). Although it can be used to treat *Mycobacterium marinum*, adult treatment failures have occurred. Pediatric dosing is based on age and weight. For children older than 8 yr of age who weigh <45 kg, the dosage is 4.4 mg/kg/day divided twice daily. Dosing for larger children and adults is 100 mg twice daily. Doxycycline is available as 50 and 100 mg capsules or tablets and in 25 mg/5 mL and 50 mg/5 mL suspensions.

Doxycycline use in children is limited by a permanent tooth discoloration, which becomes worse with long-term use. Other adverse effects include photosensitivity, liver and kidney dysfunction, and esophagitis, which can be minimized by dosing with large volumes of liquid. Doxycycline can decrease the effectiveness of oral contraceptives. Rifampin, carbamazepine, and phenytoin can decrease the concentration of doxycycline.

Routine laboratory monitoring with long-term use includes kidney and liver function tests as well as CBC.

#### Macrolides
Clarithromycin and azithromycin belong to the macrolide family of antibiotics. Clarithromycin is a methoxy derivative of erythromycin. Macrolides act by binding the 50S subunit of ribosomes, subsequently inhibiting protein synthesis. Resistance mechanisms for mycobacteria are not well understood but might involve binding site alterations. Clarithromycin appears to have synergistic antitymbacterial activity when combined with rifamycins, ethambutol, or clofazimine.

Clarithromycin is widely used for the prophylaxis and treatment of *M. avium* complex disease and also has activity against *Mycobacterium abscessus, M. fortuitum*, and *M. marinum*. Azithromycin has significantly different pharmacokinetics compared with other macrolide agents and has not been studied and is not indicated for mycobacterial infections. The pediatric dosage of clarithromycin for primary
prophylaxis of *M. avium* complex infections is 7.5 mg/kg/dose PO given twice daily, not to exceed 500 mg/day. This dosage is used for recurrent *M. avium* complex disease in combination with ethambutol and rifampin. The adult dosage is 500 mg PO twice daily to be used as a single agent for primary prophylaxis or as part of combination therapy with ethambutol and rifampin. Dosage adjustment is needed for renal insufficiency but not liver failure. Clarithromycin is available in 250 and 500 mg tablets and suspensions of 125 mg/5 mL and 250 mg/5 mL.

The primary adverse effect of clarithromycin is GI upset, including vomiting (6%), diarrhea (6%), and abdominal pain (3%). Other adverse effects include taste disturbances, headache, and QT prolongation if used with inhaled anesthetics, clotrimazole, antiarrhythmic agents, or azoles. Clarithromycin should be used cautiously in patients with renal insufficiency or liver failure.

Routine laboratory monitoring with prolonged use of clarithromycin includes periodic liver enzyme tests. Diarrhea is an early sign of pseudomembranous colitis.

**Trimethoprim-Sulfamethoxazole**

Trimethoprim-sulfamethoxazole (TMP-SMX) is formulated in a fixed ratio of 1 part TMP to 5 parts SMX. SMX is a sulfonamide that inhibits synthesis of dihydrofolate acid by competitively inhibiting PABA, similar to dapsone. TMP blocks production of tetrahydrofolic acid and downstream biosynthesis of nucleic acids and protein by reversibly binding to dihydrofolate reductase. The combination of the 2 agents is synergistic and often bactericidal.

TMP-SMX is often used in combination therapy for mycobacterial disease (see Table 214-3). Oral or IV dosing for pediatric patients is TMP 15-20 mg/kg/day divided every 6-8 hr for serious infections and 10-12 mg/kg/day divided every 12 hr for mild infections. The adult dosage is 160 mg TMP and 800 mg SMX every 12 hr. Dosage reduction may be needed in renal insufficiency. TMP-SMX is available in single-strength tablets (80/400 mg TMP/SMX) and double-strength tablets (160/800 mg TMP/SMX) and in a suspension of 40 mg TMP and 200 mg SMX per 5 mL.

The most common adverse effect with TMP-SMX is myelosuppression. It must be used with caution in patients with glucose-6-phosphate dehydrogenase deficiency. Other adverse effects include renal abnormalities, rash, aseptic meningitis, GI disturbances (e.g., pancreatitis, diarrhea), and prolonged QT interval if coadministered with inhaled anesthetics, azoles, or macrolides.

Routine laboratory monitoring includes monthly CBC and periodic electrolytes and creatinine to monitor renal function.

*Bibliography is available at Expert Consult.*
Bibliography


Tuberculosis has caused human disease for more than 4,000 yr and is one of the most important infectious diseases worldwide. Tuberculosis was first recognized as a clinical entity in the early 19th century by Schönlein, who used the term *tuberculosis* in 1830, which was derived from the English term “tuberce,” or lesion of consumption.

**ETIOLOGY**

There are 3 closely related mycobacteria in the *Mycobacterium tuberculosis* complex: *M. tuberculosis*, *Mycobacterium bovis*, *Mycobacterium africanum*, *Mycobacterium microti*, and *Mycobacterium canetti*. *M. tuberculosis* is the most important cause of tuberculosis disease in humans. The tubercle bacilli are non-spore-forming, nonmotile, pleomorphic, weakly Gram-positive curved rods 1-5 μm long, typically slender and slightly bent. They can appear beaded or clumped under microscopy. They are obligate aerobes that grow in synthetic media containing glycerol as the carbon source and ammonium salts as the nitrogen source (Löwenstein-Jensen culture media). These mycobacteria grow best at 37-41°C (98.6-105.8°F), produce niacin, and lack pigmentation. A lipid-rich cell wall accounts for resistance to the bactericidal actions of antibody and complement. A hallmark of all mycobacteria is acid fastness—the capacity to form stable mycolate complexes with arylmethane dyes (crystal violet, carbolfuchsin, auramine, and rhodamine). They resist decoloration with ethanol and hydrochloric or other acids.

Mycobacteria grow slowly, with a generation time of 12-24 hr. Isolation from clinical specimens on solid synthetic media usually takes 3-6 wk, and drug susceptibility testing requires an additional 2-4 wk. Growth can be detected in 1-3 wk in selective liquid medium using radiolabeled nutrients (e.g., the BACTEC radiometric system), and drug susceptibilities can be determined in an additional 3-5 days. Once mycobacterial growth is detected, the species of mycobacteria present can be determined within hours using high-pressure liquid chromatography analysis (identifying the mycolic acid fingerprint of each species) or DNA probes. Restriction fragment length polymorphism profiling of mycobacteria is a helpful tool to study the epidemiology of tuberculosis strain relatedness in both outbreaks and routine epidemiology of tuberculosis in a community.

**TERMINOLOGY: EXPOSURE, INFECTION, DISEASE**

There are 3 major clinical stages of tuberculosis: exposure, infection, and disease. Exposure means a child has had significant contact (“shared the air”) with an adult or adolescent with infectious tuberculosis but lacks proof of infection. In this stage, the tuberculin skin test (TST) or interferon-γ release assay (IGRA) result is negative, the chest radiograph is normal, the physical examination is normal, and the child lacks signs or symptoms of disease. However, the child may be infected and develop tuberculosis disease rapidly, as there may not have been enough time for the TST or IGRA to turn positive. Infection occurs when the individual inhales droplet nuclei containing *M. tuberculosis*, which survive intracellularly within the lung and associated lymphoid tissue. The hallmark of tuberculosis infection is a positive TST or IGRA result. In this stage, the child has no signs or symptoms, a normal physical examination is normal, and the chest radiograph is either normal or reveals only granuloma or calcifications in the lung parenchyma. Disease occurs when signs or symptoms or radiographic manifestations caused by *M. tuberculosis* become apparent. Not all infected individuals have the same risk of developing disease. An immunocompetent adult with untreated tuberculosis infection has approximately a 5-10% lifetime risk of developing disease. In contrast, an infected child younger than 1 yr of age has a 40% chance of developing disease within 9 mo.

**EPIDEMIOLOGY**

The World Health Organization estimates that tuberculosis remains the second leading cause of death from an infectious disease worldwide (after HIV) and that almost one-third of the world’s population (2.5 billion people) is infected with *M. tuberculosis*. Approximately 95% of tuberculosis cases occur in the developing world. The highest numbers of cases are in Asia, Africa, and the eastern Mediterranean region. An estimated 8.7 million incident cases, 12 million prevalent cases, and 1.4 million deaths from tuberculosis occurred worldwide in 2013 (Fig. 215-1). The World Health Organization estimates that in 2013, there were 550,000 childhood cases and 80,000 tuberculosis-associated deaths among non–HIV-infected children; no estimates were given for HIV-infected children who likely bear an even greater burden of tuberculosis. The global burden of tuberculosis is influenced by several factors including: the HIV pandemic; the development of multidrug-resistant (MDR) tuberculosis; and the disproportionate access of populations in low-resource settings worldwide to both diagnostic tests and effective medical therapy.

In the United States, tuberculosis case rates decreased steadily during the first half of the 20th century, long before the advent of antituberculosis drugs, as a result of improved living conditions and, likely, genetic selection favoring persons resistant to developing disease. A resurgence of tuberculosis in the late 1980s was associated primarily with the HIV epidemic; transmission of the organism in congregate settings including healthcare institutions; disease occurring in recent immigrants; and poor conduct of community tuberculosis control. Since 1992, the number of reported cases of tuberculosis has decreased each year, reaching a record low of 9,582 cases (a rate of 3.0 cases per 100,000 persons) in 2013 (Fig. 215-2). Of the cases in 2011, 786 (6.1%) occurred in children younger than 15 yr of age (rate 1.3 per 100,000 population). Despite the overall declining rates nationwide, racial and ethnic minorities and foreign-born persons are disproportionately affected by tuberculosis in the United States. In 2011, the Centers for Disease Control and Prevention (CDC) reported that 84% of all tuberculosis cases were among ethnic minority populations. The tuberculosis case rate among Asians, blacks, and Hispanics were 25.0, 7.3, and 6.6 times as high as among non-Hispanic whites, respectively. The tuberculosis rate among foreign-born persons in the United States was 11.5 times higher than among U.S.-born persons and accounted for 62% of all tuberculosis cases in 2011 (Fig. 215-3). In the non-Hispanic white population tuberculosis rates are highest among the elderly who acquired the infection decades ago. In contrast, among nonwhite populations, tuberculosis is most common in young adults and children younger than 5 yr of age. The age range of 5-14 yr is often called the “favored age”; in all human populations, this group has the lowest rate of tuberculosis disease. Among adults, two-thirds of cases occur in men, but in children there is no significant difference by gender.

Among children in the United States, being born in a country with a high rate of tuberculosis and being a household contact to a domestic case of tuberculosis are the most important risk factors for having tuberculosis infection. Most children are infected with *M. tuberculosis* in their home by someone close to them, but outbreaks of childhood tuberculosis also have occurred in elementary and high schools, nursery schools, daycare centers and homes, churches, school buses, and sports teams. HIV-infected adults with tuberculosis can transmit *M. tuberculosis* to children, and children with HIV infection are at increased risk for developing tuberculosis after infection. Specific groups are at high risk for acquiring tuberculosis infection and progressing from latent tuberculosis infection (LTBI) to tuberculosis (Table 215-1).
Infectious Diseases

M. tuberculosis. Transmission rarely occurs by direct contact with an infected discharge or a contaminated fomite. The chance of transmission increases when the patient has a positive acid-fast smear of sputum, an extensive upper lobe infiltrate or cavity, copious production of thin sputum, and severe and forceful cough. Environmental factors such as poor air circulation enhance transmission. Most adults no longer transmit the organism within several days to 2 weeks after beginning adequate chemotherapy, but some patients remain infectious for many weeks. Young children with tuberculosis rarely infect other children or adults. Tubercle bacilli are sparse in the endobronchial secretions of children with pulmonary tuberculosis, and cough is often absent or lacks the tussive force required to suspend infectious particles of the correct size. Children and adolescents with adult-type cavitary or endobronchial pulmonary tuberculosis can transmit the organism.

The incidence of drug-resistant tuberculosis has increased dramatically throughout the world. The estimate for MDR tuberculosis is 4% globally, but rates as high as 26% have been reported in countries formerly part of the Soviet Union. A total of 127 cases of MDR tuberculosis were reported in the United States in 2011; of those, 85.8% were foreign-born (Fig. 215-4). MDR-TB is defined as resistance to at least isoniazid and rifampin; extensively drug-resistant tuberculosis includes MDR-TB plus resistance to any fluoroquinolone and at least 1 of 3 injectable drugs (kanamycin, capreomycin, amikacin).

TRANSMISSION

Transmission of M. tuberculosis is usually by inhalation of airborne mucus droplet nuclei, particles 1-5 µm in diameter that contain M. tuberculosis. Transmission rarely occurs by direct contact with an infected discharge or a contaminated fomite. The chance of transmission increases when the patient has a positive acid-fast smear of sputum, an extensive upper lobe infiltrate or cavity, copious production of thin sputum, and severe and forceful cough. Environmental factors such as poor air circulation enhance transmission. Most adults no longer transmit the organism within several days to 2 weeks after beginning adequate chemotherapy, but some patients remain infectious for many weeks. Young children with tuberculosis rarely infect other children or adults. Tubercle bacilli are sparse in the endobronchial secretions of children with pulmonary tuberculosis, and cough is often absent or lacks the tussive force required to suspend infectious particles of the correct size. Children and adolescents with adult-type cavitary or endobronchial pulmonary tuberculosis can transmit the organism.


Figure 215-2 Reported tuberculosis cases in the United States for the years 1982-2011. (From National Tuberculosis Surveillance System Highlights from 2011 an accompaniment to: Centers for Disease Control and Prevention: Reported tuberculosis in the United States, 2011. Atlanta, 2011, U.S. Department of Health and Human Services.)

Figure 215-3 Tuberculosis cases, percentages, and case rates per 100,000 by Hispanic ethnicity and non-Hispanic race in the United States during the years 1991-2011. (From the Centers for Disease Control and Prevention: Reported tuberculosis in the United States, 2011. Atlanta, 2011, U.S. Department of Health and Human Services.)
Airborne transmission of *M. bovis* and *M. africanum* also occurs. *M. bovis* can penetrate the gastrointestinal mucosa or invade the lymphatic tissue of the oropharynx when large numbers of the organism are ingested. Human infection with *M. bovis* is rare in developed countries as a result of the pasteurization of milk and effective tuberculosis-control programs for cattle. Approximately 30% of culture-proven childhood tuberculosis cases in San Diego, California, since 1990, have been caused by *M. bovis*, likely acquired by children when visiting Mexico or another country with suboptimal veterinary tuberculosis control programs.

**PATHOGENESIS**

The primary complex (or Ghon complex) of tuberculosis includes local infection at the portal of entry and the regional lymph nodes that drain the area. The lung is the portal of entry in >98% of cases. The tubercle bacilli multiply initially within alveoli and alveolar ducts. Most of the bacilli are killed, but some survive within nonactivated macrophages, which carry them through lymphatic vessels to the regional lymph nodes. When the primary infection is in the lung, the hilar lymph nodes usually are involved, although an upper lobe focus can drain into paratracheal nodes. The tissue reaction in the lung parenchyma and lymph nodes intensifies over the next 2-12 wk as the organisms grow in number and tissue hypersensitivity develops. The parenchymal portion of the primary complex often heals completely by fibrosis or calcification after undergoing caseous necrosis and encapsulation (Fig. 215-5). Occasionally, this portion continues to enlarge, resulting in focal pneumonitis and pleuritis. If caseation is intense, the center of the lesion liquefies and empties into the associated bronchus, leaving a residual cavity.

The foci of infection in the regional lymph nodes develop some fibrosis and encapsulation, but healing is usually less complete than in the parenchymal lesion. Viable *M. tuberculosis* can persist for decades within these foci. In most cases of initial tuberculosis infection, the lymph nodes remain normal in size. However, hilar and paratracheal lymph nodes that enlarge significantly as part of the host inflammatory reaction can encroach on a regional bronchus (Figs. 215-6 and 215-7).

**Table 215-1** Groups at High Risk for Acquiring Tuberculosis Infection and Developing Disease in Countries with Low Incidence

<table>
<thead>
<tr>
<th>RISK FACTORS FOR TUBERCULOSIS INFECTION</th>
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<tbody>
<tr>
<td>Children exposed to high-risk adults</td>
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<tr>
<td>Foreign-born persons from high-prevalence countries</td>
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<tr>
<td>Homeless persons</td>
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<tr>
<td>Persons who inject drugs</td>
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<tr>
<td>Present and former residents or employees of correctional institutions, homeless shelters, and nursing homes</td>
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<tr>
<td>Healthcare workers caring for high-risk patients (if infection control is not adequate)</td>
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<tr>
<th>RISK FACTORS FOR PROGRESSION OF LATENT TUBERCULOSIS INFECTION TO TUBERCULOSIS DISEASE</th>
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<tbody>
<tr>
<td>Infants and children ≤4 yr of age, especially those &lt;2 yr of age</td>
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<tr>
<td>Adolescents and young adults</td>
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<tr>
<td>Persons coinfected with HIV</td>
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<tr>
<td>Persons with skin test conversion in the past 1-2 yr</td>
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<tr>
<td>Persons who are immunocompromised, especially in cases of malignancy and solid organ transplantation, immunosuppressive medical treatments including anti–tumor necrosis factor therapies, diabetes mellitus, chronic renal failure, silicosis, and malnutrition</td>
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<thead>
<tr>
<th>RISK FACTORS FOR DRUG-RESISTANT TUBERCULOSIS</th>
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<tbody>
<tr>
<td>Personal or contact history of treatment for tuberculosis</td>
<td></td>
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<tr>
<td>Contacts of patients with drug-resistant tuberculosis</td>
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<tr>
<td>Birth or residence in a country with a high rate of drug resistance</td>
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<tr>
<td>Poor response to standard therapy</td>
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<tr>
<td>Positive sputum smears (acid-fast bacilli) or culture ≥2 mo after initiating appropriate therapy</td>
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</tbody>
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*Figure 215-4* Primary isoniazid resistance in U.S.-born vs foreign-born persons in the United States during the years 1993-2011. (From National Tuberculosis Surveillance System Highlights from 2011 an accompaniment to: Centers for Disease Control and Prevention: Reported tuberculosis in the United States, 20011. Atlanta, 2011, U.S. Department of Health and Human Services.)

*Figure 215-5* A and B, Posteroanterior and lateral chest radiograph images of an adolescent showing a 7 mm calcified granuloma in the left lower lobe (arrows). (From Lighter J, Rigaud M: Diagnosing childhood tuberculosis: traditional and innovative modalities, Curr Probl Pediatr Adolesc Health Care 39:55–88, 2009.)
Part XVII  ♦  Infectious Diseases

Infectious Diseases

remote foci usually become encapsulated, but they may be the origin of both extrapulmonary tuberculosis and reactivation pulmonary tuberculosis. The time between initial infection and clinically apparent disease is variable. Disseminated and meningeal tuberculosis are early manifestations, often occurring within 2-6 months of acquisition. Significant lymph node or endobronchial tuberculosis usually appears within 3-9 months. Lesions of the bones and joints take several years to develop, whereas renal lesions become evident decades after infection. Extra- pulmonary manifestations are more common in children than adults and develop in 25-35% of children with tuberculosis, compared to approximately 10% of immunocompetent adults.

Partial obstruction of the bronchus caused by external compression can cause hyperinflation in the distal lung segment. Complete obstruction results in atelectasis. Inflamed caseous nodes can attach to the bronchial wall and erode through it, causing endobronchial tuberculosis or a fistula tract. The caseum causes complete obstruction of the bronchus. The resulting lesion is a combination of pneumonitis and atelectasis and has been called a collapse-consolidation or segmental lesion (Fig. 215-8).

During the development of the primary complex tubercle bacilli are carried to most tissues of the body through the blood and lymphatic vessels. Although seeding of the organs of the reticuloendothelial system is common, bacterial replication is more likely to occur in organs with conditions that favor their growth, such as the lung apices, brain, kidneys, and bones. Disseminated tuberculosis occurs if the number of circulating bacilli is large and the host's cellular immune response is inadequate. More often the number of bacilli is small, leading to clinically inapparent metastatic foci in many organs. These remote foci usually become encapsulated, but they may be the origin of both extrapulmonary tuberculosis and reactivation pulmonary tuberculosis.

The time between initial infection and clinically apparent disease is variable. Disseminated and meningeal tuberculosis are early manifestations, often occurring within 2-6 months of acquisition. Significant lymph node or endobronchial tuberculosis usually appears within 3-9 months. Lesions of the bones and joints take several years to develop, whereas renal lesions become evident decades after infection. Extrapulmonary manifestations are more common in children than adults and develop in 25-35% of children with tuberculosis, compared to approximately 10% of immunocompetent adults.

Pulmonary tuberculosis that occurs more than 1 year after the primary infection is usually caused by endogenous regrowth of bacilli persisting in partially encapsulated lesions. This reactivation tuberculosis is rare

Figure 215-6 A 14-yr-old child with proven primary tuberculosis. Frontal (A) and lateral (B) views of the chest show hyperinflation, prominent left hilar lymphadenopathy, and alveolar consolidation involving the posterior segment of the left upper lobe as well as the superior segment of the left lower lobe. (From Hilton SVW, Edwards DK, editors: Practical pediatric radiology, ed 3, Philadelphia, 2003, Saunders, p. 334.)

Figure 215-7 An 8-yr-old child with a history of cough. A single frontal view of the chest shows marked right hilar and paratracheal lymphadenopathy with alveolar disease involving the right middle and lower lung fields. This was also a case of primary tuberculosis. (From Hilton SVW, Edwards DK, editors: Practical pediatric radiology, ed 3, Philadelphia, 2003, Saunders, p. 335.)

Figure 215-8 Right-sided hilar lymphadenopathy and collapse-consolidation lesions of primary tuberculosis in a 4-yr-old child.
in children but is common among adolescents and young adults. The most common form is an infiltrate or cavity in the apex of the upper lobes, where oxygen tension and blood flow are highest.

The risk for dissemination of *M. tuberculosis* is very high in HIV-infected persons. Reinfection also can occur in persons with advanced HIV or AIDS. In immunocompetent persons the response to the initial infection with *M. tuberculosis* usually provides protection against reinfection when a new exposure occurs. However, exogenous reinfection has been reported to occur in adults and children without immune compromise in highly endemic areas.

**Immunity**

Conditions that adversely affect cell-mediated immunity predispose to progression from tuberculosis infection to disease. Rare specific genetic defects associated with deficient cell-mediated immunity in response to mycobacteria include interleukin 12 receptor B1 deficiency and complete and partial interferon-γ (IFN-γ) receptor 1 chain deficiencies. Tuberculosis infection is associated with a humoral antibody response, which plays little known role in host defense. Shortly after infection, tubercle bacilli replicate in both free alveolar spaces and inactivated alveolar macrophages. Sulfatides in the mycobacterial cell wall inhibit fusion of the macrophage phagosome and lysosomes, allowing the organisms to escape destruction by intracellular enzymes. Cell-mediated immunity develops 2-12 wk after infection, along with tissue hypersensitivity (Fig. 215-9). After bacilli enter macrophages, lymphocytes that recognize mycobacterial antigens proliferate and secrete lymphokines and other mediators that attract other lymphocytes and macrophages to the area. Certain lymphokines activate macrophages, causing them to develop high concentrations of lytic enzymes that enhance their mycobactericidal capacity. A discrete subset of regulatory helper and suppressor lymphocytes modulates the immune response. Development of specific cellular immunity prevents progression of the initial infection in most persons.

The pathologic events in the initial tuberculosis infection seem to depend on the balance among the mycobacterial antigen load; cell-mediated immunity, which enhances intracellular killing; and tissue
hypersensitivity, which promotes extracellular killing. When the antigen load is small and the degree of tissue sensitivity is high, granuloma formation results from the organization of lymphocytes, macrophages, and fibroblasts. When both antigen load and the degree of sensitivity are high, granuloma formation is less organized. Tissue necrosis is incomplete, resulting in formation of caseous material. When the degree of tissue sensitivity is low, as is often the case in infants or immunocompromised persons, the reaction is diffuse and the infection is not well contained, leading to dissemination and local tissue destruction. Tumor necrosis factor and other cytokines released by specific lymphocytes promote cellular destruction and tissue damage in susceptible persons.

**CLINICAL MANIFESTATIONS**

**Primary Pulmonary Disease**

The primary complex includes the parenchymal pulmonary focus and the regional lymph nodes. Approximately 70% of lung foci are subpleural, and localized pleurisy is common. The initial parenchymal inflammation usually is not visible on chest radiograph, but a localized, nonspecific infiltrate may be seen before the development of tissue hypersensitivity. All lobar segments of the lung are at equal risk for initial infection. Two or more primary foci are present in 25% of cases. The hallmark of primary tuberculosis in the lung is the relatively large size of the regional lymphadenitis compared with the relatively small size of the initial lung focus (see Figs. 215-6 to 215-8). As delayed-type hypersensitivity develops, the hilar lymph nodes continue to enlarge in some children, especially infants, compressing the regional bronchus and causing obstruction. The usual sequence is hilar lymphadenopathy, focal hyperinflation, and then atelectasis. The resulting radiographic shadows have been called collapse-consolidation or segmental tuberculosis (see Fig. 215-8). Rarely, inflamed caseous nodes attach to the endobronchial wall and erode through it, causing endobronchial tuberculosis or a fistula tract. The caseum causes complete obstruction of the bronchus, resulting in extensive infiltrate and collapse. Enlargement of the subcarinal lymph nodes can cause compression of the esophagus and, rarely, a bronchoesophageal fistula.

Most cases of tuberculous bronchial obstruction in children resolve fully with appropriate treatment. Occasionally, there is residual calcification of the primary focus or regional lymph nodes. The appearance of calcification implies that the lesion has been present for at least 6-12 mo. Healing of the segment can be complicated by scarring or contraction associated with cylindrical bronchiectasis, but this is rare.

Children can have lobar pneumonia without impressive hilar lymphadenopathy. If the primary infection is progressively destructive, liquefaction of the lung parenchyma can lead to formation of a thin-walled primary tuberculosis cavity. Rarely, bullous tuberculous lesions occur in the lungs and lead to pneumothorax if they rupture. Erosion of a parenchymal focus of tuberculosis into a blood or lymphatic vessel can result in dissemination of the bacilli and a miliary pattern, with small nodules evenly distributed on the chest radiograph (Fig. 215-10).

The symptoms and physical signs of primary pulmonary tuberculosis in children are surprisingly meager considering the degree of radiographic changes often present. When active case finding is performed, up to 50% of infants and children with radiographically moderate to severe pulmonary tuberculosis have no physical findings. Infants are more likely to experience signs and symptoms. Nonproductive cough and mild dyspnea are the most common symptoms. Systemic complaints such as fever, night sweats, anorexia, and decreased activity occur less often. Some infants have difficulty gaining weight or develop a true failure-to-thrive syndrome that often does not improve significantly until several months of effective treatment have been taken. Pulmonary signs are even less common. Some infants and young children with bronchial obstruction have localized wheezing or decreased breath sounds that may be accompanied by tachypnea or, rarely, respiratory distress. These pulmonary symptoms and signs are occasionally alleviated by antibiotics, suggesting bacterial superinfection.

**Progressive Primary Pulmonary Disease**

A rare but serious complication of tuberculosis in a child occurs when the primary focus enlarges steadily and develops a large caseous center. Liquefaction can cause formation of a primary cavity associated with large numbers of tubercle bacilli. The enlarging focus can slough necrotic debris into the adjacent bronchus, leading to further intrapulmonary dissemination. Significant signs or symptoms are common in locally progressive disease in children. High fever, severe cough with sputum production, weight loss, and night sweats are common. Physical signs include diminished breath sounds, rales, and dullness or egophony over the cavity. The prognosis for full recovery is excellent with appropriate therapy.

**Reactivation Tuberculosis**

Pulmonary tuberculosis in adults usually represents endogenous reactivation of a site of tuberculosis infection established previously in the body. This form of tuberculosis is rare in childhood but can occur in adolescence. Children with a healed tuberculosis infection acquired when they were younger than 2 yr of age rarely develop chronic reactivation pulmonary disease, which is more common in those who acquire the initial infection when they are older than 7 yr of age. The most common pulmonary sites are the original parenchymal focus, lymph nodes, or the apical seedings (Simon foci) established during the hematogenous phase of the early infection. This form of
tuberculosis disease usually remains localized in the lungs, as the established immune response prevents further extrapulmonary spread. The most common radiographic findings are extensive infiltrates or thick-walled cavities in the upper lobes.

Older children and adolescents with reactivation tuberculosis are more likely to experience fever, anorexia, malaise, weight loss, night sweats, productive cough, hemoptysis, and chest pain than children with primary pulmonary tuberculosis. However, physical examination findings usually are minor or absent, even when cavities or large infiltrates are present. Most signs and symptoms improve within several weeks of starting effective treatment, although the cough can last for several months. This form of tuberculosis may be highly contagious if there is significant sputum production and cough. The prognosis for full recovery is excellent with appropriate therapy.

**Pleural Effusion**

Tuberculous pleural effusions, which can be local or general, originate in the discharge of bacilli into the pleural space from a subpleural pulmonary focus or caseated lymph node. Asymptomatic local pleural effusion is so common in primary tuberculosis that it is considered as part of the primary complex. Larger and clinically significant effusions occur months to years after the primary infection. Tuberculous pleural effusion is uncommon in children younger than 6 yr of age and rare in children younger than 2 yr of age. Effusions are usually unilateral but can be bilateral. They are rarely associated with a segmental pulmonary lesion and are uncommon in disseminated tuberculosis. Often the radiographic abnormality is more extensive than would be suggested by physical findings or symptoms (Fig. 215-11).

Clinical onset of tuberculous pleurisy is often sudden, characterized by low to high fever, shortness of breath, chest pain on deep inspiration, and diminished breath sounds. The fever and other symptoms can last for several weeks after the start of antituberculosis chemotherapy. The TST is positive in only 70-80% of cases. The prognosis is excellent, but radiographic resolution often takes months. Scoliosis is a rare complication from a long-standing effusion.

Examination of pleural fluid and the pleural membrane is important to establish the diagnosis of tuberculous pleurisy. The pleural fluid is usually yellow and only occasionally tinged with blood. The specific gravity is usually 1.012-1.025, the protein level is usually 2-4 g/dL, and the glucose concentration may be low, although it is usually in the low-normal range (20-40 mg/dL). Typically there are several hundred to several thousand white blood cells per microliter, with an early predominance of polymorphonuclear cells followed by a high percentage of lymphocytes. Acid-fast smears of the pleural fluid are rarely positive. Cultures of the fluid are positive in <30% of cases. Biopsy of the pleural membrane is more likely to yield a positive acid-fast stain or culture, and granuloma formation can be demonstrated.

**Pericardial Disease**

The most common form of cardiac tuberculosis is pericarditis. It is rare, occurring in 0.5-4% of tuberculosis cases in children. Pericarditis usually arises from direct invasion or lymphatic drainage from subcarinal lymph nodes. The presenting symptoms are nonspecific, including low-grade fever, malaise, and weight loss. Chest pain is unusual in children. A pericardial friction rub or distant heart sounds with pulsus paradoxus may be present. The pericardial fluid is typically serofibrinous or hemorrhagic. Acid-fast smear of the fluid rarely reveals the organism, but cultures are positive in 30-70% of cases. The culture yield from pericardial biopsy may be higher, and the presence of granulomas often suggests the diagnosis. Partial or complete pericardectomy may be required when constrictive pericarditis develops.

**Lymphohematogenous (Disseminated) Disease**

Tubercle bacilli are disseminated to distant sites, including liver, spleen, skin, and lung apices, in all cases of tuberculosis infection. Lymphohematogenous spread is usually asymptomatic. Rare patients experience protracted hematogenous tuberculosis caused by the intermittent release of tubercle bacilli as a caseous focus erodes through the wall of a blood vessel in the lung. The clinical picture subsequent to lymphohematogenous dissemination depends on the burden of organisms released from the primary focus to distant sites and the adequacy of the host's immune response. Although the clinical picture may be acute, more often it is indolent and prolonged, with spiking fever accompanying the release of organisms into the bloodstream. Multiple organ involvement is common, leading to hepatomegaly, splenomegaly, lymphadenitis in superficial or deep nodes, and papulonecrotic tuberculids appearing on the skin. Bones and joints or kidneys also can become involved. Meningitis occurs only late in the course of the disease. Early pulmonary involvement is surprisingly mild, but diffuse involvement becomes apparent with prolonged infection.

The most clinically significant form of disseminated tuberculosis is *miliary disease*, which occurs when massive numbers of tubercle bacilli are released into the bloodstream, causing disease in 2 or more organs. Miliary tuberculosis usually complicates the primary infection, occurring within 2-6 mo of the initial infection. Although this form of disease is most common in infants and young children, it is also found in adolescents and older adults, resulting from the breakdown of a previously healed primary pulmonary lesion. The clinical manifestations of miliary tuberculosis are protean, depending on the number of organisms that diseminate and where they lodge. Lesions are often larger and more numerous in the lungs, spleen, liver, and bone marrow than other tissues. Because this form of tuberculosis is most common in infants and malnourished or immunosuppressed patients, the host's immune incompetence likely plays a role in pathogenesis.

Rarely, the onset of miliary tuberculosis is explosive, and the patient can become gravely ill in several days. More often, the onset is insidious, with early systemic signs, including anorexia, weight loss, and low-grade fever. At this time, abnormal physical signs are usually absent. Generalized lymphadenopathy and hepatosplenomegaly develop within several weeks in approximately 50% of cases. The fever can then become higher and more sustained, although the chest radiograph usually is normal and respiratory symptoms are minor or absent. Within several more weeks, the lungs can become filled with tubercles, and dyspnea, cough, rales, or wheezing occur. The lesions of miliary tuberculosis are usually smaller than 2-3 mm in diameter when first visible on chest radiograph (see Fig. 215-10). The smaller lesions coalesce to form larger lesions and sometimes extensive infiltrates. As the pulmonary disease progresses, an alveolar-air block syndrome can result in frank respiratory distress, hypoxia, and pneumothorax, or pneumomediastinum. Signs or symptoms of meningitis or peritonitis are found in 20-40% of patients with advanced disease. Chronic or

![Figure 215-11 Pleural tuberculosis in a 16 yr old girl.](image-url)
recurrent headache in a patient with miliary tuberculosis usually indicates the presence of meningitis, whereas the onset of abdominal pain or tenderness is a sign of tuberculous peritonitis. Cutaneous lesions include papulonecrotic tuberculids, nodules, or purpura. Choroid tubercles occur in 13-87% of patients and are highly specific for the diagnosis of miliary tuberculosis. Unfortunately, the TST is nonreactive in up to 40% of patients with disseminated tuberculosis.

Diagnosis of disseminated tuberculosis can be difficult, and a high index of suspicion by the clinician is required. Often the patient presents with fever of unknown origin. Early sputum or gastric aspirate cultures have a low sensitivity. Biopsy of the liver or bone marrow with appropriate bacteriologic and histologic examinations more often yields an early diagnosis. The most important clue is usually history of recent exposure to an adult with infectious tuberculosis.

The resolution of miliary tuberculosis is slow, even with proper therapy. Fever usually declines within 2-3 wk of starting chemotherapy, but the chest radiographic abnormalities might not resolve for many months. Occasionally, corticosteroids hasten symptomatic relief, especially when air block, peritonitis, or meningitis is present. The prognosis is excellent with early diagnosis and adequate chemotherapy.

Upper Respiratory Tract Disease
Tuberculosis of the upper respiratory tract is rare in developed countries but is still observed in developing countries. Children with laryngeal tuberculosis have a cough-like cough, sore throat, hoarseness, and dysphagia. Most children with laryngeal tuberculosis have extensive upper lobe pulmonary disease, but occasional patients have primary laryngeal disease with a normal chest radiograph. Tuberculosis of the middle ear results from aspiration of infected pulmonary secretions into the middle ear or from hematogenous dissemination in older children. The most common signs and symptoms are painless unilateral otorrhea, tinnitus, decreased hearing, facial paralysis, and a perforated tympanic membrane. Enlargement of lymph nodes in the preauricular or anterior cervical chains can accompany this infection. Diagnosis is difficult, because stains and cultures of ear fluid are often negative, and histology of the affected tissue often shows a nonspecific acute and chronic inflammation without granuloma formation.

Lymph Node Disease
Tuberculosis of the superficial lymph nodes, often referred to as scrofula, is the most common form of extrapulmonary tuberculosis in children (Fig. 215-12). Historically, scrofula was usually caused by drinking unpasteurized cow’s milk laden with M. bovis. Most current cases occur within 6-9 mo of initial infection by M. tuberculosis, although some cases appear years later. The tonsillar, anterior cervical, submandibular, and supraclavicular nodes become involved secondary to extension of a primary lesion of the upper lung fields or abdomen. Infected nodes in the inguinal, epitrochlear, or axillary regions result from regional lymphadenitis associated with tuberculosis of the skin or skeletal system. The nodes usually enlarge gradually in the early stages of lymph node disease. They are discrete, nontender, and firm but not hard. The nodes often feel fixed to underlying or overlying tissue. Disease is most often unilateral, but bilateral involvement can occur because of the crossover drainage patterns of lymphatic vessels in the chest and lower neck. As infection progresses, multiple nodes are infected, resulting in a mass of matted nodes. Systemic signs and symptoms other than a low-grade fever are usually absent. The TST is usually reactive, but the chest radiograph is normal in 70% of cases. The onset of illness is occasionally more acute, with rapid enlargement, tenderness, and fluctuance of lymph nodes and with high fever. The initial presentation is rarely a fluctuant mass with overlying cellulitis or skin discoloration.

Lymph node tuberculosis can resolve if left untreated but more often progresses to caceation and necrosis. The capsule of the node breaks down, resulting in the spread of infection to adjacent nodes. Rupture of the node usually results in a draining sinus tract that can require surgical removal. Tuberculous lymphadenitis can usually be diagnosed by fine-needle aspiration of the node and responds well to antituberculosis therapy, although the lymph nodes do not return to normal size for months or even years. Surgical removal is not usually necessary and must be combined with antituberculosis medication, as the lymph node disease is only 1 part of a systemic infection.

A definitive diagnosis of tuberculous adenitis usually requires histologic or bacteriologic confirmation, which is best accomplished by fine-needle aspiration for culture, stain, and histology. If fine-needle aspiration is not successful in establishing a diagnosis, excisional biopsy of the involved node is indicated. Culture of lymph node tissue yields the organism in only approximately 50% of cases. Many other conditions can be confused with tuberculous adenitis, including infection caused by nontuberculous mycobacteria (NTM), cat-scratch disease (Bartonella henselae), tularemia, brucellosis, toxoplasmosis, pyogenic infection, or noninfectious causes, including tumor, branchial cleft cyst, and cystic hygroma. The most common problem is distinguishing infection caused by M. tuberculosis from lymphadenitis caused by NTM in geographic areas where NTM are common. Both conditions are usually associated with a normal chest radiograph and a reactive TST. An important clue to the diagnosis of tuberculous adenitis is an epidemiologic link to an adult with infectious tuberculosis. In areas where both diseases are common, culture of the involved tissue may be necessary to establish the exact cause of the disease.

Central Nervous System Disease
Tuberculosis of the central nervous system (CNS) is the most serious complication in children and is fatal without prompt and appropriate treatment. Tuberculous meningitis usually arises from the formation of a metastatic caseous lesion in the cerebral cortex or meninges that develops during the lymphohematogenous dissemination of the primary infection. This initial lesion increases in size and discharges small numbers of tubercle bacilli into the subarachnoid space. The resulting gelatinous exudate infiltrates the corticomedial blood vessels, producing inflammation, obstruction, and subsequent infarction of cerebral cortex. The brainstem is often the site of greatest involvement, which accounts for the commonly associated dysfunction of cranial nerves III, VI, and VII. The exudate also interferes with the normal flow of cerebrospinal fluid (CSF) in and out of the ventricular
system at the level of the basilar cisterns, leading to a communicating hydrocephalus. The combination of vasculitis, infarction, cerebral edema, and hydrocephalus results in the severe damage that can occur gradually or rapidly. Profound abnormalities in electrolyte metabolism from salt wasting or the syndrome of inappropriate antidiuretic hormone secretion also contribute to the pathophysiology of tuberculous meningitis.

Tuberculous meningitis complicates approximately 0.3% of untreated tuberculosis infections in children. It is most common in children between 6 mo and 4 yr of age. Occasionally, tuberculous meningitis occurs many years after the infection, when rupture of 1 or more of the subependymal tubercles discharges tubercle bacilli into the subarachnoid space. The clinical progression of tuberculous meningitis may be rapid or gradual. Rapid progression tends to occur more often in infants and young children, who can experience symptoms for only several days before the onset of acute hydrocephalus, seizures, and cerebral edema. More commonly, the signs and symptoms progress slowly over weeks and are divided into 3 stages.

The 1st stage typically lasts 1-2 wk and is characterized by nonspecific symptoms such as fever, headache, irritability, drowsiness, and malaise. Focal neurologic signs are absent, but infants can experience a stagnation or loss of developmental milestones. The 2nd stage usually begins more abruptly. The most common features are lethargy, nuchal rigidity, seizures, positive Kernig and Brudzinski signs, hypertension, vomiting, cranial nerve palsies, and other focal neurologic signs. The accelerating clinical illness usually correlates with the development of hydrocephalus, increased intracranial pressure, and vasculitis. Some children have no evidence of meningeal irritation but can have signs of encephalitis, such as disorientation, movement disorders, or speech impairment. The 3rd stage is marked by coma, hemi- or paraplegia, hypertension, decerebrate posturing, deterioration of vital signs, and eventually death.

The prognosis of tuberculous meningitis correlates most closely with the clinical stage of illness at the time treatment is initiated. The majority of patients in the 1st stage have an excellent outcome, whereas most patients in the 3rd stage who survive have permanent disabilities, including blindness, deafness, paraplegia, diabetes insipidus, or mental retardation. The prognosis for young infants is generally worse than for older children. It is imperative that antituberculosis treatment be considered for any child who develops basilar meningitis and hydrocephalus, cranial nerve palsy, or stroke with no other apparent etiology. Often the key to the correct diagnosis is identifying an adult who has infectious tuberculosis and is in contact with the child. Because of the short incubation period of tuberculous meningitis, the illness has not yet been diagnosed in the adult in many cases.

The diagnosis of tuberculous meningitis can be difficult early in its course, requiring a high degree of suspicion on the part of the clinician. The TST is nonreactive in up to 50% of cases, and 20-50% of children have a normal chest radiograph. The most important laboratory test for the diagnosis of tuberculous meningitis is examination and culture of the lumbar CSF. The CSF leukocyte count usually ranges from 10-500 cells/µL. Polymorphonuclear leukocytes may be present initially, but lymphocytes predominate in the majority of cases. The CSF glucose is typically <40 mg/dL but rarely <20 mg/dL. The protein level is elevated and may be markedly high (400-5,000 mg/dL) secondary to hydrocephalus and spinal block. Although the lumbar CSF is grossly normal, ventricular CSF can have normal chemistries and cell counts because this fluid is obtained from a site proximal to the inflammation and obstruction. During early stage 1, the CSF can resemble that of viral aseptic meningitis only to progress to the more-severe CSF profile over several weeks. The success of the microscopic examination of acid-fast–stained CSF and mycobacterial culture is related directly to the volume of the CSF sample. Examinations or culture of small amounts of CSF are unlikely to demonstrate M. tuberculosis. When 5-10 mL of lumbar CSF can be obtained, the acid-fast stain of the CSF sediment is positive in up to 30% of cases and the culture is positive in 50-70% of cases. Polymerase chain reaction (PCR) testing of the CSF can improve diagnosis. Cultures of other body fluids can help confirm the diagnosis.

Radiographic studies can aid in the diagnosis of tuberculous meningitis. CT or MRI of the brain of patients with tuberculous meningitis may be normal during early stages of the disease. As disease progresses, basilar enhancement and communicating hydrocephalus with signs of cerebral edema or early focal ischemia are the most common findings. Some small children with tuberculous meningitis have one or several clinically silent tuberculomas, occurring most often in the cerebral cortex or thalamic regions.

Another manifestation of CNS tuberculosis is the tuberculoma, a tumor-like mass resulting from aggregation of caseous tubercles that usually manifests clinically as a brain tumor. Tuberculomas account for up to 30% of brain tumors in some areas of the world but are rare in North America. In adults tuberculomas are most often supratentorial, but in children they are often infratentorial, located at the base of the brain near the cerebellum (Fig. 215-13). Lesions are most often singular but may be multiple. The most common symptoms are headache, fever, focal neurologic findings, and convulsions. The TST is usually reactive, but the chest radiograph is usually normal. Surgical excision is sometimes necessary to distinguish tuberculoma from other causes of brain tumor. However, surgical removal is not necessary because most tuberculomas resolve with medical management. Corticosteroids are usually administered during the 1st few wk of treatment or in the immediate postoperative period to decrease cerebral edema. On CT or MRI of the brain, tuberculomas usually appear as discrete lesions with a significant amount of surrounding edema. Contrast medium enhancement is often impressive and can result in a ring-like lesion. Since the advent of CT, the paradoxical development of tuberculomas in patients with tuberculous meningitis who are receiving ultimately effective chemotherapy has been recognized. The cause and nature of these tuberculomas are poorly understood, but they do not represent failure of antimicrobial treatment. This phenomenon should be considered whenever a child with tuberculous meningitis deteriorates or develops focal neurologic findings while on treatment. Corticosteroids can alleviate the occasionally severe clinical signs and symptoms that occur. These lesions can persist for months or years.

**Cutaneous Disease**

Cutaneous tuberculosis is rare in the United States, but occurs worldwide and accounts for 1-2% of tuberculosis (see Chapter 665).
Bone and Joint Disease
Bone and joint infection complicating tuberculosis is most likely to involve the vertebral column. The classic manifestation of tuberculous spondylitis is progression to Pott disease, in which destruction of the vertebral bodies leads to gibbus deformity and kyphosis (see Chapter 679.4). Skeletal tuberculosis is a late complication of tuberculosis and has become a rare entity since the availability of antituberculous therapy but is more likely to occur in children than in adults. Tuberculous bone lesions can resemble pyogenic and fungal infections or bone tumors. Multifocal bone involvement can occur. A bone biopsy is essential to confirm the diagnosis. Surgical intervention is generally not necessary for cure and prognosis is excellent with adequate medical treatment.

Abdominal and Gastrointestinal Disease
Tuberculosis of the oral cavity or pharynx is quite unusual. The most common lesion is a painless ulcer on the mucosa, palate, or tonsil with enlargement of the regional lymph nodes. Tuberculosis of the parotid gland has been reported rarely in endemic countries. Tuberculosis of the esophagus is rare in children but may be associated with a tracheoesophageal fistula in infants. These forms of tuberculosis are usually associated with extensive pulmonary disease and swallowing of infectious respiratory secretions. They can occur in the absence of pulmonary disease, by spread from mediastinal or peritoneal lymph nodes.

Tuberculous peritonitis occurs most often in young men and is uncommon in adolescents and rare in children. Generalized peritonitis can arise from subclinical or miliary hematogenous dissemination. Localized peritonitis is caused by direct extension from an abdominal lymph node, intestinal focus, or genitourinary tuberculosis. Rarely, the lymph nodes, omentum, and peritoneum become matted and can be palpated as a doughy irregular nontender mass. Abdominal pain or tenderness, ascites, anorexia, and low-grade fever are typical manifestations. The TST is usually reactive. The diagnosis can be confirmed by paracentesis with appropriate stains and cultures, but this procedure must be performed carefully to avoid entering a bowel that is adherent to the omentum.

Tuberculous enteritis is caused by hematogenous dissemination or by swallowing tubercle bacilli discharged from the patient's own lungs. The jejunum and ileum near Peyer patches and the appendix are the most common sites of involvement. The typical findings are shallow ulcers that cause pain, diarrhea or constipation, weight loss, and low-grade fever. Mesenteric adenitis usually complicates the infection. The enlarged nodes can cause intestinal obstruction or erode through the omentum to cause generalized peritonitis. The clinical presentation of tuberculous enteritis is nonspecific, mimicking other infections and conditions that cause diarrhea. The disease should be suspected in any child with chronic gastrointestinal complaints and a reactive TST or positive IGRA. Biopsy, acid-fast stain, and culture of the lesions are usually necessary to confirm the diagnosis.

Genitourinary Disease
Renal tuberculosis is rare in children, because the incubation period is several years or longer. Tubercle bacilli usually reach the kidney during lymphohematogenous dissemination. The organisms often can be recovered from the urine in cases of miliary tuberculosis and in some patients with pulmonary tuberculosis in the absence of renal parenchymal disease. In true renal tuberculosis, small caseous foci develop in the renal parenchyma and release _M. tuberculosis_ into the tubules. A large mass develops near the renal cortex that discharges bacteria through a fistula into the renal pelvis. Infection then spreads locally to the ureters, prostate, or epididymis. Renal tuberculosis is often clinically silent in its early stages, marked only by sterile pyuria and microscopic hematuria. Dysuria, flank or abdominal pain, and gross hematuria develop as the disease progresses. Superinfection by other bacteria is common and can delay recognition of the underlying tuberculosis. Hydronephrosis or ureteral strictures can complicate the disease. Urine cultures for _M. tuberculosis_ are positive in 80-90% of cases, and acid-fast stains of large volumes of urine sediment are positive in 50-70% of cases. The TST is nonreactive in up to 20% of patients.

A pyelogram or CT scan often reveals mass lesions, dilation of the proximal ureters, multiple small filling defects, and hydronephrosis if ureteral stricture is present. Disease is most often unilateral.

Tuberculosis of the genital tract is uncommon in prepubescent boys and girls. This condition usually originates from lymphohematogenous spread, although it can be caused by direct spread from the intestinal tract or bone. Adolescent girls can develop genital tract tuberculosis during the primary infection. The fallopian tubes are most often involved (90-100% of cases), followed by the endometrium (50%), ovaries (25%), and cervix (5%). The most common symptoms are lower abdominal pain and dysmenorrhea or amenorrhea. Systemic manifestations are usually absent, and the chest radiograph is normal in the majority of cases. The TST is usually reactive. Genital tuberculosis in adolescent boys causes epididymitis or orchitis. The condition usually manifests as a unilateral nodular painless swelling of the scrotum. Involvement of the glans penis is extremely rare. Genital abnormalities and a positive TST in an adolescent boy or girl suggest genitotral tract tuberculosis.

Pregnancy and the Newborn
Pulmonary and particularly extrapulmonary tuberculosis other than lymhadenitis in a pregnant woman is associated with increased risk for prematurity, fetal growth retardation, low birthweight, and perinatal mortality. Congenital tuberculosis is rare because the most common result of female genital tract tuberculosis is infertility. Primary infection in the mother just before or during pregnancy is more likely to cause congenital infection than is reactivation of a previous infection. Congenital transmission usually occurs from a lesion in the placenta through the umbilical vein, when tubercle bacilli infect the fetal liver, where a primary focus with periportal lymph node involvement can occur. Organisms pass through the liver into the main fetal circulation and infect many organs. The bacilli in the liver usually remain dormant until after birth, when oxygenation and pulmonary circulation increase significantly. Congenital tuberculosis can also be caused by aspiration or ingestion of infected amniotic fluid. However, the most common route of infection for the neonate is postnatal airborne transmission from an adult with infectious pulmonary tuberculosis.

Perinatal Disease
Symptoms of congenital tuberculosis may be present at birth but more commonly begin by the 2nd or 3rd wk of life. The most common signs and symptoms are respiratory distress, fever, hepatic or splenic enlargement, poor feeding, lethargy or irritability, lymphadenopathy, abdominal distention, failure to thrive, ear drainage, and skin lesions. The clinical manifestations vary in relation to the site and size of the caseous lesions. Many infants have an abnormal chest radiograph, most often with a miliary pattern. Some infants with no pulmonary findings early in the course of the disease later develop profound radiographic and clinical abnormalities. Hilar and mediastinal lymphadenopathy and lung infiltrates are common. Generalized lymphadenopathy and meningitis occur in 30-50% of patients.

The clinical presentation of tuberculosis in newborns is similar to that caused by bacterial sepsis and other congenital infections, such as syphilis, toxoplasmosis, and cytomegalovirus. The diagnosis should be suspected in an infant with signs and symptoms of bacterial or congenital infection whose response to antibiotic and supportive therapy is poor and in whom evaluation for other infections is unrevealing. The most important clue for rapid diagnosis of congenital tuberculosis is a maternal or family history of tuberculosis. Often, the mother’s disease is discovered only after the neonate’s diagnosis is suspected. The infant’s TST is negative initially but can become positive in 1-3 mo. A positive acid-fast stain of an early morning gastric aspirate from a newborn usually indicates tuberculosis. Direct acid-fast stains on middle-ear discharge, bone marrow; tracheal aspirate, or biopsy tissue (especially liver) can be useful. The CSF should be examined, cultured and sent for PCR testing. The mortality rate of congenital tuberculosis remains very high because of delayed diagnosis; many children have a complete recovery if the diagnosis is made promptly and adequate chemotherapy is started.
Disease in HIV-Infected Children

Most cases of tuberculosis in HIV-infected children are seen in developing countries. However, the rate of tuberculosis disease in untreated HIV-infected children is 30 times higher than in non–HIV-infected children in the United States. Establishing the diagnosis of tuberculosis in an HIV-infected child may be difficult, because TST reactivity can be absent (also with a negative IGRA), culture confirmation is difficult, and the clinical features of tuberculosis are similar to many other HIV-related infections and conditions. Tuberculosis in HIV-infected children is often more severe, progressive, and likely to occur in extrapulmonary sites. Radiographic findings are similar to those in children with normal immune systems, but lobar disease and lung cavitation are more common. Nonspecific respiratory symptoms, fever, and weight loss are the most common complaints. Rates of drug-resistant tuberculosis tend to be higher in HIV-infected adults and probably are also higher in HIV-infected children. Recurrent disease and relapse occur more frequently in HIV-infected children. The prognosis generally is good if tuberculosis disease is not far advanced at diagnosis and appropriate antituberculosis drugs are available.

The mortality rate of HIV-infected children with tuberculosis is high, especially as the CD4 lymphocyte numbers decrease. In adults, the host immune response to tuberculosis infection appears to enhance HIV replication and accelerate the immune suppression caused by HIV. Increased mortality rates are attributed to progressive HIV infection rather than tuberculosis. Therefore, HIV-infected children with potential exposures and/or recent infection should be promptly evaluated and treated for tuberculosis. Conversely, all children with tuberculosis disease should be tested for HIV infection.

Children with HIV infection who are given highly active antiretroviral therapy (HAART) are at high risk of developing immune reconstitution inflammatory syndrome (IRIS). IRIS should be suspected in patients who experience a worsening of tuberculosis symptoms while on antituberculosis therapy (paradoxical IRIS) or who develop new-onset tuberculosis symptoms and radiographic findings after initiation of HAART (unmasking IRIS). Factors suggesting IRIS are temporal association (within 3 mo of starting HAART), unusual clinical manifestations, unexpected clinical course, exclusion of alternative explanations, evidence of preceding immune restoration (rise in CD4 lymphocyte count), and fall in HIV viral load.

The most common clinical manifestations of IRIS in children are fever, cough, new skin lesions, enlarging lymph nodes in the thorax or neck, and appearance or enlargement of tuberculomas in the brain, with or without accompanying meningitis. The treatment of IRIS in HIV-positive children with tuberculosis should be undertaken by a clinician with specific expertise in the treatment of tuberculosis.

**DIAGNOSTIC TOOLS**

**Tuberculin Skin Testing**

The development of delayed-type hypersensitivity in most persons infected with the tubercle bacillus makes the TST a useful diagnostic tool. The Mantoux TST is the intradermal injection of 0.1 mL purified protein derivative stabilized with Tween 80. T cells sensitized by prior infection are recruited to the skin, where they release lymphokines that induce induration through local vasodilation, edema, fibrin deposition, and recruitment of other inflammatory cells to the area. The amount of induration in response to the test should be measured by a trained person 48-72 hr after administration. In some patients, the onset of induration is longer than 72 hr after placement; this is also a positive result. Immediate hypersensitivity reactions to tuberculin or other constituents of the preparation are short-lived (<24 hr) and not considered a positive result. Tuberculin sensitivity develops 3 wk to 3 mo (most often in 4-8 wk) after inhalation of organisms.

Host-related factors, including very young age, malnutrition, immunosuppression by disease or drugs, viral infections (measles, mumps, varicella, influenza), vaccination with live-virus vaccines, and overwhelming tuberculosis, can depress the skin test reaction in a child infected with *M. tuberculosis*. Corticosteroid therapy can decrease the reaction to tuberculin, but the effect is variable. TST done at the time of initiating corticosteroid therapy is usually reliable. Approximately 10% of immunocompetent children with tuberculosis disease (up to 50% of those with meningitis or disseminated disease) do not react initially to purified protein derivative; most become reactive after several months of antituberculosis therapy. False-positive reactions to tuberculin can be caused by cross-sensitization to antigens of NTM, which generally are more prevalent in the environment as one approaches the equator. These crossreactions are usually transient over months to years and produce <10-12 mm of induration. Previous vaccination with bacille Calmette-Guérin (BCG) also can cause a reaction to a TST, especially if a person has received 2 or more BCG vaccinations. Approximately 50% of the infants who receive a BCG vaccine never develop a reactive TST, and the reactivity usually wanes in 2-3 yr in those with initially positive skin test results. Older children and adults who receive a BCG vaccine are more likely to develop tuberculin reactivity, but most lose the reactivity by 5-10 yr after vaccination. When skin test reactivity is present, it usually causes <10 mm of induration, although larger reactions occur in some persons.

The appropriate size of induration indicating a positive Mantoux TST result varies with related epidemiologic and risk factors. In children with no risk factors for tuberculosis, skin test reactions are usually false-positive results. The American Academy of Pediatrics and the CDC discourage routine testing of all children and recommend targeted tuberculin testing of children at risk identified through periodic screening questionnaires (see Tables 215-1 and 215-2). Possible exposure to an adult with or at high risk for infectious pulmonary tuberculosis disease should be tested for HIV infection.

CHILDREN FOR WHOM IMMEDIATE TST OR IGRA IS INDICATED:

- Contacts of people with confirmed or suspected contagious tuberculosis (contact investigation)
- Children with radiographic or clinical findings suggesting tuberculosis disease
- Children immigrating from countries with endemic infections (e.g., Asia, Middle East, Africa, Latin America, countries from the former Soviet Union), including international adoptees
- Children with travel histories to countries with endemic infection and substantial contact with indigenous people from such countries
- Children who should have annual TST or IGRA:
  - Children infected with HIV

CHILDREN AT INCREASED RISK FOR PROGRESSION OF LTBI TO TUBERCULOSIS DISEASE

Children with other medical conditions, including diabetes mellitus, chronic renal failure, malnutrition, and congenital or acquired immunodeficiencies deserve special consideration. Without recent exposure, these children are not at increased risk of acquiring tuberculosis infection. Underlying immunodeficiencies associated with these conditions theoretically would enhance the possibility for progression to severe disease. Initial histories of potential exposure to tuberculosis should be included for all of these patients. If these histories or local epidemiologic factors suggest a possibility of exposure, immediate and periodic TST should be considered. An initial TST or IGRA should be performed before initiation of immunosuppressive therapy, including prolonged steroid administration, use of tumor necrosis factor-α antagonists, or immunosuppressive therapy in any child requiring these treatments.

*Bacille Calmette-Guérin immunization is not a contraindication to a TST.
*Beginning as early as 3 mo of age.
*If the child is well and has no history of exposure, the TST or IGRA should be delayed up to 10 wk after return.

HIV, human immunodeficiency virus; IGRA indicates interferon-γ release assay; LTBI, latent tuberculosis infection; TST, tuberculin skin test.

Table 215-3  Definitions of Positive Tuberculin Skin Test Results in Infants, Children, and Adolescents∗

<table>
<thead>
<tr>
<th>Definition</th>
<th>Age Limit(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>INDURATION ≥5 MM</td>
<td>Children in close contact with known or suspected contagious people with tuberculosis disease</td>
</tr>
<tr>
<td></td>
<td>Children suspected to have tuberculosis disease:</td>
</tr>
<tr>
<td></td>
<td>• Findings on chest radiograph consistent with active or previously tuberculosis disease</td>
</tr>
<tr>
<td></td>
<td>• Clinical evidence of tuberculosis disease†</td>
</tr>
<tr>
<td></td>
<td>Children receiving immunosuppressive therapy‡ or with immunosuppressive conditions, including HIV infection</td>
</tr>
<tr>
<td>INDURATION ≥10 MM</td>
<td>Children at increased risk of disseminated tuberculosis disease:</td>
</tr>
<tr>
<td></td>
<td>• Children born in high-prevalence regions of the world</td>
</tr>
<tr>
<td></td>
<td>• Children often exposed to adults who are HIV infected, homeless, users of illicit drugs, residents of nursing homes, incarcerated or institutionalized, or migrant farm workers</td>
</tr>
<tr>
<td></td>
<td>• Children who travel to high-prevalence regions of the world</td>
</tr>
<tr>
<td>INDURATION ≥15 MM</td>
<td>Children ≥4 yr of age without any risk factors</td>
</tr>
</tbody>
</table>

Table 215-4  Recommendations for Use of the Tuberculin Skin Test and an Interferon-γ Release Assay in Children

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>TST preferred, IGRA acceptable</td>
<td>Children &lt;5 yr of age*</td>
</tr>
<tr>
<td>IGRA preferred, TST acceptable</td>
<td>Children &gt;5 yr of age who have received the BCG vaccine</td>
</tr>
<tr>
<td></td>
<td>Children &gt;5 yr of age who are unlikely to return for TST reading</td>
</tr>
<tr>
<td></td>
<td>TST and IGRA should be considered when:</td>
</tr>
<tr>
<td></td>
<td>• The initial and repeat IGRA are indeterminate</td>
</tr>
<tr>
<td></td>
<td>• The initial TST (TST or IGRA) is negative and:</td>
</tr>
<tr>
<td></td>
<td>• Clinical suspicion for tuberculosis disease is moderate to high†</td>
</tr>
<tr>
<td></td>
<td>• Risk of progression and poor outcome is high†</td>
</tr>
<tr>
<td></td>
<td>• The initial TST is positive and:</td>
</tr>
<tr>
<td></td>
<td>• &gt;5 yr of age and history of BCG vaccination</td>
</tr>
<tr>
<td></td>
<td>• Additional evidence needed to increase compliance</td>
</tr>
<tr>
<td></td>
<td>• Nontuberculous mycobacterial disease is suspected</td>
</tr>
</tbody>
</table>

*Positive result of either test is considered significant in these groups. †IGRAs should not be used in children younger than 2 yr of age unless tuberculosis disease is suspected. In children 2-4 yr of age, there are limited data about the usefulness of IGRAs in determining tuberculosis infection, but IGRA testing can be performed if tuberculosis disease is suspected. IGRA indicates interferon-γ release assay; TST, tuberculin skin test. From American Academy of Pediatrics. Red book. 2012 report of the Committee on Infectious Diseases, ed 29. Elk Grove Village, IL, 2012, American Academy of Pediatrics, p. 737.

Table 215-4  Recommendations for Use of the Tuberculin Skin Test and an Interferon-γ Release Assay in Children

The most specific confirmation of pulmonary tuberculosis is isolation of M. tuberculosis from a clinical sample. Sputum specimens for culture should be collected from adolescents and older children who are able to expectorate. Induced sputum with a jet nebulizer, inhaled saline and chest percussion followed by nasopharyngeal suctioning is effective in children as young as 1 yr of age. Sputum induction provides samples for both culture and acid-fast bacilli staining. The traditional culture specimen in young children is the early morning gastric acid obtained before the child has arisen and peristalsis has emptied the stomach of the pooled respiratory secretions that have been swallowed overnight. However, even under optimal conditions, 3 consecutive morning gastric aspirates yield the organisms in <50% of cases. The culture yield from bronchoscopy is even lower, but this procedure can demonstrate the presence of endobronchial disease or a fistula. Negative cultures never exclude the diagnosis of tuberculosis in a child. The presence of a positive TST or IGRA, an abnormal chest radiograph consistent with tuberculosis, and history of exposure to an adult with infectious tuberculosis is adequate for the probable diagnosis of tuberculosis disease. If a likely adult source case has been identified, drug susceptibility test results of the isolate from the adult source can be used to determine the best therapeutic regimen for the child. Cultures should be obtained from the child whenever the source case is unknown, there are multiple possible source cases, or the source case has possible or confirmed drug-resistant tuberculosis.

Confirmation of extrapulmonary tuberculosis is best achieved with a positive culture. However, for many forms of tuberculosis, the culture yield is only 25-50%, and probable diagnosis is by a combination of clinical signs and symptoms, analysis of body fluids when possible, radiographic or histopathologic evidence of tuberculosis, and elimination of other possible diagnoses.

Tuberculosis is the most crucial risk factor for children. Reaction size limits for determining a positive tuberculin test result vary with the person’s risk for infection (Table 215-3). In those at highest risk of progression to tuberculosis disease, TST sensitivity is most important whereas specificity is more important for persons at low risk of progression.

Interferon-γ Release Assays

Two blood tests (T-SpOT.TB and QuantiFERON-TB) detect IFN-γ generation by the patient’s T cells in response to specific M. tuberculosis antigens (ESAT-6, CFP-10, and TB7.7). The QuantiFERON-TB test measures whole blood concentrations of IFN-γ, and the T-SpOT.TB test measures the number of lymphocytes/monocytes producing IFN-γ. The test antigens are not present on BCG, M. bovis–BCG and Mycobacterium avium complex, the major group of environmental mycobacteria, so one would expect higher specificity compared with the TST and fewer false-positive results. Both IGRAs have internal positive and negative controls. Like the TST, IGRAs cannot differentiate between tuberculosis infection and disease. Two clear advantages of the IGRAs are the need for only 1 patient encounter (vs 2 with the TST) and the lack of crossreaction with BCG vaccination and most other mycobacteria.

IGRAs should be interpreted with caution when used for children younger than 5 yr of age and immunocompromised patients owing to the relative lack of data and the increased propensity for indeterminate results in these groups, making TSTs preferred in these populations. IGRAs are preferred and TSTs are considered acceptable in the BCG-immunized older child (≥5 yr) and in those ≥5 yr who are unlikely to return for TST reading. Both TST and IGRA testing should be obtained in children with an indeterminate initial and repeat IGRA testing; in those in whom initial TST or IGRA testing is negative and the suspicion for tuberculosis disease or risk of progression to disease is high; in those ≥5 yr who have a positive TST and have received the BCG vaccine; in those whose family is reluctant to treat infection based on a TST result alone; and in those in whom nontuberculous mycobacterial disease is suspected (Table 215-4). As most studies have not shown a consistent, significant difference between the IGRAs, the CDC recommends that the assays may be used interchangeably.

Mycobacterial Sampling, Susceptibility and Culture
Nucleic Acid Amplification
The main form of nucleic acid amplification studied in children with tuberculosis is PCR, which uses specific DNA sequences as markers for microorganisms. Evaluation of PCR in childhood tuberculosis has been limited. Compared with a clinical diagnosis of pulmonary tuberculosis in children, the sensitivity of PCR has varied from 25-83%, and specificity has varied from 80-100%. A negative PCR result never eliminates the diagnosis of tuberculosis, and the diagnosis is not confirmed by a positive PCR result.

Gene Xpert MTB/RIF is a real-time PCR assay for M. tuberculosis that simultaneously detects rifampin resistance, which is often used as a proxy for MDR tuberculosis. This assay uses a self-contained cartridge system, which yields results from direct specimens in 2 hr and is less operator dependent than traditional PCR detection methods. Sensitivity and specificity were 72-77% and 99% in smear-negative adults and 98-99% and 99-100% in smear-positive adults, respectively. Pediatric studies reveal that compared to smear microscopy, this technology has superior diagnostic capability on direct sputum and gastric aspirates. Although cartridges for the Xpert system are expensive, it offers advantages in rapid detection of MDR tuberculosis and is especially useful in settings lacking laboratory infrastructure. Xpert should never replace mycobacterial cultures.

TREATMENT
The basic principles of management of tuberculosis disease in children and adolescents are the same as those in adults. Several drugs are used to affect a relatively rapid cure and prevent the emergence of secondary drug resistance during therapy (Tables 215-5 and 215-6). The choice of regimen depends on the extent of tuberculosis disease, the host, and the likelihood of drug resistance (see Chapter 214 and Table 214-1). The standard therapy of intrathoracic tuberculosis (pulmonary disease and/or hilar lymphadenopathy) in children, as recommended by the CDC and American Academy of Pediatrics, is a 6 mo regimen of isoniazid and rifampin supplemented in the 1st 2 mo of treatment by pyrazinamide and ethambutol. Several clinical trials have shown that this regimen yields a success rate approaching 100%, with an incidence of clinically significant adverse reactions of <2%. Nine-month regimens of only isoniazid and rifampin are also highly effective for drug-susceptible tuberculosis, but the necessary length of treatment, the need for good adherence by the patient, and the relative lack of protection against possible initial drug resistance have led to the favoring of treatment regimens with additional drugs for a short time period. Most experts recommend that all drug administration be directly observed, meaning that a healthcare worker is physically present when the medications are administered to the patients. When directly observed therapy is used, intermittent (twice or thrice weekly) administration of drugs after an initial period as short as 2 wk of daily therapy is as effective in children as daily therapy for the entire course.

Extrapulmonary tuberculosis is usually caused by small numbers of mycobacteria. In general, the treatment for most forms of extrapulmonary tuberculosis in children, including cervical lymphadenopathy, is the same as for pulmonary tuberculosis. Exceptions are bone and joint, disseminated, and CNS tuberculosis, for which there are inadequate data to recommend 6 mo of therapy. These conditions are treated for 9-12 mo. Surgical débridement in bone and joint disease and ventriculoperitoneal shunting in CNS disease may be necessary adjuncts to medical therapy.

The optimal treatment of tuberculosis in HIV-infected children has not been established. HIV-seropositive adults with tuberculosis can be treated successfully with standard regimens that include isoniazid, rifampin, pyrazinamide, and ethambutol. The total duration of therapy should be 6-9 mo, or 6 mo after culture of sputum becomes sterile, whichever is longer. Data for children are limited to relatively small series. Most experts believe that HIV-infected children with drug-susceptible tuberculosis should receive the standard 4-drug regimen for the 1st 2 mo followed by isoniazid and rifampin for a total duration of at least 9 mo. Children with HIV infection appear to have more frequent adverse reactions to antituberculosis drugs and must be monitored closely during therapy. Co-administration of rifampin and some antiretroviral agents results in subtherapeutic blood levels of protease inhibitors and nonnucleoside reverse transcriptase inhibitors and toxic levels of rifampin. Concomitant administration of these drugs is not recommended. Treatment of HIV-infected children is often empiric based on epidemiologic and radiographic information, because the radiographic appearance of other pulmonary complications of HIV in children, such as lymphoid interstitial pneumonitis and bacterial pneumonia, may be similar to that of tuberculosis. Therapy should be considered when tuberculosis cannot be excluded.

<table>
<thead>
<tr>
<th>DRUG</th>
<th>DOSAGE FORMS</th>
<th>DAILY DOSAGE, mg/kg</th>
<th>TWICE A WEEK DOSAGE, mg/kg PER DOSE</th>
<th>MAXIMUM DOSE</th>
<th>ADVERSE REACTIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethambutol</td>
<td>Tablets: 100 mg 400 mg</td>
<td>20</td>
<td>50</td>
<td>2.5 g</td>
<td>Optic neuritis (usually reversible), decreased red-green color discrimination, gastrointestinal tract disturbances, hypersensitivity</td>
</tr>
<tr>
<td>Isoniazid*</td>
<td>Scored tablets: 100 mg 300 mg Syrup: 10 mg/mL</td>
<td>10-15†</td>
<td>20-30</td>
<td>Daily, 300 mg Twice a week, 900 mg</td>
<td>Mild hepatic enzyme elevation, hepatitis, peripheral neuritis, hypersensitivity</td>
</tr>
<tr>
<td>Pyrazinamide*</td>
<td>Scored tablets: 500 mg</td>
<td>30-40</td>
<td>50</td>
<td>2 g</td>
<td>Hepatotoxic effects, hyperuricemia, arthralgias, gastrointestinal tract upset</td>
</tr>
<tr>
<td>Rifampin*</td>
<td>Capsules: 150 mg 300 mg Syrup formulated from capsules</td>
<td>10-20</td>
<td>10-20</td>
<td>600 mg</td>
<td>Orange discoloration of secretions or urine, staining of contact lenses, vomiting, hepatitis, influenza-like reaction, thrombocytopenia, pruritus; oral contraceptives may be ineffective</td>
</tr>
</tbody>
</table>

*Rifamate is a capsule containing 150 mg of isoniazid and 300 mg of rifampin. Two capsules provide the usual adult (i.e., person weighing >50 kg) daily doses of each drug. Rifater, in the United States, is a capsule containing 50 mg of isoniazid, 120 mg of rifampin, and 300 mg of pyrazinamide. Isoniazid and rifampin also are available for parenteral administration.

†When isoniazid in a dosage exceeding 10 mg/kg per day is used in combination with rifampin, the incidence of hepatotoxic effects may be increased.

Drug-Resistant Tuberculosis

The incidence of drug-resistant tuberculosis is increasing in many areas of the world, including North America. There are two major types of drug resistance. **Primary resistance** occurs when a person is infected with *M. tuberculosis* that is already resistant to a particular drug. **Secondary resistance** occurs when drug-resistant organisms emerge as the dominant population during treatment. The major causes of secondary drug resistance are poor adherence to the medication by the patient or inadequate treatment regimens prescribed by the physician. Nonadherence to 1 drug is more likely to lead to secondary resistance than is failure to take all drugs. Secondary resistance is rare in children because of the small size of their mycobacterial population. Consequently, most drug resistance in children is primary, and patterns of drug resistance among children tend to mirror those found among adults in the same population. The main predictors of drug-resistant tuberculosis among adults are history of previous antituberculosis treatment, coinfection with HIV, and exposure to another adult with infectious drug-resistant tuberculosis.

Treatment of drug-resistant tuberculosis is successful only when at least 2 bactericidal drugs are given to which the infecting strain of *M. tuberculosis* is susceptible. When a child has possible drug-resistant tuberculosis, usually 4 or 5 drugs should be administered initially until the susceptibility pattern is determined and a more-specific regimen can be designed. The specific treatment plan must be individualized for each patient according to the results of susceptibility testing on the isolates from the child or the adult source case. Treatment duration of 9 mo with rifampin, pyrazinamide, and ethambutol is usually adequate for isoniazid-resistant tuberculosis in children. When resistance to isoniazid and rifampin is present, the total duration of therapy often must be extended to 12-24 mo, and intermittent regimens should not be used. The prognosis of single- or multidrug-resistant tuberculosis in children is usually good if the drug resistance is identified early in the treatment, appropriate drugs are administered under directly observed therapy, adverse reactions from the drugs are minor, and the child and family are in a supportive environment. The treatment of drug-resistant tuberculosis in children always should be undertaken by a clinician with specific expertise in the treatment of tuberculosis.

Corticosteroids

Corticosteroids are useful in treating some children with tuberculosis disease. They are most beneficial when the host inflammatory reaction contributes significantly to tissue damage or impairment of organ function. There is convincing evidence that corticosteroids decrease...
mortality rates and long-term neurologic sequelae in some patients with **tuberculous meningitis** by reducing vasculitis, inflammation, and, ultimately, intracranial pressure. Lowering the intracranial pressure limits tissue damage and favors circulation of antituberculosis drugs through the brain and meninges. Short courses of corticosteroids also may be effective for children with **endobronchial tuberculosis** that causes respiratory distress, localized emphysema, or segmental pulmonary lesions. Several randomized clinical trials have shown that corticosteroids can help relieve symptoms and constriction associated with acute tuberculous **pericardial effusion**. Corticosteroids can cause dramatic improvement in symptoms in some patients with tuberculous pleural effusion and shift of the mediastinum. However, the long-term course of disease is probably unaffected. Some children with severe **miliary tuberculosis** have dramatic improvement with corticosteroid therapy if the inflammatory reaction is so severe that alveolocapillary block is present. There is no convincing evidence to support a specific corticosteroid preparation. The most commonly used regimen is prednisone, 1-2 mg/kg/day in 1-2 divided doses orally for 4-6 wk, followed by a taper.

**Supportive Care**

Children receiving treatment should be followed carefully to promote adherence to therapy, to monitor for toxic reactions to medications, and to ensure that the tuberculosis is being adequately treated. Adequate nutrition is important. Patients should be seen at monthly intervals and should be given just enough medication to last until the next visit. Anticipatory guidance with regard to the administration of medications to children is crucial. The physician should foresee difficulties that the family might have in introducing several new medications in inconvenient dosage forms to a young child. The clinician must report all cases of suspected tuberculosis in a child to the local health department to be sure that the child and family receive appropriate care and evaluation.

Nonadherence to treatment is the major problem in tuberculosis therapy. The patient and family must know what is expected of them through verbal and written instructions in their primary language. Approximately 30-50% of patients taking long-term treatment are significantly nonadherent with self-administered medications, and clinicians are usually not able to determine in advance which patients will be nonadherent. Preferably, directly observed therapy should be instituted by the local health department.

**Latent Mycobacterium tuberculosis Infection**

The following aspects of the natural history and treatment of LTBI in children must be considered in the formulation of recommendations about therapy: (1) infants and children younger than 5 yr of age with LTBI have been infected recently; (2) the risk for progression to disease is high; (3) untreated infants with LTBI have up to a 40% chance of development of tuberculosis disease; (4) the risk for progression decreases gradually through childhood, until adolescence when the risk increases; (5) infants and young children are more likely to have life-threatening forms of tuberculosis, including meningitis and disseminated disease; and (6) children with LTBI have more years at risk for development of disease than adults. Because of these factors, and the excellent safety profile of isoniazid in children, there is a tendency to err on the side of overtreatment in infants, young children and adolescents.

Isoniazid therapy for LTBI appears to be more effective for children than adults, with several large clinical trials demonstrating risk reduction of 70-90%. The risk of isoniazid-related hepatitis is minimal in infants, children, and adolescents, who tolerate the drug better than adults.

The recommended regimen for treatment of LTBI in United States children is a 9 mo course of isoniazid as self-administered daily therapy or by twice-weekly directly observed therapy. Analysis of data from several studies demonstrates that the efficacy decreased significantly if isoniazid was taken for <9 mo. However, the international standard is 6 mo treatment with isoniazid. Isoniazid given twice weekly has been used extensively to treat LTBI in children, especially schoolchildren and close contacts of case patients. Directly observed therapy should be considered when it is unlikely that the child and family will adhere to daily self-administration, or if the child is at increased risk for rapid development of disease (newborns and infants, recent contacts, immunocompromised children). For healthy children taking isoniazid but no other potentially hepatotoxic drugs, routine biochemical monitoring and supplementation with pyridoxine are not necessary. A 3 mo regimen of rifampin and isoniazid has been used in Europe, with programmatic data suggesting that the regimen is effective, but this regimen is not recommended in the United States. Rifapentine alone for 4-6 mo has been used for the treatment of LTBI in infants, children, and adolescents when isoniazid could not be tolerated or the child has had contact with a source case infected with an isoniazid-resistant but rifampin-susceptible organism. However, no controlled clinical trials have been conducted. Rifapentine is a rifamycin with a very long half-life, allowing for weekly administration in conjunction with isoniazid. Studies have demonstrated that 12 doses of once weekly isoniazid and rifapentine are as effective for treating LTBI and as safe as 9 mo of daily isoniazid, and this regimen is recommended by the American Academy of Pediatrics and the CDC for treatment of LTBI in patients 12 yr of age and older. Given the risk of selecting for drug-resistant isolates by missing intermittent doses of rifampicins, this treatment regimen currently is recommended only under directly observed therapy under the supervision of local health departments.

For children with multidrug-resistant tuberculosis infection, the regimen will depend on the drug-susceptibility profile of the contract case's organism; an expert in tuberculosis should be consulted. Few controlled studies have been published regarding the efficacy of any form of treatment for LTBI in HIV-infected children. A 9-mo course of daily isoniazid is recommended. Most experts recommend that routine monitoring of serum hepatic enzyme concentrations be performed and pyridoxine be given when HIV-infected children are treated with isoniazid. The optimal duration of rifampin therapy in children with LTBI is not known, but many experts recommend at least a 6 mo course.

Isoniazid should be given to children younger than 5 yr of age who have a negative TST or IGRA result but who have known recent exposure to an adult with potentially contagious tuberculosis disease. This practice is often referred to as **window prophylaxis**. By the time delayed hypersensitivity develops (2-3 mo), an untreated child already may have developed severe tuberculosis. For these children, tuberculin skin or IGRA testing is repeated 3 mo after contact with the source case for tuberculosis has been broken (broken contact is defined as physical separation or adequate initial treatment of the source case). If the second test result is positive, isoniazid therapy is continued for 9 mo, but if the result is negative, treatment can be stopped.

**PREVENTION**

The highest priority of any tuberculosis control program should be case finding and treatment, which interrupts transmission of infection between close contacts. All children and adults with symptoms suggestive of tuberculosis disease and those in close contact with an adult with suspected infectious pulmonary tuberculosis should be tested for tuberculosis infection (by TST or IGRA) and examined as soon as possible. On average, 30-50% of household contacts to infectious cases are infected, and 1% of contacts already have overt disease. This scheme relies on effective and adequate public health response and resources. Children, particularly young infants, should receive high priority during contact investigations, because their risk for infection is high and they are more likely to rapidly develop severe forms of tuberculosis.

Mass testing of large groups of children for tuberculosis infection is an inefficient process. When large groups of children at low risk for tuberculosis are tested, the vast majority of TST reactions are actually false-positive reactions because of biologic variability or cross sensitization with NTM. However, testing of high-risk groups of adults or children should be encouraged, because most of these persons with positive TST or IGRA results have tuberculosis infection. Testing
should take place only if effective mechanisms are in place to ensure adequate evaluation and treatment of the persons who test positive.

**Bacille Calmette-Guérin Vaccination**

The only available vaccine against tuberculosis is the BCG vaccine. The original vaccine organism was a strain of *M. bovis* attenuated by subculture every 3 wk for 13 yr. This strain was distributed to dozens of laboratories that continued to subculture the organism on different media under various conditions. The result has been production of many BCG vaccines that differ widely in morphology, growth characteristics, sensitizing potency, and animal virulence.

The administration route and dosing schedule for the BCG vaccines are important variables for efficacy. The preferred route of administration is intradermal injection with a syringe and needle, because it is the only method that permits accurate measurement of an individual dose.

The BCG vaccines are extremely safe in immunocompetent hosts. Local ulceration and regional suppurative adenitis occur in 0.1-1% of vaccine recipients. Local lesions do not suggest underlying host immune defects and do not affect the level of protection afforded by the vaccine. Most reactions are mild and usually resolve spontaneously, but chemotherapy is needed occasionally. Surgical excision of a suppurative draining node is rarely necessary and should be avoided if possible. Osteitis is a rare complication of BCG vaccination that appears to be related to certain strains of the vaccine that are no longer in wide use. Systemic complaints such as fever, convulsions, loss of appetite, and irritability are extraordinarily rare after BCG vaccination.

Profoundly immunocompromised patients can develop disseminated BCG infection after vaccination. Children with HIV infection appear to have rates of local adverse reactions to BCG vaccines that are comparable with rates in immunocompetent children. However, the incidence in these children of disseminated infection months to years after vaccination is currently unknown.

Recommended vaccine schedules vary widely among countries. The official recommendation of the World Health Organization is a single dose administered during infancy, in populations where the risk for tuberculosis is high. However, infants with known HIV infection should not receive a BCG vaccination. In some countries repeat vaccination is universal, although no clinical trials support this practice. In others, it is based on either TST or the absence of a typical scar. The optimal age for administration and dosing schedule are unknown because adequate comparative trials have not been performed.

Although dozens of BCG trials have been reported in various human populations, the most useful data have come from several controlled trials. The results of these studies have been disparate. Some demonstrated a great deal of protection from BCG vaccines, but others showed no efficacy at all. A meta-analysis of published BCG vaccination trials suggested that BCG is 50% effective in preventing pulmonary tuberculosis in adults and children. The protective effect for disseminated and meningeval tuberculosis appears to be slightly higher, with BCG preventing 50-80% of cases. A variety of explanations for the varied responses to BCG vaccines have been proposed, including methodologic and statistical variations within the trials, interaction with NTM that either enhances or decreases the protection afforded by BCG, different potencies among the various BCG vaccines, and genetic factors for BCG response within the study populations.

BCG vaccination administered during infancy has little effect on the ultimate incidence of tuberculosis in adults, suggesting waning protection with time.

BCG vaccination has worked well in some situations but poorly in others. Clearly, BCG vaccination has had little effect on the ultimate control of tuberculosis throughout the world, because more than 5 billion doses have been administered but tuberculosis remains endemic in most regions. BCG vaccination does not substantially influence the chain of transmission, because cases of contagious pulmonary tuberculosis in adults that can be prevented by BCG vaccination constitute a small fraction of the sources of infection in a population. The best use of BCG vaccination is to prevent life-threatening forms of tuberculosis in infants and young children.

BCG vaccination has never been adopted as part of the strategy for the control of tuberculosis in the United States. Widespread use of the vaccine would render subsequent TSTs less useful. However, BCG vaccination can contribute to tuberculosis control in selected population groups. BCG is recommended for TST-negative, HIV-negative infants and children who are at high risk for intimate and prolonged exposure to persistently untreated or ineffectively treated adults with infectious pulmonary tuberculosis and who cannot be removed from the source of infection or placed on long-term preventive therapy. It also is recommended for those who are continuously exposed to persons with tuberculosis who have bacilli that are resistant to isoniazid and rifampin.

Any child receiving BCG vaccination should have a documented negative TST before receiving the vaccine. After receiving the vaccine, the child should be separated from the possible sources of infection until it can be demonstrated that the child has had a vaccine response, demonstrated by tuberculin reactivity, which usually develops within 1-3 mo.

Active research to develop new tuberculosis vaccines has led to the creation and preliminary testing of several vaccine candidates based on attenuated strains of mycobacteria, subunit proteins, or DNA. The genome of *M. tuberculosis* has been sequenced, allowing researchers to further study and better understand the pathogenesis and host immune responses to tuberculosis.

**Prevention of Perinatal Tuberculosis**

The most effective way of preventing tuberculosis infection and disease in the neonate or young infant is through appropriate testing and treatment of the mother and other family members. High-risk pregnant women should be tested with a TST or IGRA, and those with a positive test result should receive a chest radiograph with appropriate abdominal shielding. If the mother has a negative chest radiograph and is clinically well, no separation of the infant and mother is needed after delivery. The child needs no special evaluation or treatment if the child remains asymptomatic. Other household members should undergo testing for tuberculosis infection and further evaluation as indicated.

If the mother has suspected tuberculosis at the time of delivery, the newborn should be separated from the mother until the chest radiograph is obtained. If the mother’s chest radiograph is abnormal, separation should be maintained until the mother has been evaluated thoroughly, including examination of the sputum. If the mother’s chest radiograph is abnormal but the history, physical examination, sputum examination, and evaluation of the radiograph show no evidence of current active tuberculosis, it is reasonable to assume that the infant is at low risk for infection. The mother should receive appropriate treatment, and she and her infant should receive careful follow-up care.

If the mother’s chest radiograph or acid-fast sputum smear shows evidence of current tuberculosis disease, additional steps are necessary to protect the infant. Isoniazid therapy for newborns has been so effective that separation of the mother and infant is no longer considered mandatory. Separation should occur only if the mother is ill enough to require hospitalization, has been or is expected to become nonadherent to treatment, or has suspected drug-resistant tuberculosis. Isoniazid treatment for the infant should be continued until the mother is sputum culture negative for ≥3 mo. At that time, a Mantoux TST should be placed on the child. If the test is positive, isoniazid is continued for a total duration of 9-12 mo; if the test is negative, isoniazid can be discontinued. Once the mother and child are taking adequate therapy, it is usually safe for the mother to breastfeed, as the medications, although found in milk, are present in low concentrations. If isoniazid resistance is suspected or the mother’s adherence to medication is in question, continued separation of the infant from the mother should be considered. The duration of separation must be at least as long as is necessary to render the mother noninfectious. An expert in tuberculosis should be consulted if the young infant has potential exposure to the mother or another adult with tuberculosis disease caused by an isoniazid-resistant strain of *M. tuberculosis*.

Although isoniazid is not thought to be teratogenic, the treatment of pregnant women who have asymptomatic tuberculosis infection is
often deferred until after delivery. However, symptomatic pregnant women or those with radiographic evidence of tuberculosis disease should be appropriately evaluated. Because pulmonary tuberculosis is harmful to both the mother and the fetus and represents a great danger to the infant after delivery, tuberculosis in pregnant women always should be treated. The most common regimen for drug-susceptible tuberculosis is isoniazid, rifampin, and ethambutol. The aminoglycosides and ethionamide should be avoided because of their teratogenic effect. The safety of pyrazinamide in pregnancy has not been established.

Bibliography is available at Expert Consult.
Bibliography
Leprosy is a heterogeneous, chronic mycobacterial infection that primarily affects the upper airway, skin, and peripheral nerves. Disease manifestations are determined by the host's immunopathologic response to infection, resulting in a wide clinical spectrum. Hansen disease (HD) is currently the accepted designation of leprosy. Contrary to historical folklore, HD is not highly transmissible and is treatable. In addition, the associated morbidity and disability can be prevented with early diagnosis and appropriate treatment.

ETIOLOGY
Mycobacterium leprae, the etiologic agent of leprosy, is an obligate intracellular acid-fast Gram-positive bacillus of the family Mycobacteriaceae measuring 1-8 μm in length. It grows optimally at 27-33°C (80.6-91.4°F) yet cannot be cultured in vitro. Natural infection occurs in humans and possibly in armadillos, although mice and certain primates can be infected with M. leprae in the laboratory. Based on assays in footpads of immunodeficient mice, the doubling time of M. leprae is estimated to be 11-13 days. The incubation period between natural infection and overt clinical disease in humans ranges from 3 mo to 20 yr, with a mean of 4 yr for tuberculoid leprosy and 10 yr for lepromatous leprosy. The infectiousness of patients with HD becomes negligible within 24 hr of the first administration of effective multidrug therapy.

EPIDEMIOLOGY
The World Health Organization's goal to eliminate leprosy as a public health problem, defined as reduction in the prevalence of leprosy to less than 1 case per 10,000 population, was achieved at the global level in 2000. Yet, despite an overall decline in reported prevalence since the introduction of effective antimycobacterial therapy in the early 1980s, HD continues to afflict more than 2 million people worldwide. Approximately 245,000 new cases were reported globally in 2009, with more than 80% of cases occurring in Southeast Asia, Africa, and South America. In the United States, HD is a notifiable disease with 12,685 new HD cases since 1894. In 2009, there were 213 new U.S. cases, with 65% of them occurring in Texas, Louisiana, Hawaii, California, Florida, New York, Massachusetts, and Puerto Rico. Seventy-four percent of cases were among immigrants, with the largest proportion identifying themselves as Asian or South Pacific islanders. Less than 4% of U.S. cases in 2009 occurred in children younger than 16 yr of age. Although infection in infants is rare, the youngest patient reported in the literature is a 3 mo old.

The likelihood of developing HD is determined by several variables: age (with 2 incidence peaks: 10-14 yr and 30 yr), gender (male: female 2:1), and contact with a patient with multibacillary disease. Approximately 5% of people are genetically susceptible to infection with M. leprae. Whole-genome sequencing has allowed identification of genes and polymorphisms associated with increased susceptibility to leprosy. HD in immunocompromised hosts has been reported in solid-organ and bone marrow transplant recipients and patients receiving tumor necrosis factor (TNF)–blocking monoclonal antibodies. Patients with HIV infection do not appear to be at increased risk of acquiring leprosy, to have increased disease severity, or to have a poor response to treatment. However, clinicians should be aware that concomitant HIV infection and leprosy can result in worsening of symptoms of leprosy during HIV treatment as a result of an immune reconstitution inflammatory syndrome.

The exact mechanism of transmission is not fully understood but is thought to occur primarily via the respiratory route. Up to 10⁷ viable bacilli per day can be shed in the respiratory secretions of patients with multibacillary leprosy. Type of disease (multibacillary) and proximity to contact cases are important determinants of human-to-human transmission; the relative risk for developing disease in household contacts is 8-10 for lepromatous disease and 2-4 for the tuberculoid form. Transmissions via breast milk and entry through broken skin have been reported. Autochthonous cases of leprosy have also been reported in the southern Gulf Coast area of the United States and represent a probable zoonosis from armadillos, though the transmission risk is low.

PATHOGENESIS
M. leprae is the only bacterium known to infect nerves. The mechanism of mycobacterial dissemination from the respiratory tract to the skin and nerves is thought to occur hematogenously but has not been completely elucidated. M. leprae has been shown to colonize the perineural space and gain entry into the endoneural space. The organism then binds to the laminin-2 glycoprotein present in the basal lamina of Schwann cells in peripheral nerves. It is then taken up inside the Schwann cell, where it replicates slowly intracellularly over several years. Specific T cells recognize the mycobacterial antigens within the nerve and initiate a chronic inflammatory response. In addition to the direct nerve invasion by M. leprae, the immune response to infection also contributes to nerve damage. Schwann cells express human leukocyte antigen class 2 molecules and play an important role in the immunologic reaction by presenting mycobacterial peptides to the human leukocyte antigen class 2–restricted CD4-positive T cells. This likely explains the nerve damage seen in paucibacillary disease and in reversal reactions. Swelling within the perineurium leads to ischemia, further nerve damage, and eventually to fibrosis and axonal death.

CLINICAL MANIFESTATIONS
Skin and serologic studies suggest that up to 90% of infected people develop immunity after exposure, without manifesting clinical disease. In susceptible individuals with sufficient exposure to become infected, the spectrum of clinical manifestations reflects M. leprae's unique tropism for peripheral nerves, the host's immunologic response to infection, and disease subtype. Classic manifestations of leprosy include hypopigmented, erythematous, or infiltrative skin lesions with or without neurologic symptoms such as hypoesthesia or anesthesia, weakness, autonomic dysfunction, and peripheral nerve thickening.

Skin Involvement
Examination of the skin should ideally be performed in natural sunlight and be tested for hypoesthesia to light touch, pin prick, temperature, and anhidrosis. The most common skin lesions are macules or plaques. Diffuse infiltrative lesions and subcutaneous nodules are less common. Initial lesions are insidious hypopigmented macules, although they may appear erythematous on pale skin. Lesions may involve any area of the body, are more pronounced in cooler areas (for
example the earlobes and nose), and occur less frequently on the scalp, axillae, or perineum. Approximately 70% of skin lesions have reduced sensation; the degree of hypoesthesia depends on the location and size of the lesion and degree of Th1 immune response. Patients with tuberculous leprosy generally have 1-3 well-demarcated macules or plaques with elevated borders (Fig. 216-1) and reduced or absent sensation. In the lepromatous form, multiple lesions are present but are not all hypoesthetic or anesthetic.

Nerve Involvement

The skin lesions overlying a nerve trunk distribution predict the involvement of nerves in the vicinity. Peripheral nerves are most commonly affected early in the disease course and should be palpated for thickness (Fig. 216-2) and tenderness and evaluated for both motor and sensory function (particularly temperature and light touch). The posterior tibial nerve (medial malleolus) is the most common nerve affected, followed by the ulnar (elbow), median (wrist), lateral popliteal (fibular neck), and facial nerves. There is a pure neuritic form of leprosy, occurring most commonly in India and Nepal, in which patients present with asymmetrical neuropathy, but lack skin lesions. A nerve biopsy (usually of the sural nerve) is required to demonstrate granulomatous histopathology, thereby confirming the diagnosis.

Other Involvement

Ocular involvement leading to vision loss results from both direct bacillary invasion of the eye and optic nerve damage. Lagophthalmos occurs when there is destruction of the facial nerve. Facial skin lesions are associated with a 10-fold higher risk of facial nerve damage. Damage to the trigeminal nerve causes anesthesia of the cornea and conjunctiva, leading to abrasions. Systemic involvement of other organs is seen mainly in patients with lepromatous leprosy where a high bacillary burden leads to infiltration of the nasal mucosa, bones, and testes. Renal involvement and amyloidosis are rare findings.

Patients may also present with leprosy reactions. Leprosy reactions are acute clinical exacerbations reflecting disturbances of the immunologic balance to M. leprae infection occurring in 30-50% of all leprosy patients. These sudden changes occur most commonly during the initial years after infection and in patients with borderline and multibacillary leprosy, but can occur before, during, or after completion of treatment. Three types of leprosy reactions have been described and require immediate treatment so as to prevent complications.

1. Type 1 reactions (also known as reversal reactions) occur in one-third of patients with borderline disease and are caused by a spontaneous increase in T-cell–mediated reactivity to mycobacterial antigens. This increase in the Th1 cellular immune response causes local production and increased infiltration of interferon-γ and TNF-α–secreting CD4+ lymphocytes into cutaneous and neural sites. Reversal reactions are characterized by acute edema and increased erythema, warmth, and painful inflammation of preexisting cutaneous plaques or nodules with acute swelling and tenderness of peripheral nerves that can quickly progress to cause nerve abscesses and necrosis. There may be a peripheral lymphocytosis and an increased cytokine response, but systemic symptoms are uncommon. Rapid and sustained reversal of the inflammatory process using corticosteroids is essential to prevent continued nerve damage.

2. Type 2 reactions (erythema nodosum leprosum [ENL]) occur in borderline lepromatous and lepromatous forms, as these patients have the highest levels of M. leprae antigens and antibodies, most commonly in the 1st 2 yr after starting therapy. ENL is distinguished from reversal reactions by the development of new painful, erythematous subcutaneous nodules with an accompanying systemic inflammatory response. ENL is accompanied by high circulating concentrations of TNF-α. Patients develop high fever and signs of systemic toxicity, and in severe cases, ENL can be life-threatening, presenting with features similar to septic shock. Patients present with either a single, acute episode, a relapsing form comprised of multiple acute episodes, or a chronic, continuous form. Deposition of extravascular immune complexes leads to neutrophil infiltration and activation of complement in the skin and other organs. Tender, erythematous dermal papules or nodules (resembling erythema nodosum) occur in clusters, typically on extensor surfaces of the lower extremities and face. Immune complex deposition also contributes to migrating polyarthralgias, painful swelling of lymph nodes and spleen, iridocyclitis, vasculitis, orchitis, and, rarely, nephritis.

3. Lucio’s phenomenon (erythema necroticans) is an uncommon, but potentially fatal reaction distinct from type 1 or 2 reactions that occurs in patients with untreated lepromatous leprosy, most commonly from Mexico. It is a necrotizing vasculitis caused by M. leprae directly invading the endothelium. Clinically, patients develop violaceous or hemorrhagic plaques, followed by ulcerations in the absence of systemic complaints. Secondary bacterial infections are common.
DIAGNOSIS

The diagnosis of HD requires high clinical suspicion and should be considered in any patient with a hypoesthetic or anesthetic skin rash, especially if they have resided in an endemic region. Patients are considered to have HD if they have one or more of the 3 cardinal signs: loss of sensation in a localized skin lesion, thickened peripheral nerve with loss of sensation or weakness of muscles enervated by that nerve, or the presence of acid-fast bacilli on biopsy. The positive predictive value for the diagnosis of leprosy in patients meeting all 3 criteria is 98%. Histopathologic examination of full-thickness biopsies taken of active lesions is considered the gold standard for establishing the diagnosis and allows for precise disease classification. Two classification schemes are frequently applied:

A. The World Health Organization classification is a simple field classification based on the number of skin lesions.
   1. Paucibacillary, single lesion
   2. Paucibacillary (2-5 patches)
   3. Multibacillary (≥6 patches)

B. The Ridley-Jopling scale is commonly used in the United States and describes the 5 types of leprosy, according to clinical spectrum of disease, bacillary load, and findings on histopathology.
   1. Tuberculoid form: Patients usually have a vigorous and specific cellular immune response to M. leprae antigens and have a small number of skin lesions. The lesions are infiltrated by T-helper type 1 T cells producing abundant interferon-γ and TNF-α, forming well-demarcated granulomas, with few, if any bacilli found within the lesions.
   2. Borderline tuberculoid form
   3. Borderline
   4. Borderline lepromatous
   5. Lepromatous form: Patients have an absence of specific cellular immunity to M. leprae but intact immunity to Mycobacterium tuberculosis. Patients with lepromatous form have the most severe form of the disease, characterized by many skin lesions, clinically apparent infiltration of peripheral nerves and skin lesions, and a high load of bacilli in the absence of an effective cell mediated immune response. They also have involvement of the nasal mucosa causing nasal congestion and epistaxis. Skin biopsies reveal extensive infiltration of the skin and nerves, containing messenger RNA for T-helper type 2-like cytokines such as interleukin-4 and interleukin-10, poorly formed granulomas, and uncontrolled proliferation of bacilli within foamy macrophages. A large amount of circulating antibody to M. leprae is present but does not confer protective immunity. Over time, patients with the lepromatous form develop symmetrical peripheral nerve involvement and a diffuse infiltrative dermopathy that includes thickening of the facial skin with accentuation of the skin creases and hair loss of the eyelashes and eyebrows (madarosis), leading to the classic presentation of the “leonine facies.”

Patients with the extremes of the disease (tuberculoid and lepromatous forms) are considered to have stable cell-mediated immunity, as their disease manifestations do not change much over time. In contrast, patients with borderline disease (borderline tuberculoid, borderline, borderline lepromatous) have unstable cell-mediated immunity and demonstrate changes in their clinical manifestations over time toward the polar forms or sudden reversal reactions. From borderline tuberculoid to borderline lepromatous forms, there is a progressive reduction in cellular immune responses, an increase in bacillary load, more frequent hypopigmented skin lesions (Fig. 216-3) and nerve involvement, and higher antibody titers.

Indeterminate leprosy is the earliest form of leprosy in which patients have a single hypopigmented macule with poorly defined borders, without erythema or induration. Anesthesia is minimal or absent, especially if the lesion is on the face. The diagnosis is usually one of exclusion in the setting of a contact investigation. Tissue biopsies show diagnostic evidence of leprosy but do not meet sufficient criteria for classification. Up to 50-75% of the lesions will heal spontaneously, while the rest will progress to another form of leprosy.

To confirm the diagnosis, a full-thickness skin biopsy should be taken from the most active skin lesion, entirely within the lesion and including the active margin. M. leprae is best identified in tissue using the Fite stain. Lesions from patients with the lepromatous form reveal numerous acid fast bacilli in clumps (globi), whereas patients with the tuberculoid form of the disease rarely have mycobacteria identified but demonstrate well-formed noncaseating granulomas and nerve involvement. The presence of neural inflammation differentiates leprosy from other granulomatous disorders. Hematoxylin-and-eosin staining and immunohistochemistry may also contribute to the diagnosis. Mycobacterial culture of lesions is performed to exclude M. tuberculosis and nontuberculous cutaneous infections. Antibodies to M. leprae are present in 90% of patients with untreated lepromatous disease, 40-50% with paucibacillary disease, and 1-5% of healthy controls. Serologic testing is insensitive, however, and is not used for diagnosis.

In endemic countries with few medical resources, diagnosis is based primarily on clinical evidence. In areas with laboratory access, a slit-skin smear may be performed in lieu of a biopsy. The slit-skin procedure involves making a small incision in the dermis of a suspected lesion, scraping the dermal surface and edge of the lesion, smearing the scraping on a glass slide, heat fixing, and staining (Fite) the specimen to detect the mycobacteria. Although slit-skin smears have high specificity, they have low sensitivity, as only 30% of patients are smear positive, usually patients with the lepromatous form. The bacterial index can range from 0 (no bacilli in 100 oil-immersion fields), as is generally seen in paucibacillary disease, to 6+ (>1,000 bacilli/field), as can be seen in multibacillary disease.

Diagnostic and histopathologic consultation in the United States is available through the National Hansen’s Disease Programs (NHDP; http://www.hrsa.gov/hansens or 800-642-2477). Specimens (formalin or paraffin embedded) can be sent to the NHDP for pathologic analysis free of charge. A polymerase chain reaction (PCR) test for M. leprae is
not readily available in clinical practice but may be performed at the NHDP. In nonendemic areas, PCR may be useful for diagnosis when acid-fast bacilli are discernable in tissue, but clinical and histopathologic features are not typical. *M. leprae* DNA is detectable by PCR in 95% of multibacillary disease (sensitivity >90%) and 55% of paucibacillary disease (sensitivity of 34-80%). PCR has also allowed detection of the organism in nasal secretions from asymptomatic people. Molecular testing for mutations causing drug resistance is also available through the NHDP.

**TREATMENT**

In the United States, clinical providers considering a diagnosis and treatment of a patient with HD should obtain consultation from the NHDP. The primary goal of treatment is early antimicrobial therapy to prevent permanent neuropathy. Effective treatment of leprosy requires multidrug therapy (MDT) with dapsone, clofazimine, and rifampin. Combination therapy is employed to prevent antimicrobial resistance. The recommended combination MDT can be obtained free of charge in the United States from the NHDP (Table 216-1) and in other countries, from the World Health Organization (Table 216-2).

Before starting combination MDT, patients should be tested for glucose-6-phosphate dehydrogenase deficiency, have a baseline complete blood cell count and liver function testing, and be evaluated for evidence of concomitant tuberculosis infection. The latter is imperative so as to avoid giving rifampin monotherapy to someone with active tuberculosis. Darkening of the skin is a common adverse reaction to clofazimine; this generally resolves 6-12 mo after completing therapy. Bone marrow suppression and hepatotoxicity have been reported and must be distinguished from the more common leprosy immunologic reactions. Patients who have a bacillary index of ≥4 pre-MDT or ≥3 at the completion of MDT have the highest risk of relapse. When relapse occurs, it is usually within 5-10 yr of MDT completion and a result of reactivation of drug-susceptible mycobacteria, thus patients are treated with the same MDT regimen. Resistance to dapsone and rifampin has been documented, although it rarely occurs with combination therapy. Minocycline, clarithromycin, rifapentine, diarylquinoline, and some fluoroquinolones (ofloxacin, moxifloxacin) have been shown to be bactericidal against *M. leprae*. Given limited data, these alternative antimicrobials are used in selected cases of intolerance to the routine combination MDT regimen or for documented resistance. It is important to note that some patients who have been adequately treated for HD may later show evidence of chronic reversal reactions and late neuropathies but are bacillus negative, thus they should not be considered relapses. In these patients, low-dose clofazimine (50-100 mg thrice weekly) is generally employed until all signs of the reaction have abated.

Treatment of leprosy reactions can be complicated and requires expert consultation. Generally, continuation of antimycobacterial drugs, effective and prolonged antiinflammatory therapy, and adequate analgesia and physical support is essential for patients with active neuritis to prevent nerve damage. For type 1 reactions, the addition of

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### Table 216-1  
**NHDP Recommended Multidrug Therapy Regimens for Hansen Disease in the United States**

<table>
<thead>
<tr>
<th>TYPE OF LEPROSY</th>
<th>ANTIMICROBIAL THERAPY</th>
<th>ADULT DOSING (GIVEN ORALLY)</th>
<th>PEDIATRIC DOSING* (GIVEN ORALLY)</th>
<th>DURATION OF THERAPY</th>
</tr>
</thead>
<tbody>
<tr>
<td>MULTIBACILLARY LEPROSY (LL, BL, BB)</td>
<td>Dapsone and Rifampin and Clofazimine</td>
<td>100 mg/day 600 mg/day 50 mg/day</td>
<td>1 mg/kg/day 10-20 mg/kg/day 1 mg/kg/day</td>
<td>24 months 24 months 24 months</td>
</tr>
<tr>
<td>PAUCIBACILLARY LEPROSY (TT, BT)</td>
<td>Dapsone and Rifampin</td>
<td>100 mg/day 600 mg/day</td>
<td>1-2 mg/kg/day 10-20 mg/kg/day</td>
<td>12 months 12 months</td>
</tr>
</tbody>
</table>

NHDP multidrug therapy therapy is daily and of longer duration than World Health Organization recommended regimen.

*Daily pediatric mg/kg dose should not exceed adult daily maximum.

Clofazimine is only available through NHDP Investigational New Drug (IND) program; minimum formulation is 50 mg and capsules should not be cut. Alternative dosing includes: clofazimine 2 mg/kg every other day or clarithromycin 7.5 mg/kg/day.

BR: borderline; BL, borderline lepromatous; BT, borderline tuberculoid; LL, lepromatous; NHDP, National Hansen’s Disease Program; TT, tuberculoid.

### Table 216-2  
**World Health Organization Recommended Multidrug Therapy Regimens for Hansen Disease**

<table>
<thead>
<tr>
<th>TYPE OF LEPROSY</th>
<th>MONTHLY (SUPERVISED)</th>
<th>DAILY (SELF-ADMINISTERED)</th>
<th>DURATION OF THERAPY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multibacillary (LL, BL, BB)</td>
<td>Adult Pediatric*</td>
<td>Rifampicin 600 mg and clofazimine 300 mg Rifampicin 450 mg and clofazimine 150 mg</td>
<td>Dapsone 100 mg and clofazimine 50 mg Rifampicin 50 mg and clofazimine 50 mg</td>
</tr>
<tr>
<td></td>
<td>Pediatric*</td>
<td>Rifampicin 600 mg Rifampicin 450 mg</td>
<td>Dapsone 100 mg Rifampicin 50 mg</td>
</tr>
<tr>
<td>Paucibacillary (TT, BT)</td>
<td>Adult Pediatric*</td>
<td>Rifampicin 600 mg Rifampicin 450 mg</td>
<td>Dapsone 100 mg Rifampicin 50 mg</td>
</tr>
<tr>
<td>Paucibacillary (single lesion)*</td>
<td>Rifampicin 600 mg and ofloxacin 400 mg and minocycline 100 mg</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*In children younger than 10 yr of age, dosages of multidrug therapy should be in mg/kg, not to exceed the adult daily maximum: rifampicin 10 mg/kg once monthly, dapsone 2 mg/kg/day, clofazimine 1 mg/kg on alternate days.

*Paucibacillary single lesion, one-time single-dose therapy may be less effective than the 6 mo paucibacillary multidrug therapy regimen.

BR, borderline; BL, borderline lepromatous; BT, borderline tuberculoid; LL, lepromatous; TT, tuberculoid.
prednisone 1 mg/kg/day orally (40-60 mg) with a slow taper (decreasing by 5 mg every 2-4 wk after evidence of improvement over 3-6 mo) is recommended in addition to standard MDT. If there is evidence of peripheral nerve deterioration, higher doses and longer tapers may be needed. Nerve function improves after corticosteroid treatment in 60-70% of patients who did not have preexisting neuritis. For type 2 reactions in patients older than 12 yr of age with systemic symptoms, thalidomide (100 mg/day for 4 days) is the drug of choice. Given the teratogenicity of thalidomide, the drug is only available from the Celgene Corporation under the System for Thalidomide Education and Prescribing Safety (STEPS) program (http://www.celgene.com/888-771-0141). In younger patients or pregnant females in whom thalidomide is contraindicated or in older patients with thalidomide-refractory ENL, corticosteroids may be used in daily doses of 1 mg/kg for 12 wk. Monitoring and management of the deleterious side effects of chronic corticosteroid therapy is challenging in chronic cases. Clofazimine (300 mg/day tapering to <100 mg/day for 12 mo) has been useful in managing patients with chronic ENL as well. Lucio’s phenomenon is managed with corticosteroids and treatment of underlying infections.

In regards to care of the exposed contacts of index patients, standard isolation precautions are recommended in the hospital setting. Hand hygiene is recommended for all people in contact with a patient with lepromatous leprosy. Disinfection of nasal secretions and handkerchiefs should be performed until treatment is established. Household contacts of patients, particularly patients with multibacillary disease, should be examined at baseline and then yearly for 5 yr. Any suspected or newly diagnosed case of leprosy in the United States should be reported to local and state public health departments, the Centers for Disease Control and Prevention, and the NHDP. In endemic countries, close monitoring of household contacts of HD patients, particularly those with multibacillary disease and either chemoprophylaxis or early treatment to contacts with evidence of early HD are effective control strategies. A single dose of bacilli Calmette-Guérin (BCG) vaccine gives variable protective efficacy against leprosy ranging from 28-80%; an additional dose demonstrated increased protection. A heat-killed leprosy vaccine, given as an immunotherapeutic adjuvant along with combination MDT, is approved for use in India. In nonendemic areas, disease presenting in the contacts of patients with HD is rare. Chemoprophylaxis after contact is not routinely recommended in the United States, but local public health departments should be contacted for consultation on individual cases. There are no leprosy vaccines available or recommended for use in the United States.

**LONG-TERM COMPLICATIONS**

Serious consequences of leprosy occur from the mycobacterium’s direct effect on skin and nerve involvement as well as from immune reactions. Indeed, leprosy is a leading cause of permanent physical disability among communicable diseases worldwide. The major chronic complications and deformities of leprosy are caused by segmental demyelination and permanent nerve injury. The prognosis for arresting progression of tissue and nerve damage is good if therapy is started early, but recovery of lost sensory and motor function is variable and frequently incomplete. Nerve impairment may be purely sensory, motor, or autonomic, or may be a combination. Sensory deficits lead to undetected trauma, ulceration, and osteomyelitis. Motor deficits result in muscle paralysis, atrophy, and limb deformities, especially of small muscles of the hand and foot (claw hand or foot, foot drop). Autonomic deficits can lead to skin drying and cracking. The most chronic residual deformity is that of an insensitive foot and requires frequent, routine surveillance of the plantar aspect of both feet. Painful neuropathy is also observed. Nerve function impairment can occur before diagnosis, during MDT, or after MDT and can develop during a reaction or without overt signs of skin or nerve inflammation (silent neuropathy). Patients at highest risk of nerve impairment are those with multibacillary leprosy and preexisting nerve damage. These patients should undergo regular monthly surveillance during therapy and for at least 2 yr from the time of diagnosis. From 3-10% of children will develop deformities, with the risk being 6.1 times higher in children with nerve enlargement as compared with children who do not have nerve enlargement. Other factors contributing to risk of deformities include increasing age of children, delay in accessing medical care, multiple skin lesions, multibacillary disease, smear positivity, multiple nerve involvement, and leprosy reaction at the time of presentation. An ophthalmologist should routinely examine all patients with HD because ocular complications, such as lagophthalmos and blindness, can occur. Given the proclivity for testicular invasion in multibacillary leprosy with resultant testicular dysfunction and infertility, males should be screened for elevated follicle-stimulating hormone or luteinizing hormone concentrations and decreased testosterone levels.

**PREVENTION**

Patient education is key to the successful management of HD. Patients should be encouraged to be compliant with MDT, educated about the signs and symptoms of neuritis, and advised to practice self-examination and seek prompt medical care should they develop neuritis or other symptoms of clinical exacerbations or leprosy reactions. Surgery and rehabilitation therapies such as physical and occupational therapy as well as counseling for the social and psychologic effects of the disease may also be required for optimal outcomes. Patient reassurance of the ability to lead a normal and productive social life and education of the community, including refuting myths and social stigma, are important parts of management.

*Bibliography is available at Expert Consult.*
Bibliography


Nontuberculous mycobacteria (NTM), also referred to as atypical mycobacteria or mycobacteria other than tuberculosis, are all members of the genus *Mycobacterium* other than *Mycobacterium tuberculosis* complex and *Mycobacterium leprae*. The NTM constitute a highly diverse group of bacteria that differ from *M. tuberculosis* complex bacteria in their pathogenicity, interhuman transmissibility, nutritional requirements, ability to produce pigments, enzymatic activity, and drug susceptibility. In contrast to the *M. tuberculosis* complex, NTM are acquired from environmental sources and not by person-to-person spread, although the latter is now under debate, especially in patients with cystic fibrosis. Their omnipresence in our environment implies that the clinical relevance of NTM isolation from clinical specimens is often unclear; a positive culture might reflect occasional presence or contamination rather than true NTM disease. NTM are associated with pediatric lymphadenitis, otomastoiditis, serious lung infections, and, albeit rarely, disseminated disease. Treatment is long-term and cumbersome and often requires adjunctive surgical intervention. Guidelines on diagnosis and treatment are provided by the American and British Thoracic Societies.

**ETIOLOGY**

NTM are ubiquitous in the environment all over the world, existing as saprophytes in soil and (tap) water, environmental niches that are the supposed sources of human infections. Owing to the introduction of molecular identification tools such as 16S recombinant DNA gene sequencing, the number of identified NTM species has grown to more than 150; the clinical relevance (i.e., the percentage of isolates that are causative agents of true NTM disease, rather than occasional presence) differs significantly by species.
**Mycobacterium avium** complex (MAC; i.e., *M. avium, Mycobacterium intracellulare* and several closely related but more rare species) and *Mycobacterium kansasii* are most often isolated from clinical samples, yet the isolation frequency of these species differs significantly by geographic area. MAC bacteria have been commonly isolated from natural and synthetic environments, and cases of MAC disease have been successfully linked to home exposure to shower and tap water. Although the designation *M. avium* suggests that human *M. avium* infections are acquired from birds (*avium* being Latin for “of birds”), molecular typing has established that *M. avium* strains that cause pediatric lymphadenitis and adult pulmonary disease represent the *M. avium hominissuis* subgrouping that is mainly found in humans and pigs and not in birds.

Some NTM have well-defined ecologic niches that help explain infection patterns. The natural reservoir for *Mycobacterium marinum* is fish and other cold-blooded animals, and the “fish-tank granuloma,” a localized skin infection caused by *M. marinum*, follows skin injury in an aquatic environment. *Mycobacterium fortuitum* complex bacteria and *Mycobacterium chelonae* are ubiquitous in water and have caused clusters of nosocomial surgical wound and venous catheter–related infections. *Mycobacterium ulcerans* is associated with severe, chronic skin infections (*Buruli ulcer disease*) and is endemic mainly in West Africa and Australia, although other foci exist. Its incidence is highest in children younger than 15 yr old. *ulcerans* had been commonly detected in environmental samples by polymerase chain reaction but was only recently recovered by culture from a Water Strider (*Gerris* sp.) from Benin.

**EPIDEMIOLOGY**

Humans are exposed to NTM on a daily basis. In rural counties in the United States, where *M. avium* is prevalent in swamps, the prevalence of asymptomatic infections with *M. avium* complex, as measured by skin test sensitization, approaches 70% by adulthood. Still, the incidence and prevalence of the various NTM disease types remain largely unknown, especially for pediatric NTM disease. In Australian children, the overall incidence of NTM infection is 0.84 per 100,000, with lymphadenitis accounting for two-thirds of cases. The incidence of pediatric NTM disease in the Netherlands is estimated at 0.77 infections per 100,000 children per year, with lymphadenitis making up 92% of all infections.

In comparison, estimations of the prevalence of NTM from respiratory samples in adults are 5-15 per 100,000 persons per year, with important differences between countries or regions. Because pulmonary NTM disease progresses slowly, over years rather than months, and usually takes several years to cure, the prevalence of pulmonary NTM disease is much higher than incidence rates would suggest. The paradigm that NTM disease is a rare entity limited to developed countries is changing. In recent studies in African countries with a high prevalence of HIV infection, it has been found that NTM might play a much larger role as a cause of tuberculosis-like disease of children and adults than previously assumed and thus confuse the diagnosis of tuberculosis.

Although it is generally believed that NTM infections are contracted from environmental sources, recent whole genome sequence analysis of *Mycobacterium abscessus* strains of patients in a cystic fibrosis clinic in the United Kingdom has raised the possibility of nosocomial transmission among patients with cystic fibrosis.

**PATHOGENESIS**

The histologic appearances of lesions caused by *M. tuberculosis* and NTM are often indistinguishable. The classic pathologic lesion consists of *caseating granulomas*. Compared to *M. tuberculosis* infections, NTM infections are more likely to result in granulomas that are noncaseating, ill defined (nonpalisading), irregular or serpiginous or even absent, with only chronic inflammatory changes observed. The histology likely reflects the immune status of the patient.

In patients with AIDS and disseminated NTM infection, the inflammatory reaction is usually scant and tissues are filled with large numbers of histiocytes packed with acid-fast bacilli. These disseminated NTM infections typically occur only after the number of CD4 T-lymphocytes has fallen below 50/μL, suggesting that specific T-cell products or activities are required for immunity to mycobacteria. The pivotal roles of interferon-γ, interleukin (IL)-12, and tumor necrosis factor-α in disease pathogenesis are demonstrated by the high incidence of mostly disseminated NTM disease in children with interferon-γ and IL-12 pathway deficiencies and in persons treated with agents that neutralize tumor necrosis factor-α.

Observed differences in pathogenicity, clinical relevance, and spectrum of clinical disease associated with the various NTM species emphasize the importance of bacterial factors in the pathogenesis of NTM disease, although exact virulence factors remain largely unknown.

**CLINICAL MANIFESTATIONS**

Lymphadenitis of the superior anterior cervical or submandibular lymph nodes is the most common manifestation of NTM infection in children (Table 217-1). Preauricular, posterior cervical, axillary, and inguinal nodes are involved occasionally. Lymphadenitis is most

<table>
<thead>
<tr>
<th>Table 217-1</th>
<th>Diseases Caused by Nontuberculous Mycobacterial Species</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CLINICAL DISEASE</strong></td>
<td><strong>COMMON SPECIES</strong></td>
</tr>
<tr>
<td>Cutaneous infection</td>
<td><em>Mycobacterium cheloneae, Mycobacterium fortuitum, Mycobacterium abscessus, Mycobacterium marinum</em></td>
</tr>
<tr>
<td>Lymphadenitis</td>
<td>MAC</td>
</tr>
<tr>
<td>Otitic infection</td>
<td><em>M. abscessus, MAC</em></td>
</tr>
<tr>
<td>Pulmonary infection</td>
<td>MAC, <em>M. kansasii, M. abscessus</em></td>
</tr>
<tr>
<td>Catheter-associated infection</td>
<td><em>M. cheloneae, M. fortuitum</em></td>
</tr>
<tr>
<td>Skeletal infection</td>
<td>MAC, <em>M. kansasii, M. fortuitum</em></td>
</tr>
<tr>
<td>Disseminated</td>
<td>MAC</td>
</tr>
</tbody>
</table>

*Endemic in West Africa and Australia, minor foci in East Asia and Latin America.
†Found primarily in Northern Europe.
MAC, *Mycobacterium avium* complex.
common in children 1-5 yr of age and has been related to soil exposure (e.g., playing in sandpits) and teething, although exact predisposing conditions have not been found. Given the constant environmental exposure to NTM, the occurrence of these infections might also reflect an atypical immune response of a subset of the infected children during or after their first contact with NTM.

Affected children usually lack constitutional symptoms and present with a unilateral subacute and slowly enlarging lymph node or group of closely approximated nodes >1.5 cm in diameter that are firm, painless, freely movable, and not erythematous (Fig. 217-1). The involved nodes occasionally resolve without treatment, but most undergo rapid suppuration after several weeks (Fig. 217-2). The center of the node becomes fluctuant, and the overlying skin becomes erythematous and thin. Eventually, the nodes rupture and form cutaneous sinus tracts that drain for months or years, resembling the classic scrofula of tuberculosis (Fig. 217-3).

In the United States and Western Europe, *M. avium* complex accounts for approximately 80% of NTM lymphadenitis in children. Birds are an unlikely source of these *M. avium* complex infections, as molecular typing has shown that the lymphadenitis-associated *M. avium* bacteria are of the human or porcine subtype rather than the bird type. *M. kansasii* accounts for most other cases of lymphadenitis in the United States. *Mycobacterium malmoense* and *Mycobacterium haemophilum* have also been described as causative agents of lymphadenitis. The former is only common in Northwestern Europe; for the latter, underestimation of its importance is likely because the bacteria require specific culture conditions (hemin-enriched media, low incubation temperatures). On the basis of polymerase chain reaction analysis of lymph node samples from lymphadenitis cases in the Netherlands, *M. haemophilum* is the second most common cause of this infection after *M. avium* complex. One study suggests that children with *M. avium* complex lymphadenitis are significantly younger than those infected by *M. haemophilum*, possibly related to age-specific environmental exposures.

**Cutaneous disease** caused by NTM is rare in children (see Table 217-1). Infection usually follows percutaneous inoculation with fresh or salt water contaminated by *M. marinum*. Within 2-6 wk after exposure, an erythematous papule develops at the site of minor abrasions on the elbows, knees, or feet (*swimming pool granuloma*) and on the hands and fingers of fish tank owners, mostly infected during tank cleaning (*fish tank granuloma*). These lesions are usually nontender and enlarge over 3-5 wk to form violaceous plaques. Nodules or pustules can develop and occasionally will ulcerate, resulting in a serosanguineous discharge. The lesions sometimes resemble sporotrichosis, with satellite lesions near the site of entry, extending along the superficial lymphatics. Lymphadenopathy is usually absent. Although most infections remain localized to skin, penetrating *M. marinum* infections can result in tenosynovitis, bursitis, osteomyelitis, or arthritis.

*M. ulcerans* infection is the third most common mycobacterial infection in immunocompetent patients, after *M. tuberculosis* and *M. leprae* infection, and causes cutaneous disease in children living in tropical regions of Africa, South America, Asia, and parts of Australia. In some communities in West Africa, up to 16% of people have been affected. Infection follows percutaneous inoculation from minor trauma, such as pricks and cuts from plants or insect bites. After an incubation period of approximately 3 mo, lesions appear as an erythematous nodule, most commonly on legs or arms. The lesion undergoes central necrosis and ulceration. The lesion, often called a *Buruli ulcer* after the region in Uganda where a large number of cases was reported, has a characteristic undermined edge, expands over several weeks, and can result in extensive, deep soft-tissue destruction or bone involvement. Lesions are typically painless, and constitutional symptoms are unusual. Lesions might heal slowly over 6-9 mo or might continue to spread, leading to deformities and contractures.

Skin and soft-tissue infections caused by rapidly growing mycobacteria, such as *M. fortuitum*, *M. chelonae*, or *M. abscessus*, are rare in children and usually follow percutaneous inoculation from puncture or surgical wounds, minor abrasions, or following tattooing. Clinical disease usually arises after a 4-6 wk incubation period and manifests as localized cellulitis, painful nodules, or a draining abscess. *M. haemophilum* can cause painful subcutaneous nodules, which often ulcerate and suppurate in immunocompromised patients, particularly after kidney transplantation.

NTM are an uncommon cause of *catheter-associated infections* but are becoming increasingly recognized in this respect. Infections caused
Infectious Diseases

There are indications that NTM infections in patients with cystic fibrosis further accelerate the decline in lung function; antimycobacterial therapy can result in weight gain and improved lung function in affected patients.

Disseminated disease is usually associated with *M. avium* complex infection and occurs in immunocompromised children. The first category of patients with disseminated disease includes persons with mutations in genes coding for the interferon-γ receptor (IFNGR) or the IL-12 receptor, or for IL-12 production. Patients with complete IFNGR deficiency have severe disease that is difficult to treat. Those with partial IFNGR deficiency or IL-12 pathway mutations have milder disease that can respond to interferon-γ and antimycobacterial therapy.

Multifocal osteomyelitis is particularly prevalent in persons with the IFNGR1 818del4 mutation. Recurrences, even years after a course of treatment, and multiple infections are well documented. The second

**Figure 217-4** Computed tomography images of the middle ear of a 6 yr old child infected with *Mycobacterium abscessus* demonstrating extensive bone destruction in the right mastoid and associated right-sided mucosal swelling. **A**, Bone tissue window setting. **B**, Soft-tissue window setting.

by *M. fortuitum, M. chelonae*, or *M. abscessus* can manifest as bacteremia or localized catheter tunnel infections.

Otomastoiditis, or chronic otitis media, is a rare extrapulmonary NTM disease type that specifically affects children with tympanostomy tubes and a history of topical antibiotic or steroid use. *M. abscessus* is the most common causative agent, followed by *M. avium* complex (see Table 217-1). Patients present with painless, chronic otorrhoea resistant to antibiotic therapy. CT imaging can reveal destruction of the mastoid bone with mucosal swelling (Fig. 217-4). Delayed or unsuccessful treatment can result in permanent hearing loss. In unusual circumstances, NTM causes other **bone and joint infections** that are indistinguishable from those produced by *M. tuberculosis* or other bacterial agents. Such infections usually result from operative incision or accidental puncture wounds. *M. fortuitum* infections from puncture wounds of the foot resemble infections caused by *Pseudomonas aeruginosa* and *Staphylococcus aureus*.

**Pulmonary infections** are the most common form of NTM illness in adults but are rare in children. *M. avium* complex bacteria, the most commonly identified organisms (see Table 217-1), are capable of causing acute pneumonitis, chronic cough, or wheezing associated with paratracheal or peribronchial lymphadenitis and airway compression in normal children. Associated constitutional symptoms such as fever, anorexia, and weight loss occur in 60% of these children. Chest radiographic findings are very similar to those for primary tuberculosis, with unilateral infiltrates and hilar lymphadenopathy (Fig. 217-5). Pleural effusion is uncommon. Rare cases of progression to endobronchial granulation tissue have been reported.

**Pulmonary infections** usually occur in adults with underlying chronic lung disease. The onset is insidious and consists of cough and fatigue, progressing to weight loss, night sweats, low-grade fever, and generalized malaise in severe cases. Thin-walled cavities with minimal surrounding parenchymal infiltrates are characteristic, but radiographic findings can resemble those of tuberculosis. A separate disease manifestation occurs in postmenopausal women and is radiologically characterized by bronchiectasis and nodular lesions, often affecting the middle lobe and lingula.

**Chronic pulmonary infections** specifically affect children with cystic fibrosis and are generally caused by *M. abscessus* and *M. avium* complex. *M. abscessus* primarily affects children, and *M. avium* complex is most common among adults. The percentage of patients with cystic fibrosis with at least 1 sputum culture positive for NTM is 6–8.1% overall and increases with age; in cystic fibrosis patients younger than 12 yr of age, a prevalence of 3.9% has been reported. The strong representation of *M. abscessus* in these patients is remarkable, because this bacterium is an uncommon isolate in other categories of patients.

There are indications that NTM infections in patients with cystic fibrosis further accelerate the decline in lung function; antimycobacterial therapy can result in weight gain and improved lung function in affected patients.

**Disseminated disease** is usually associated with *M. avium* complex infection and occurs in immunocompromised children. The first category of patients with disseminated disease includes persons with mutations in genes coding for the interferon-γ receptor (IFNGR) or the IL-12 receptor, or for IL-12 production. Patients with complete IFNGR deficiency have severe disease that is difficult to treat. Those with partial IFNGR deficiency or IL-12 pathway mutations have milder disease that can respond to interferon-γ and antimycobacterial therapy.

**Multifocal osteomyelitis** is particularly prevalent in persons with the IFNGR1 818del4 mutation. Recurrences, even years after a course of treatment, and multiple infections are well documented. The second
category of patients affected by disseminated disease is patients with AIDS. Disseminated NTM disease in patients with AIDS usually appears when CD4 cell counts are <50 cells/μL; in younger children (especially those <2 yr of age) these infections occur at higher CD4 cell counts. The most recent estimate of the incidence of disseminated NTM disease is 0.14-0.2 episodes per 100 person-years, a 10-fold decrease from its incidence before highly active antiretroviral therapy (HAART) was available.

Colonization of the respiratory or gastrointestinal tract probably precedes disseminated M. avium complex infections, but screening studies of respiratory secretions or stool samples are not useful to predict dissemination. Continuous high-grade bacteremia is common, and multiple organs are infected, most commonly including lymph nodes, liver, spleen, bone marrow, and gastrointestinal tract. Thyroid, pancreas, adrenal gland, kidney, muscle, and brain can also be involved. The most common signs and symptoms of disseminated M. avium complex infections in patients with AIDS are fever, night sweats, chills, anorexia, marked weight loss, wasting, weakness, generalized lymphadenopathy, and hepatosplenomegaly. Jaundice, elevated alkaline phosphatase or lactate dehydrogenase levels, anemia, and neutropenia can occur. Imaging studies usually demonstrate massive lymphadenopathy of hilar, mediastinal, mesenteric, or retroperitoneal nodes. The survival in children with AIDS has improved considerably with the availability of HAART therapy.

Disseminated disease in children without any apparent immunodeficiency is exceedingly rare.

**DIAGNOSIS**

For infections of lymph nodes, skin, bone, and soft tissues, isolation of the causative NTM bacteria by Mycobacterium culture, preferably with histologic confirmation of granulomatous inflammation, normally suffices for diagnosis. The differential diagnosis of NTM lymphadenitis includes acute bacterial lymphadenitis, tuberculosis, cat scratch disease (Bartonella henselae), mononucleosis, toxoplasmosis, brucellosis, tularemia, and malignancies, especially lymphomas. Differentiation between NTM and M. tuberculosis may be difficult, but children with NTM lymphadenitis usually have a Mantoux tuberculin skin test reaction of <15 mm induration, unilateral anterior cervical node involvement, a normal chest x-ray, and no history of exposure to adult tuberculosis. Definitive diagnosis requires excision of the involved nodes for culture and histology. Fine-needle aspiration for polymerase chain reaction and culture can enable earlier diagnosis, before excisional biopsy.

The diagnosis of pulmonary NTM infection in children is difficult because many species of NTM, including M. avium complex, are omnipresent in our environment and can contaminate, or occasionally be present in clinical samples. As a result, isolation of these bacteria from nonsterile specimens (respiratory and digestive tract) does not necessarily reflect true disease. To determine the clinical relevance of isolation of NTM, the diagnostic criteria of the American and British Thoracic Societies are an important support. These criteria take into consideration clinical features and radiologic, pathologic, and microbiologic findings. The hallmark of these criteria is the need for multiple positive cultures yielding the same NTM species to make a definitive diagnosis of pulmonary NTM disease. In children, definitive diagnosis often requires invasive procedures such as bronchoscopy and pulmonary or endobronchial biopsy; in patients with cystic fibrosis, more-aggressive sample pretreatment is necessary to prevent overgrowth by other species, especially Pseudomonas spp. The chance that isolation of NTM is clinically relevant differs significantly by species; some species are more likely causative agents of true pulmonary disease (M. avium, M. kansasii, M. abscessus, M. malmoense), whereas others are most likely contaminants (Mycobacterium gordoniae, M. fortuitum, M. chelonae).

Blood cultures are 90-95% sensitive in AIDS patients with disseminated infection. M. avium complex may be detected within 7-10 days of inoculation in nearly all patients by automated blood culture systems. In adults, liver biopsy cultures and stains have, in some studies, shown to be more sensitive than blood culture or bone marrow biopsy work-up. Commercially available DNA probes differentiate NTM from M. tuberculosis. If DNA probes cannot identify the causative mycobacteria, DNA sequencing of bacterial housekeeping genes will always yield a clue to the identity of these NTM. Identification of histiocytes containing numerous acid-fast bacilli from bone marrow and other biopsy tissues provides a rapid presumptive diagnosis of disseminated mycobacterial infection.

**TREATMENT**

Therapy for NTM infections is long-term and cumbersome; expert consultation is advised. Therapy involves medical, surgical, or combined treatment (see Chapter 214 and Table 214-3). Isolation of the infecting strain followed by drug-susceptibility testing is ideal, because it provides a baseline for drug susceptibility. Important discrepancies exist between in vitro drug susceptibility and in vivo response to treatment, explained in part by synergism, mainly among first-line antituberculosis drugs. In vitro, slow growers (M. kansasii, M. marinum, Mycobacterium xenopi, M. ulcersans, and M. malmoense) are usually susceptible to the first-line antituberculosis drugs rifampicin and ethambutol; M. avium complex bacteria are often resistant to these drugs alone but susceptible to the combination and have variable susceptibility to other antibiotics, most importantly the macrolides. Rapid growers (M. fortuitum, M. chelonae, M. abscessus) are highly resistant to antituberculosis drugs and often have inducible macrolide resistance mechanisms. Susceptibility to macrolides, aminoglycosides, carbapenems, tetracyclines, and glycyclines are most relevant for therapy guidance. In all NTM infections, multiple-drug therapy is essential to avoid development of resistance.

The preferred treatment of NTM lymphadenitis is complete surgical excision; clinical trials revealed that it is more effective than antibiotic treatment (see Table 214-3 in Chapter 214). Nodes should be removed while still firm and encapsulated. Excision is more difficult if extensive caseation with extension to surrounding tissue has occurred, and complications of facial nerve damage or recurrent infection are more likely in such cases. Incomplete surgical excision is not advised, because chronic drainage can develop. If there is concern for possible M. tuberculosis infection, therapy with isoniazid, rifampin, ethambutol, and pyrazinamide should be administered until cultures confirm the cause to be NTM (see Chapter 215). If for some reason surgery of NTM lymphadenitis cannot be performed, removal of infected tissue is incomplete, or recurrence or chronic drainage develops, a 3 mo trial of chemotherapy is warranted. Clarithromycin or azithromycin combined with rifabutin or ethambutol are the most commonly reported therapy regimens (see Table 214-3 in Chapter 214). In selected cases, a wait-and-see approach can be chosen, as the disease can resolve spontaneously.

Posttraumatic cutaneous NTM lesions in immunocompetent patients usually heal spontaneously after incision and drainage without other therapy (see Table 214-3 in Chapter 214). M. marinum is susceptible to rifampin, amikacin, ethambutol, sulfonamides, trimethoprim-sulfamethoxazole, and tetracycline. Therapy with a combination of these drugs, particularly clarithromycin and ethambutol, may be given for until 1 month after the lesion has disappeared. Corticosteroid injections should not be used. Superficial infections with M. fortuitum or M. chelonae usually resolve after surgical incision and open drainage, but deep-seated or cather-related infections require removal of infected central lines and therapy with parenteral amikacin plus cefoxitin, ciprofloxacin, or clarithromycin.

Some localized forms of M. ulcersans skin disease (Buruli ulcer) can heal spontaneously; for most forms, excisional surgery with primary closure or skin grafting is recommended. Provisional guidelines by the World Health Organization recommend treatment with rifampin and streptomycin, with or without surgery. Currently, all-oral regimens of rifampicin and fluoroquinolones or macrolides are tested in clinical trials. In clinical experience, a drug treatment duration of 8 wk generally leads to low recurrence levels. Physiotherapy after surgery is essential to prevent contractures and functional disabilities.

**Pulmonary infections** should be treated initially with isoniazid, rifampin, ethambutol, and pyrazinamide pending culture identification
and drug-susceptibility testing. For slow-growing NTM, a combination of rifampin or rifabutin, ethambutol, and clarithromycin is recommended; exceptions are *M. kansasii*, for which a regimen of isoniazid, rifampicin, and ethambutol is advised, and *M. simiae*, for which no effective regimen is known and regimens are usually designed on the basis of in vitro drug susceptibilities. After culture conversion, treatment should be continued for at least 1 yr. For pulmonary disease caused by rapidly growing NTM, a combination of macrolides, fluoroquinolones, aminoglycosides, cefoxitin, and carbapenems is the optimal therapy; 3 or 4 drug regimens are selected on the basis of drug-susceptibility testing results. In patients with cystic fibrosis, there may be a role for inhaled antibiotics.

Patients with disseminated *M. avium* complex and IL-12 pathway defects or IFNGR deficiency should be treated for at least 12 mo with clarithromycin or azithromycin combined with rifampin or rifabutin and ethambutol. In vitro susceptibility testing for clarithromycin is important to guide therapy. Once the clinical illness has resolved, lifelong daily prophylaxis with azithromycin or clarithromycin is advisable to prevent recurrent disease. The use of interferon adjunctive therapy is determined by the specific genetic defect.

In children with *AIDS*, prophylaxis with azithromycin or clarithromycin is indicated to prevent infection with *M. avium* complex. Although few pediatric studies exist, the U.S. Public Health Service recommends either azithromycin (20 mg/kg once weekly PO; maximum: 1,200 mg/dose) or clarithromycin (7.5 mg/kg/dose twice daily PO; maximum: 500 mg/dose) for HIV-infected children with significant immune deficiency as defined by the CD4 count (children ≥6 yr, CD4 count <50/µL; 2-6 yr, CD4 count <75/µL; 1-2 yr, CD4 count <100/µL; <1 yr, CD4 count <750/µL). Prophylaxis may be safely discontinued in children older than 2 yr of age receiving stable HAART for longer than 6 mo and experiencing sustained (>3 mo) CD4 cell recovery well above the age-specific target for initiation of prophylaxis: >100 cells/µL for children ≥6 yr of age and >200 cells/µL for children 2-5 yr of age. For children younger than 2 yr of age, no specific recommendations for discontinuing MAC prophylaxis exist.

*Bibliography is available at Expert Consult.*
Bibliography


Syphilis is a chronic systemic sexually transmitted infection that can be easily treated if detected early but manifests with protean clinical symptoms and significant morbidity if left unchecked.

**ETIOLOGY**

Syphilis is caused by *Treponema pallidum*, a delicate, tightly spiraled, motile spirochete with finely tapered ends belonging to the family Spirochaetaceae. The pathogenic members of this genus include *T. pallidum* subsp. *pallidum* (venereal syphilis), *T. pallidum* subsp. *pertenue* (yaws), *T. pallidum* subsp. *endemicum* (bejel or endemic syphilis), and *T. pallidum* subsp. *carateum* (pinta).

Because these microorganisms stain poorly and are below the detection limits of conventional light microscopy, detection in clinical specimens requires dark-field or phase contrast microscopy or direct immunofluorescent staining. *T. pallidum* cannot be cultured in vitro.

**EPIDEMIOLOGY**

In addition to presentation at sexually transmitted disease clinics, patients with syphilis are increasingly seen by primary care providers in private practice settings. Two forms of syphilis occur in children and adolescents.

*Acquired syphilis* is transmitted almost exclusively by sexual contact, including vaginal, anal, and oral exposure. Less-common modes of transmission include transfusion of contaminated blood or direct contact with infected tissues. After an epidemic resurgence of primary and secondary syphilis in the United States that peaked in 1989, the annual rate declined 90% by 2000. The total number of cases of primary and secondary syphilis has subsequently increased since 2000, particularly among men who have sex with men. Despite a decrease among women for almost a decade, their rates increased every year from 2004-2008. Cases of congenital syphilis rose in the same time period, but have fallen from 2008 through 2011, reflecting the slight decrease among women (*Fig. 218-1*). Rates in the southern United States, in some urban areas, and among non-Hispanic blacks remain disproportionately high.

*Congenital syphilis* results from transplacental transmission of spirochetes or during birth by contact with infectious lesions. Women with primary and secondary syphilis and spirochetemia are more likely to transmit infection to the fetus than are women with latent infection. Transmission can occur at any stage of pregnancy, resulting in early fetal loss, preterm or low birthweight infants, stillbirths, neonatal deaths, or infants born with congenital disease. The incidence of congenital infection in offspring of untreated or inadequately treated infected women remains highest during the 1st 4 yr after acquisition of primary infection, secondary infection, and early latent disease. Maternal factors associated with congenital syphilis are limited access to healthcare, late or no prenatal care, drug use, multiple sex partners, unprotected sexual contact, work in the sex trade, and inadequate treatment of syphilis during pregnancy (*Fig. 218-2*). Confirmed cases of both acquired and congenital syphilis must be reported to the local health department.

**CLINICAL MANIFESTATIONS AND LABORATORY FINDINGS**

Many persons infected with syphilis are asymptomatic for years or do not recognize the early signs of disease or seek treatment. The Centers for Disease Control and Prevention (CDC) recommends selective testing of adolescents, based on lesions or risk factors (those with other sexually transmitted diseases, men who have sex with men, women with other indications, and women who are pregnant). The risk factors include having other risk factors for sexually transmitted infections, such as having an untreated or inadequately treated infection, having multiple sex partners, or not using condoms. The disease is characterized by primary lesion(s), secondary lesions, and tertiary lesions, which are divided into late latent (2-10 years), early latent (1-2 years), and tertiary syphilis. The late latent stage is characterized by neurosyphilis, which is associated with meningovascular disease, myelopathy, spinal cord compression, or other conditions. Congenital syphilis can be diagnosed ante partum or post partum. Ante partum epidemiologic screening (by maternal serum screening with a specific test for syphilis) is recommended for all pregnant women at ≥16 weeks of gestation. In cases of congenital syphilis, serological testing for infection is performed on the affected infant. Laboratory findings include a positive antibody test for syphilis, a positive VDRL test, and a positive桩herel test.
Syphilis

Syphilis is a chronic infection caused by the spirochete Treponema pallidum. It affects various body systems, including the cardiovascular, central nervous, and gastrointestinal systems. The disease is characterized by three stages: primary, secondary, and tertiary syphilis.

**Primary Syphilis**

This stage occurs after the initial infection and is characterized by the development of a chancre (a painless ulcer) at the site of entry, usually the genitals. Other symptoms may include fever, headache, and malaise. Untreated primary syphilis can progress to secondary syphilis.

**Secondary Syphilis**

Secondary syphilis usually develops 6-12 weeks after the primary stage and is marked by various cutaneous and mucous membrane lesions. These include a generalized nonpruritic maculopapular rash, which can be confused with cellulitis or eczema, generalized lymphadenopathy, and a florid infectious like illness with low-grade fever, headache, malaise, anorexia, weight loss, sore throat, myalgia, arthralgia, and generalized lymphadenopathy.

**Tertiary Syphilis**

This stage of syphilis occurs months to years after the initial infection and can involve the cardiovascular, central nervous, and gastrointestinal systems. The clinical course of syphilis and its tissue manifestations reflect the immunopathobiology of the host humoral and delayed-type hypersensitivity responses.

**Congenital Infection**

Untreated syphilis during pregnancy has a vertical transmission rate approaching 100%, with profound effects on pregnancy outcome. Fetal or perinatal death occurs in 40% of affected infants. Premature delivery can also occur. Neonates can also be infected at delivery by contact with an active genital lesion. Most infected infants are asymptomatic at birth and are identified only by routine prenatal screening. In the absence of treatment, symptoms develop within weeks or months. Among infants symptomatic at birth or in the 1st few mo of life, manifestations have traditionally been divided into early and late stages. All stages of congenital syphilis are characterized by a vasculitis, with progression to necrosis and fibrosis. The early signs appear during the 1st 2 yr of life, and the late signs appear gradually during the 1st 2 decades. Early manifestations vary and involve multiple organ systems, resulting from transplacental spirochtemia and are analogous to the secondary stage of acquired syphilis (Table 218-1).

**Figure 218-2** Diagnoses of congenital syphilis in the United States, 2002. (From Centers for Disease Control and Prevention [CDC]: Primary and secondary syphilis—United States, 2002, MMWR Morb Mortal Wkly Rep 52:1117–1120, 2003.)

**Figure 218-3** Secondary syphilis. Ham-colored palmar macules on an adolescent with secondary syphilis. (From Weston WL, Lane AT, Morelli JG: Color textbook of pediatric dermatology, ed 3. St. Louis, 2002, Mosby.)

Untreated patients develop manifestations of **secondary syphilis** related to spirochetemia 2-10 wk after the chancre heals. Manifestations of secondary syphilis include a generalized nonpruritic maculopapular rash, notably involving the palms and soles (Fig. 218-3). Pustular lesions can also develop. Condylomata lata, gray-white to erythematous wart-like plaques, can occur in moist areas around the anus and vagina, and white plaques (mucous patches) may be found in mucous membranes. Secondary syphilis should be considered in the differential diagnosis of virtually any rash of unknown etiology. A **flu-like illness** with low-grade fever, headache, malaise, anorexia, weight loss, sore throat, myalgia, arthralgia, and generalized lymphadenopathy is often present. Renal, hepatic, and ophthalmologic manifestations may be present. Meningitis occurs in 30% of patients with secondary syphilis and is characterized by cerebrospinal fluid (CSF) pleocytosis and elevated protein level. Patients with meningitis might not show neurologic symptoms. Even without treatment, secondary infection becomes **latent** within 1-2 mo after onset of rash. Relapses with secondary manifestations can occur during the 1st yr of latency (the early latent period). **Late syphilis** follows and may be either asymptomatic (late latent) or symptomatic (tertiary). Tertiary disease follows in about one-third of untreated cases and is marked by neurologic, cardiovascular, and **gummatous lesions** (nonsuppurative granulomas of the skin, bone, and liver, resulting from the host cytotoxic T-cell response). The clinical course of syphilis and its tissue manifestations reflect the immunopathobiology of the host humoral and delayed-type hypersensitivity responses.

**Figure 218-4** Condylomata lat a (Treponema pallidum).

**Figure 218-5** Condylomata lata (Treponema pallidum).

Bone involvement is common. Roentgenographic abnormalities include Wimberger lines (metaphyseal demineralization of the medial aspect of the proximal tibia), multiple sites of osteochondritis at the wrists, elbows, ankles, and knees, and periostitis of the long bones and rarely the skull. The osteochondritis is painful, often resulting in irritability and refusal to move the involved extremity (pseudoparalysis of Parrot).

Congenital neurosyphilis is often asymptomatic in the neonatal period although CSF abnormalities can occur even in such infants.
Failure to thrive, chorioretinitis, nephritis, and nephrotic syndrome can also be seen. Manifestations of renal involvement include hypertension, hematuria, proteinuria, hypoproteinemia, hypercholesterolemia, and hypocomplementemia, probably related to glomerular deposition of circulating immune complexes. Less-common clinical manifestations of early congenital syphilis include gastroenteritis, peritonitis, pancreatitis, pneumonia, eye involvement (glaucoma and chorioretinitis), nonimmune hydrops, and testicular masses.

Late manifestations (children >2 yr of age) are rarely seen in developed countries. These result primarily from chronic granulomatous inflammation of bone, teeth, and central nervous system and are summarized in Table 218-1. Skeletal changes are caused by persistent or recurrent periostitis and associated thickening of the involved bone. Dental abnormalities, such as Hutchinson teeth (Fig. 218-7), are common. Defects in enamel formation lead to repeated caries and eventual tooth destruction. Saddle nose (Fig. 218-8) is a depression of the nasal root and may be associated with a perforated nasal septum.

Other late manifestations of congenital syphilis can manifest as hypersensitivity phenomena. These include unilateral or bilateral interstitial keratitis and the Clutton joint (see Table 218-1). Other common ocular manifestations include choroiditis, retinitis, vascular occlusion, and optic atrophy. Soft-tissue gummas (identical to those of acquired disease) and paroxysmal cold hemoglobinuria are rare hypersensitivity phenomena.

### Table 218-1 Late Manifestations of Congenital Syphilis

<table>
<thead>
<tr>
<th>SYMPTOM/SIGN</th>
<th>DESCRIPTION/COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olympian brow</td>
<td>Bony prominence of the forehead caused by persistent or recurrent periostitis</td>
</tr>
<tr>
<td>Clavicular or Higoumenakia sign</td>
<td>Unilateral or bilateral thickening of the sternoclavicular third of the clavicle</td>
</tr>
<tr>
<td>Saber shins</td>
<td>Anterior bowing of the midportion of the tibia</td>
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<tr>
<td>Scaphoid scapula</td>
<td>Convexity along the medial border of the scapula</td>
</tr>
<tr>
<td>Hutchinson teeth</td>
<td>Peg-shaped upper central incisors; they erupt during 6th yr of life with abnormal enamel, resulting in a notch along the biting surface</td>
</tr>
<tr>
<td>Mulberry molars</td>
<td>Abnormal 1st lower (6 yr) molars characterized by small biting surface and excessive number of cusps</td>
</tr>
<tr>
<td>Saddle nose*</td>
<td>Depression of the nasal root, a result of syphilitic rhinitis destroying adjacent bone and cartilage</td>
</tr>
<tr>
<td>Rhagades</td>
<td>Linear scars that extend in a spoke-like pattern from previous mucocutaneous fissures of the mouth, anus, and genitalia</td>
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<tr>
<td>Juvenile paresis</td>
<td>Latent meningo-vascular infection; it is rare and typically occurs during adolescence with behavioral changes, focal seizures, or loss of intellectual function</td>
</tr>
<tr>
<td>Juvenile tabs</td>
<td>Rare spinal cord involvement and cardiovascular involvement with aortitis</td>
</tr>
<tr>
<td>Hutchinson triad</td>
<td>Hutchinson teeth, interstitial keratitis, and 8th nerve deafness</td>
</tr>
<tr>
<td>Clutton joint</td>
<td>Unilateral or bilateral painless joint swelling (usually involving knees) from synovitis with sterile synovial fluid; spontaneous remission usually occurs after several weeks</td>
</tr>
<tr>
<td>Interstitial keratitis</td>
<td>Manifests with intense photophobia and lacrimation, followed within weeks or months by corneal opacification and complete blindness</td>
</tr>
<tr>
<td>8th nerve deafness</td>
<td>May be unilateral or bilateral, appears at any age, manifests initially as vertigo and high-tone hearing loss, and progresses to permanent deafness</td>
</tr>
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</table>

*A perforated nasal septum may be an associated abnormality.

Figure 218-4 Osteochondritis and periostitis in a newborn with congenital syphilis.

**DIAGNOSIS**

Fundamental limitations of the currently available tests for syphilis are vexing, but results must always be interpreted in the context of patient history and physical examination. Physicians should treat presumptively when syphilis is suspected by clinical and epidemiologic data. Diagnosis of primary syphilis is confirmed when *T. pallidum* is demonstrated by darkfield microscopy or direct fluorescent antibody testing on specimens from skin lesions, placenta, or umbilical cord. Nucleic acid–based amplification assays, such as polymerase chain reaction, are not commercially available. Despite the absence of a true gold standard serologic assay, serologic testing for syphilis remains the principal means for diagnosis and traditionally involves screening.
with a nontreponemal test followed by a confirmatory treponemal test (Fig. 218-9A).

The Venereal Disease Research Laboratory (VDRL) and rapid plasma reagin (RPR) tests are sensitive nontreponemal tests that detect antibodies against phospholipid antigens on the treponeme surface that crossreact with cardiolipin-lecithin-cholesterol antigens of damaged host cells. The quantitative results of these tests are helpful both in screening and in monitoring therapy. Titers increase with active disease, including treatment failure or reinfection, and decline with adequate treatment (Fig. 218-10). Nontreponemal tests usually become nonreactive within 1 yr of adequate therapy for primary syphilis and within 2 yr of adequate treatment for secondary disease. Uncommonly some patients become serofast (nontreponemal titers persisting at low levels for long periods). In congenital infection, these tests become nonreactive within a few months after adequate treatment. Certain conditions such as infectious mononucleosis and other viral infections, autoimmune diseases, and pregnancy can give false-positive VDRL results. False-positive results are less common with the use of purified cardiolipin-lecithin-cholesterol antigen. All pregnant women should be screened early in pregnancy and at delivery. All positive maternal serologic tests for syphilis, regardless of titer, necessitate thorough investigation. Antibody excess can give a false-negative reading unless the serum is diluted (prozone effect). False-negative results can also occur in early primary syphilis, in latent syphilis of long duration, and in late congenital syphilis.

Treponemal tests traditionally are used to confirm diagnosis and measure specific T. pallidum antibodies (immunoglobulin [Ig] G, IgM and IgA), which appear earlier than nontreponemal antibodies. These treponemal tests include the T. pallidum particle agglutination test, the T. pallidum hemagglutination assay, and the fluorescent treponemal antibody absorption test. Treponemal antibody titers become positive soon after initial infection and usually remain positive for life, even with adequate therapy (see Fig. 218-10). These antibody titers do not correlate with disease activity. Traditionally they are useful for diagnosis of a first episode of syphilis and for distinguishing false-positive results of nontreponemal antibody tests but cannot accurately identify length of time of infection, response to therapy, or reinfection.

There is limited crossreactivity of treponemal antibody tests with other spirochetes, including the causative organisms of Lyme disease.
Infectious Diseases

Figure 218-9 A, Traditional laboratory testing algorithm for syphilis. B, CDC-recommended algorithm for reverse sequence syphilis screening (treponemal test screening followed by nontreponemal test confirmation). Despite these recommendations for reverse sequence screening, the CDC continues to recommend the traditional algorithm with reactive nontreponemal tests confirmed by treponemal testing. EIA/CIA, enzyme immunoassay/chemiluminescence immunoassay; FTA-ABS, fluorescent treponemal antibody absorption; RPR, rapid plasma reagin; TP-PA, Treponema pallidum particle agglutination; VDRL, Venereal Disease Research Laboratory. *If nontreponemal test is positive qualitatively, a titer is then quantitated. †If incubating or primary syphilis is suspected, treat with benzathine penicillin G 2.4 million units intramuscularly in a single dose. ‡Evaluate clinically, determine whether treated for syphilis in the past, assess risk for infection, and administer therapy according to CDC’s 2010 STD Treatment Guidelines (available at http://www.cdc.gov/std/treatment/2010). ¶If at risk for syphilis, repeat RPR in several weeks. (A based on data from Workowski KA, Berman S; Centers for Disease Control and Prevention [CDC]: Sexually transmitted diseases treatment guidelines, 2010. MMWR Recomm Rep 59[RR-12]:1-110, 26-29, 2010; B from Centers for Disease Control and Prevention [CDC]: Discordant results from reverse sequence syphilis screening—five laboratories, United States, 2006-2010. MMWR Morb Mortal Wkly Rep 60(5):133-137, 2011.)

Figure 218-10 Common patterns of serologic reactivity in syphilis patients. FTA-Abs, fluorescent treponemal antibody absorption (test); RPR, rapid plasma reagin (test); TPHA, Treponema pallidum hemagglutination assay; VDRL, Venereal Disease Research Laboratory (test). (From Peeling RW, Ye H: Diagnostic tools for preventing and managing maternal and congenital syphilis: an overview, Bull World Health Organ 82:439—446, 2004.)
Syphilis

Enzyme immunoassays and chemiluminescence immunoassays to detect treponemal IgG and IgM have been developed. These assays have increased sensitivity and are amenable to automation and high volume use. Such assays should allow developing countries quality screening programs at the point-of-service because the World Health Organization currently relies on syndromic management of sexually transmitted infections, where patients are treated for all likely causes of their constellation of signs and symptoms. In the United States, use of enzyme immunoassays has confounded screening because it switches the traditional algorithm: the treponemal-specific testing is done before the nontreponemal testing. Because the former remain positive for life, clinical and epidemiologic data are required to provide clear guidelines to distinguish cured disease, early syphilis, untreated late latent disease, and true false-positive tests. The benefits of reverse screening are increased detection of transmissible early syphilis and of late latent disease to afford monitoring for tertiary disease. Although the CDC continues to recommend the traditional screen (see Fig. 218-9A), they have provided guidelines for interpretation of the reverse screening algorithm (see Fig. 218-9B). Interpretation of nontreponemal and treponemal serologic tests in the newborn can be confounded by maternal IgG antibodies transferred to the fetus. Passively acquired antibody is suggested by a neonatal titer at least 4-fold (i.e., a 2 tube dilution) less than the maternal titer. This conclusion can be verified by gradual decline in antibody in the infant, usually becoming undetectable by 3-6 mo of age.

The diagnosis of neurosyphilis remains difficult but is often established by demonstrating pleocytosis and increased protein in the CSF and a positive CSF VDRL test along with neurologic symptoms. The CSF VDRL test is specific but relatively insensitive (22-69%) for neurosyphilis. CSF polymerase chain reaction (polymerase chain reaction) and IgM immunoblot tests are under development to assist in diagnosis of neurosyphilis.

**Figure 218-11** Algorithm for evaluating and treating infants born to mothers with reactive serologic tests for syphilis. (From American Academy of Pediatrics: Red book: 2012 report of the Committee on Infectious Diseases, ed 29. Elk Grove Village, IL, 2012, American Academy of Pediatrics, Fig. 3-7, p. 695.)
Part XVII  Infectious Diseases

**Table 218-2** Clues That Suggest a Diagnosis of Congenital Syphilis*

<table>
<thead>
<tr>
<th>EPIDEMIOLOGIC BACKGROUND</th>
<th>CLINICAL FINDINGS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Untreated early syphilis in the mother</td>
<td>Osteochondritis, periosisitis</td>
</tr>
<tr>
<td>Untreated latent syphilis in the mother</td>
<td>Snuffles, hemorrhagic rhinitis</td>
</tr>
<tr>
<td>An untreated mother who has contact with a known syphilitic during pregnancy</td>
<td>Condylomata lata</td>
</tr>
<tr>
<td>Mother treated for syphilis during pregnancy with a drug other than penicillin</td>
<td>Bullous lesions, palmar or plantar rash</td>
</tr>
<tr>
<td>Mother treated for syphilis during pregnancy without follow-up to demonstrate 4-fold change in titer</td>
<td>Mucous patches</td>
</tr>
<tr>
<td>Mother coinfected with HIV</td>
<td>Hepatomegaly, splenomegaly</td>
</tr>
<tr>
<td></td>
<td>Jaundice</td>
</tr>
<tr>
<td></td>
<td>Nonimmune hydrops fetalis</td>
</tr>
<tr>
<td></td>
<td>Generalized lymphadenopathy</td>
</tr>
<tr>
<td></td>
<td>Central nervous system signs; elevated cell count or protein in cerebrospinal fluid</td>
</tr>
<tr>
<td></td>
<td>Hemolytic anemia, diffuse intravascular coagulation, thrombocytopenia</td>
</tr>
<tr>
<td></td>
<td>Pneumonitis</td>
</tr>
<tr>
<td></td>
<td>Nephrotic syndrome</td>
</tr>
<tr>
<td></td>
<td>Placental villitis or vasculitis (unexplained enlarged placenta)</td>
</tr>
<tr>
<td></td>
<td>Intrauterine growth restriction</td>
</tr>
</tbody>
</table>

*Arranged in decreasing order of confidence of diagnosis.


**Table 218-3** Recommended Management of Neonates (≤1 Month of Age) Born to Mothers with Serologic Tests for Syphilis

<table>
<thead>
<tr>
<th>CLINICAL STATUS</th>
<th>EVALUATION (IN ADDITION TO PHYSICAL EXAMINATION AND QUANTITATIVE NONTREPONEMAL TESTING)</th>
<th>ANTIMICROBIAL THERAPY*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proven or highly probable disease†</td>
<td>CSF analysis for VDRL, cell count, and protein CBC and platelet count</td>
<td>Aqueous crystalline penicillin G, 100,000-150,000 units/kg/day, administered as 50,000 units/kg/dose IV q12hr during the 1st 7 days of life and 18 hr thereafter for a total of 10 days or Penicillin G procaine, 50,000 units/kg/day IM in a single dose × 10 days</td>
</tr>
<tr>
<td>NORMAL PHYSICAL EXAMINATION AND SERUM QUANTITATIVE NONTREPONEMAL TITER ≤4 TIMES THE MATERNAL TITER:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(a) (i) Mother was not treated or inadequately treated or has no documented treatment; (ii) mother was treated with erythromycin or other nonpenicillin regimen; (iii) mother received treatment ≥4 wk before delivery; (iv) maternal evidence of reinfection or relapse (&lt;4-fold decrease in titers)</td>
<td>CSF analysis for VDRL, cell count, and protein† CBC and platelet count† Long-bone radiography‡</td>
<td>Aqueous crystalline penicillin G IV × 10 days† or Penicillin G procaine† 50,000 units/kg IM in a single dose × 10 days or Penicillin G benzathine† 50,000 units/kg IM in a single dose‡ Clinical, serologic follow-up, and penicillin G benzathine 50,000 units/kg IM in a single dose‡</td>
</tr>
<tr>
<td>(b) (i) Adequate maternal therapy given &gt;4 wk before delivery; (ii) mother has no evidence of reinfection or relapse</td>
<td>None</td>
<td>None‡</td>
</tr>
<tr>
<td>(c) Adequate therapy before pregnancy and mother’s nontreponemal serologic titer remained low and stable during pregnancy and at delivery</td>
<td>None</td>
<td>None‡</td>
</tr>
</tbody>
</table>

*If more than 1 day of therapy is missed, the entire course should be restarted.
†Abnormal physical examination, serum quantitative nontreponemal titer that is 4-fold greater than the mother’s titer, or positive result of darkfield or fluorescent antibody test of body fluid(s).
‡Penicillin G benzathine and penicillin G procaine are approved for IM administration only.
§A complete evaluation (CSF analysis, bone radiography, CBC) is not necessary if 10 days of parenteral therapy is administered, but it may be useful to support a diagnosis of congenital syphilis. If a single dose of penicillin G benzathine is used, then the infant must be evaluated fully, results of the full evaluation must be normal, and follow-up must be certain. If any part of the infant’s evaluation is abnormal or not performed or if the CSF analysis is uninterpretable, the 10-day course of penicillin is required.
¶Some experts would treat with penicillin G benzathine, 50,000 units/kg, as a single IM injection, if follow-up is uncertain.
‖Some experts would not treat the infant but would provide close serologic follow-up.


evaluating and managing asymptomatic infants who are considered at risk for congenital syphilis because the maternal nontreponemal and treponemal serology is positive. Internationally adopted children should also be screened.

Diagnosis of neurosyphilis in the newborn with syphilitic infection is confounded by poor sensitivity of the CSF VDRL test in this age group and lack of CSF abnormalities. A positive CSF VDRL test in a newborn warrants treatment for neurosyphilis, even though it might reflect passive transfer of antibodies from serum to CSF. It is now accepted that all infants with a presumptive diagnosis of congenital syphilis should be treated with regimens effective for neurosyphilis because central nervous system involvement cannot be reliably excluded. Diagnosis of syphilis beyond early infancy should lead to consideration of possible child abuse.
Acquired Syphilis
Primary, secondary, and early latent disease is treated with a single dose of benzathine penicillin G (50,000 units/kg IM, maximum 2.4 million units). Persons with late latent or tertiary disease require 3 doses at 1 wk intervals. Nonpregnant penicillin-allergic patients without neurosyphilis may be treated with either doxycycline (100 mg PO twice daily for 2 wk) or tetracycline (500 mg PO 4 times daily for 2 wk). Emerging azalide and macrolide resistance has been documented in several U.S. cities, compromising the effective use of these antibiotics. Careful serologic follow-up is always necessary. Less than a 4-fold decline in titer reflects treatment failure.

The CDC recommends that all persons with syphilis be tested for HIV. Patients coinfected with HIV are at increased risk for neurologic complications and higher rates of treatment failure. CDC guidelines recommend the same treatment of primary and secondary syphilis as for patients who are not infected with HIV, but some experts recommend 3 weekly doses of benzathine penicillin G. HIV-infected patients with late latent syphilis or latent syphilis of unknown duration should have a CSF evaluation for neurosyphilis before treatment.

Sex partners of infected persons of any stage should be evaluated and treated. Persons exposed for 90 days or less preceding diagnosis in a sex partner should be treated presumptively even if seronegative. Persons exposed for more than 90 days before the diagnosis in a sex partner should be treated if seropositive or if serologic tests are not available. Follow-up serology should be performed on treated patients to establish adequacy of therapy, and all patients should be tested for other sexually transmitted diseases, including HIV.

### Table 218-4

**Recommended Treatment for Syphilis in Patients Older Than 1 Month of Age**

<table>
<thead>
<tr>
<th>STATUS</th>
<th>CHILDREN</th>
<th>ADULTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congenital syphilis</td>
<td>Aqueous crystalline penicillin G 200,000-300,000 units/kg/day IV administered as 50,000 units/kg q4-6hr x 10 days*</td>
<td>Penicillin G benzathine**, 2.4 million units IM in a single dose or If allergic to penicillin and not pregnant, doxycycline 100 mg PO bid x 14 days or Tetracycline 500 mg PO qid x 14 days</td>
</tr>
<tr>
<td>Primary, secondary, and early latent syphilis1</td>
<td>Penicillin G benzathine†, 50,000 units/kg, IM, up to the adult dose of 2.4 million units in a single dose</td>
<td>Penicillin G benzathine†, 7.2 million units total administered as 3 doses of 2.4 million units IM, each at 1 wk intervals or If allergic to penicillin and not pregnant, doxycycline 100 mg PO bid x 4 wk or Tetracycline 500 mg PO qid x 4 wk</td>
</tr>
<tr>
<td>Late latent syphilis1 or syphilis of unknown duration</td>
<td>Penicillin G benzathine†, 50,000 units/kg IM up to the adult dose of 2.4 million units, administered as 3 single doses at 1 wk intervals (total 150,000 units/kg, up to the adult dose of 7.2 million units)</td>
<td>Penicillin G benzathine†, 7.2 million units total administered as 3 doses of 2.4 million units IM, each at 1 wk intervals or If allergic to penicillin and not pregnant, doxycycline 100 mg PO bid x 4 wk or Tetracycline 500 mg PO qid x 4 wk</td>
</tr>
<tr>
<td>Tertiary syphilis</td>
<td>Penicillin G benzathine†, 7.2 million units total, administered as 3 doses of 2.4 million units IM at 1 wk intervals If allergic to penicillin and not pregnant, same as for late latent syphilis</td>
<td>Aqueous crystalline penicillin G 18-24 million units/day administered as 3-4 million units IV q4hr x 10-14 days or Penicillin G procaine, 2.4 million units IM once daily plus probenecid 500 mg PO qid, both x 10-14 days</td>
</tr>
<tr>
<td>Neurosyphilis2</td>
<td>Aqueous crystalline penicillin G 200,000-300,000 units/kg/day q4-6hr x 10-14 days in doses not to exceed the adult dose</td>
<td>Aqueous crystalline penicillin G 18-24 million units/day administered as 3-4 million units IV q4hr x 10-14 days or Penicillin G procaine, 2.4 million units IM once daily plus probenecid 500 mg PO qid, both x 10-14 days</td>
</tr>
</tbody>
</table>

*If the patient has no clinical manifestations of disease, the CSF examination is normal, and the CSF VDRL result is negative, some experts would treat with up to 3 weekly doses of penicillin G benzathine 50,000 units/kg IM. Some experts also suggest giving these patients a single dose of penicillin G benzathine 50,000 units/kg IM after the 10-day course of IV aqueous penicillin.

1Early latent syphilis is defined as being acquired within the preceding year.

2Penicillin G benzathine and penicillin G procaine are approved for IM administration only.

3Late latent syphilis is defined as syphilis beyond 1 year’s duration.

4Patients who are allergic to penicillin should be desensitized.

5Some experts administer penicillin G benzathine 2.4 million units IM, once per week for up to 3 wk after completion of these neurosyphilis treatment regimens.

6CSF, cerebrospinal fluid; VDRL, Venereal Disease Research Laboratory.

Syphilis in Pregnancy
When clinical or serologic findings suggest active infection or when diagnosis of active syphilis cannot be excluded with certainty, treatment is indicated. Patients should be treated with the penicillin regimen appropriate for the woman's stage of syphilis. Women who have been adequately treated in the past do not require additional therapy unless quantitative serology suggests evidence of reinfection (4-fold elevation in titer). Doxycycline and tetracycline should not be administered during pregnancy, and macrolides do not effectively prevent fetal infection. Pregnant patients who are allergic to penicillin should be desensitized and treated with penicillin.

Bibliography is available at Expert Consult.

Congenital Syphilis
Adequate maternal therapy should eliminate the risk for congenital syphilis. All infants born to mothers with syphilis should be followed until nontreponemal serology is negative. The infant should be treated if there is any uncertainty about the adequacy of maternal treatment. Any infant at risk of congenital syphilis should be evaluated for HIV.

Congenital syphilis is treated with aqueous penicillin G (100,000-150,000 units/kg/24 hr divided every 12 hr IV for the 1st wk of life, and every 8 hr thereafter) or procaine penicillin G (50,000 units/kg IM once daily) given for 10 days. Both penicillin regimens are recognized as adequate therapy for congenital syphilis, but higher concentrations of penicillin are achieved in the CSF of infants treated with intravenous aqueous penicillin G than in those treated with intramuscular procaine penicillin. Treated infants should be followed every 2-3 mo to confirm at least a 4-fold decrease in nontreponemal titers. Treated infants with congenital neurosyphilis should undergo clinical and CSF evaluation at 6-mo intervals until CSF is normal. In a very-low-risk neonate who is asymptomatic and whose mother was treated appropriately, without evidence of relapse or reinfection, but with a low and stable VDRL titer (serofast), no evaluation is necessary. Some specialists would treat such an infant with a single dose of benzathine penicillin G 50,000 units/kg IM.

PREVENTION
Syphilis, including congenital syphilis, is a reportable disease in all 50 states and the District of Columbia. Testing is indicated at any time for persons with suspicious lesions, a history of recent sexual exposure to a person with syphilis, or diagnosis of another sexually transmitted infection, including HIV infection. Timely treatment lessens risk of community spread. Vaccine prevention remains elusive, confounded by the treponeme's ability to evade the immune system.

Congenital Syphilis
Congenital syphilis is a preventable disease, with primary prevention tied to prevention of syphilis in women of childbearing age and secondary prevention being early diagnosis and prompt treatment of women and their partners. Routine prenatal screening for syphilis remains the most important factor in identifying infants at risk for developing congenital syphilis. Screening all women at the beginning of prenatal care is an evidence-based standard of care and legally required in all states. In pregnant women without optimal prenatal care, serologic screening for syphilis should be performed at the time pregnancy is diagnosed. Any woman who is delivered of a stillborn infant at 20 wk or fewer of gestation should be tested for syphilis. In communities and populations with a high prevalence of syphilis and in patients at high risk, testing should be performed at least 2 additional times: at the beginning of the 3rd trimester (28 wk) and at delivery. Some states mandate repeat testing at delivery for all women, underscoring the importance of preventive screening. Women at high risk for syphilis should be screened even more frequently, either monthly or pragmatically in the case of inconsistent prenatal care, at every medical encounter because they can have repeat infections during pregnancy or reinfection late in pregnancy. Follow-up serologic testing of all treated women should be done after treatment to document titer decline, relapse, or reinfection.

No newborn should leave the hospital without the maternal serologic status having been determined at least once during pregnancy. In states conducting newborn screening for syphilis, both the mother's and infant's serologic results should be known before discharge. In addition, all previously uninvestigated infants of an infected mother should be screened.
Nonvenereal treponemal infections—yaws, bejel (endemic syphilis), and pinta—are caused by different subspecies of *Treponema pallidum* and occur in tropical and subtropical areas. The causative agents of nonvenereal treponematoses—*T. pallidum pertenue*, *T. pallidum subspecies endemicum*, and *Treponema carateum*—cannot be distinguished from *T. pallidum pallidum* by morphologic or serologic tests.

In general, nonvenereal treponematoses have prominent cutaneous manifestations and relapsing courses, as in venereal syphilis, but they are not found in urban centers, they are not sexually transmitted, and they are not congenitally acquired. Transmission is primarily through body contact, poor hygiene, crowded conditions, and poor access to healthcare. Children also serve as the primary reservoirs for these organisms, spreading infection via skin-to-skin and skin-to-mucous membrane contact, and possibly via fomites as well.

Penicillin remains the treatment of choice for syphilis and nonvenereal treponemal infections.

**Bibliography is available at Expert Consult.**

### 219.1 Yaws (*Treponema pertenue*)

Yaws is the most prevalent nonvenereal treponematosis. The causative agent, *Treponema pertenue* bears very close genomic resemblance to *T. pallidum*. The *T. pallidum pertenue* genome was sequenced in 2010 and compared with *T. pallidum pallidum* strains; the overall sequence identity between the 2 genomes was 99.8%. It is a contagious, chronic, relapsing infection involving the skin and bony structures caused by the spirochete *T. pertenue*, which is identical to *T. pallidum* microscopically and serologically. It occurs in tropical regions with heavy rainfall and annual temperatures ≥27°C (80°F). Almost all cases occur in children in tropical and subtropical countries. It is also referred to as “framboesia,” “pian,” “parangi,” and “bouba.” A high percentage of the population is infected in endemic areas.

*T. pertenue* is transmitted by direct contact from an infected lesion through a skin abrasion or laceration. Transmission is facilitated by overcrowding and poor personal hygiene in the rain forest areas of the world. Yaws predominantly affects children, with approximately 75% of cases being reported in children younger than 15 yr of age. This population also constitutes the reservoir for disease transmission. The initial papular lesion, which constitutes **primary yaws**, also described as the “mother yaws,” occurs 2-8 wk after inoculation. This lesion typically involves the buttocks or lower extremities. The papule develops
Bibliography


into a raised, raspberry-like papilloma and is often accompanied by regional lymphadenopathy. The skin pathology is very similar to that of venereal syphilis, consisting of epidermal hyperplasia and papilomatosis. Healing of the mother yaw leaves a hypopigmented scar. The secondary stage lesions can erupt anywhere on the body before or after the healing of the mother yaw and may be accompanied by lymphadenopathy, anorexia, and malaise. Multiple cutaneous lesions (daughter yaws, pianomas, or frambesias) appear, spread diffusely, ulcerate, and are covered by exudates containing treponemes. Secondary lesions heal without scarring. Recurrent lesions are common within 5 yr after the primary lesion.

The lesions are often associated with bone pain resulting from underlying periostitis or osteomyelitis, especially of the fingers, nose, and tibia. The initial period of clinical activity is followed by a 5-10 yr period of latency. The appearance of tertiary stage lesions develops in approximately 10% of infected patients, with onset typically at puberty with solitary and destructive lesions. These lesions occur as painful papillomas on the hands and feet, gummatus skin ulcerations, or osteitis. Bony destruction and deformity, juxtaarticular nodules, depigmentation, and painful hyperkeratosis (“dry crab yaws”) of the palms and soles are common. Approximately 10% of patients may progress and develop tertiary stage lesions after 5 yr or more of untreated infection, although this is now rare.

The diagnosis is based on the characteristic clinical manifestations of the disease in an endemic area. Darkfield examination of cutaneous lesions for treponemes and both treponemal and nontreponemal serologic tests for syphilis, which are positive because of crossreactivity, are used to confirm the diagnosis. The nonselective agglutination tests such as the rapid plasma reagin and Veneral Diseases Research Laboratory tests are positive in untreated cases, and these tests can be used for test of cure, because they revert to negative following treatment. However, the treponemal tests (T. pallidum hemagglutination assay, T. pallidum particle agglutination assay, and fluorescent treponemal antibody absorption) are more specific and remain positive for life. New immunochromatographic test strips that can be applied for testing both whole blood and serum were developed. These are simple, cheap, and easy to use and do not require refrigeration.

Differential diagnosis includes other conditions with similar cutaneous manifestations such as eczema, psoriasis, excreted chronic scabies, tinea, leishmaniasis, tropical ulcer cutaneous mycoses, and verrucae. Involvement of the bone may mimic dactylitis that is commonly associated with sickle cell disease.

Treatment of yaws consists of a single dose of the long-acting benzathine penicillin G (1.2 million units IM for adults and 0.6 million units for children <10 yr) for index patients and all contacts. Patients allergic to penicillin may be treated with erythromycin or tetracycline at appropriate doses for venereal syphilis (see Chapter 218). One oral dose of azithromycin (30 mg/kg; maximum: 2 g) is as effective as benzathine penicillin. Treatment cures the lesions of active yaws, renders them noninfectious, and prevents relapse. Family members, contacts, and patients with latent infection should receive the same dose as those with active disease. Eradication of yaws from some endemic areas has been accomplished by treating the entire population with penicillin or azithromycin.

219.2 Bejel (Endemic Syphilis; Treponema pallidum endemicum)

Bejel, or endemic syphilis, affects children in remote rural communities living in poor hygienic conditions. Bejel, unlike yaws, can occur in temperate as well as dry, hot climates. Infection with T. pallidum subspecies endemicum follows penetration of the spirochete through traumatized skin or mucous membranes. In experimental infections, a primary papule forms at the inoculation site after an incubation period of 3 wk. A primary lesion is almost never visualized in human infections; however, primary ulcers have been described surrounding the nipples of nursing mothers with infected children.

The clinical manifestations of the secondary stage typically occur 3-6 mo after inoculation and are confined to the skin and mucous membranes. They consist of highly infectious mucous patches on the oral mucosa and condyloma-like lesions on the moist areas of the body, especially the axilla and anus. These mucocutaneous lesions resolve spontaneously over a period of several months, but recurrences are common. The secondary stage is followed by a variable latency period before the onset of late or tertiary bejel. The tertiary stage can occur as early as 6 mo or as late as several years after resolution of initial symptoms. The lesions in the tertiary stage are identical to those of yaws and include gumma formation in skin, subcutaneous tissue, and bone, resulting in painful destructive ulcerations, swelling, and deformity.

The diagnosis is based on the characteristic clinical manifestations of the disease in an endemic area. Dark-field examination of cutaneous lesions for treponemes and both treponemal and nontreponemal serologic tests for syphilis, which are positive because of crossreactivity, are used to confirm the diagnosis.

Differentiation from genital syphilis is extremely difficult in an endemic area. Bejel is distinguished by the absence of a primary chancre and lack of involvement of the central nervous system and cardiovascular system during the late stage.

Treatment of early infection consists of a single dose of benzathine penicillin G (1.2 million units IM for adults and 0.6 million units for children <10 yr). Late infection is treated with 3 injections of the same dosage at intervals of 7 days. Patients allergic to penicillin may be treated with erythromycin or tetracycline.

219.3 Pinta (Treponema carateum)

Stephen K. Obaro and H. Dele Davies

Pinta is a chronic, nonvenereally transmitted infection caused by T. pallidum subsp. carateum, a spirochete morphologically and serologically indistinguishable from other human treponemes. This is perhaps the mildest of the nonvenereal treponematoses. The disease is endemic in Mexico, Central America, South America, and parts of the West Indies and largely affects children younger than 15 yr of age.

Infection follows direct inoculation of the treponeme through abraded skin. After a variable incubation period of days, the primary lesion appears at the inoculation site as a small asymptomatic erythematos papule resembling localized psoriasis or eczema. The regional lymph nodes are often enlarged. Spirochetes can be visualized on darkfield examination of skin scrapings or from biopsy of the involved lymph nodes. After a period of enlargement, the primary lesion disappears. Unlike primary yaws, the lesion does not ulcerate but can expand with central depigmented resolution. Secondary lesions follow within 6-8 mo and consist of small macules and papules on the face, scalp, and other sun-exposed portions of the body. These pigmented, highly infectious lesions are scaly and nonpruritic and can coalesce to form large plaque-like elevations resembling psoriasis. In the late or tertiary stage, atrophic and depigmented lesions develop on the hands, wrists, ankles, feet, face, and scalp. Hyperkeratosis of palms and soles is uncommon.

The diagnosis is based on the characteristic clinical manifestations of the disease in an endemic area. Darkfield examination of cutaneous lesions for treponemes and both treponemal and nontreponemal serologic tests for syphilis, which are positive because of crossreactivity, are used to confirm the diagnosis.

Treatment consists of a single dose of benzathine penicillin G (1.2 million units IM for adults and 0.6 million units for children <10 yr). Tetracycline and erythromycin are alternatives for patients allergic to penicillin. Treatment campaigns and improvement of standards of living are necessary for reduction and elimination of disease.

Bibliography is available at Expert Consult.
Bibliography
Leptospirosis is a common and widespread zoonosis caused by aerobic, motile spirochetes of the genus *Leptospira*.

**ETIOLOGY**
Pathogenic leptospires belong to 9 species, which include more than 300 antigenically distinct serovars. A single serovar can produce a variety of distinct syndromes, and a single clinical manifestation may be caused by multiple serotypes.

**EPIDEMIOLOGY**
Most human cases of leptospirosis occur in tropical and subtropical countries, but the distribution is worldwide. Leptospires survive for days to weeks in warm and damp environmental conditions, including water and moist soil. In the United States, Hawaii reports approximately 50% of all cases, with Pacific coastal states and Southern states having higher incidence than the remainder of the country. Leptospires infect many species of animals, including rats, mice, moles, livestock (such as cattle, goats, sheep, horses, and pigs), wild mammals like raccoons or opossums, and domestic dogs. Infected animals excrete leptospires in their urine for prolonged periods. Worldwide, most human cases result from occupational exposure to water or soil contaminated with rat urine; however, the major animal reservoir in the United States is the dog. Groups at high risk for leptospirosis include persons exposed occupationally or recreationally to contaminated soil, water, or infected animals, including agricultural workers, veterinarians, abattoir workers, meat inspectors, rodent control workers, laboratory workers, and military personnel. Transmission via animal bites and direct contact from person to person has been rarely reported.

**PATHOLOGY AND PATHOGENESIS**
Leptospires enter humans through mucous membranes (primarily eyes, nose, and mouth) or abraded skin or by ingestion of contaminated water. After penetration, they circulate in the bloodstream to all body organs, causing endothelial lining damage of small blood vessels resulting in permanent visual impairment. Central nervous system symptoms usually resolve spontaneously within 1 wk, with almost no mortality.

**Infectious Diseases**

**CLINICAL MANIFESTATIONS**
The spectrum of human leptospirosis ranges from asymptomatic infection (most cases) to severe disease with multiorgan dysfunction and death. The onset is usually abrupt, and the illness tends to follow a biphasic course (Fig. 220-1). After an incubation period of 7-12 days, there is an initial or septicemic phase lasting 2-7 days, during which leptospires can be isolated from the blood, cerebrospinal fluid (CSF), and other tissues. This phase may be followed by a brief period of well-being before onset of a second symptomatic immune or leptospiruric phase. This phase is associated with the appearance of circulating immunoglobulin M antibody, disappearance of organisms from the blood and CSF, and appearance of signs and symptoms associated with localization of leptospires in the tissues. Despite the presence of circulating antibody, leptospires can persist in the kidney, urine, and aqueous humor. The immune phase can last for several weeks. Symptomatic infection may be anicteric or icteric.

**Anicteric Leptospirosis**
The septicemic phase of anicteric leptospirosis has an abrupt onset with flu-like symptoms of fever, shaking chills, lethargy, severe headache, malaise, nausea, vomiting, and severe debilitating myalgia most prominent in the lower extremities, lumbosacral spine, and abdomen. Bradycardia and hypotension can occur, but circulatory collapse is uncommon. Conjunctival suffusion with photophobia and orbital pain (in the absence of chemosis and purulent exudate), generalized lymphadenopathy, and hepatosplenomegaly may also be present. A transient (<24 hr) erythematous maculopapular, urticarial, petechial, purpuric, or desquamating rash occurs in 10% of cases. Rarer manifestations include pharyngitis, pneumonitis, arthritis, carditis, cholecystitis, and orchitis. The second or immune phase can follow a brief asymptomatic interlude and is characterized by recurrence of fever and aseptic meningitis. Although 80% of infected children have abnormal CSF profiles, only 50% have clinical meningeal manifestations. CSF abnormalities include a modest elevation in pressure, pleocytosis with early polymorphonuclear leukocytosis followed by mononuclear predominance rarely exceeding 500 cells/µL, normal or slightly elevated protein levels, and normal glucose values. Encephalitis, cranial and peripheral neuropathies, papilledema, and paralysis are uncommon. A self-limited unilateral or bilateral uveitis can occur during this phase, rarely resulting in permanent visual impairment. Central nervous system symptoms usually resolve spontaneously within 1 wk, with almost no mortality.

**Icteric Leptospirosis (Weil Syndrome)**
Weil syndrome is a rare (<1% of cases) severe form of leptospirosis seen more commonly in adults (>30 yr) than in children. The initial manifestations are similar to those described for anicteric leptospirosis. The immune phase, however, is characterized by jaundice, renal failure, thrombocytopenia, and, in fulminant cases, hemorrhage and cardiovascular collapse. Hepatic involvement leads to right upper quadrant pain, hepatomegaly, direct and indirect hyperbilirubinemia, and death. The onset is usually abrupt, and the illness tends to follow a biphasic course (Fig. 220-1). After an incubation period of 7-12 days, there is an initial or septicemic phase lasting 2-7 days, during which leptospires can be isolated from the blood, cerebrospinal fluid (CSF), and other tissues. This phase may be followed by a brief period of well-being before onset of a second symptomatic immune or leptospiruric phase. This phase is associated with the appearance of circulating immunoglobulin M antibody, disappearance of organisms from the blood and CSF, and appearance of signs and symptoms associated with localization of leptospires in the tissues. Despite the presence of circulating antibody, leptospires can persist in the kidney, urine, and aqueous humor. The immune phase can last for several weeks. Symptomatic infection may be anicteric or icteric.

**Figure 220-1 Stages of anicteric and icteric leptospirosis.**
modestly elevated serum levels of hepatic enzymes. Liver function usually returns to normal after recovery. All patients have abnormal findings on urinalysis (hematuria, proteinuria, and casts), and anemia is common, often associated with oliguria or anuria. Acute kidney failure occurs in 16-40% of cases and is the principal cause of death. Abnormal electrocardiograms are present in 90% of cases, but congestive heart failure is uncommon. Transient thrombocytopenia occurs in >50% of cases. Rarely, hemorrhagic manifestations occur, including epistaxis, hemoptysis, and pulmonary, gastrointestinal, and adrenal hemorrhage. The mortality rate is 5-15%.

**DIAGNOSIS**
Leptospirosis should be considered in the differential diagnosis of acute flu-like febrile illnesses with a history of direct contact with animals or with soil or water contaminated with animal urine. This disease may be difficult to distinguish clinically from dengue or malaria.

The diagnosis is most often confirmed by serologic testing and less often by isolation of the infecting organism from clinical specimens. The “gold-standard” diagnostic method is the **microscopic agglutination test**, a serogroup-specific assay using live antigen suspension of leptospiral serovars and dark-field microscopy for agglutination. A 4-fold or greater increase in titer in paired sera confirms the diagnosis. Agglutinins usually appear by the 12th day of illness and reach a maximum titer by the 3rd wk. Low titers can persist for years. Approximately 10% of infected persons do not have detectable agglutinins, presumably because available antisera do not identify all *Leptospira* serotypes. Additionally, enzyme-linked immunosorbent assay methods, latex agglutination, and immunochromatography are commercially available, and DNA polymerase chain reaction diagnostics have been developed but are not in common clinical usage. Phase-contrast and darkfield microscopy are insensitive for spirochete detection, but organisms may be identified using Warthin-Starry silver stain or fluorescent antibody staining of tissue or body fluids. Unlike other pathogenic spirochetes, leptospires can be recovered from the blood or CSF during the 1st 10 days of illness and from urine after the 2nd wk by repeated culture of small inoculum (i.e., 1 drop of blood or CSF in 5 mL of medium) on commercially available selective media. However, the inoculum in clinical specimens is small, and growth can take up to 13 wk.

**TREATMENT**
Despite in vitro sensitivity of *Leptospira* to penicillin and tetracyclines, the effectiveness of these antibiotics in treating human leptospirosis is unclear because of the naturally high spontaneous recovery rates. Some studies suggest that initiation of treatment before the 7th day shortens the clinical course and decreases the severity of the infection; thus treatment with penicillin G, cefotaxime, or doxycycline (in children ≥8 yr of age) should be instituted early when the diagnosis is suspected. Parenteral penicillin G (6-8 million units/m²/day divided every 4 hr IV for 7 days) is recommended, with doxycycline 2 mg/kg/day divided in 2 doses with maximum of 100 mg twice daily as an alternative for patients allergic to penicillin. Azithromycin was evaluated in a randomized, nonblinded clinical trial and shown to be as effective as doxycycline and can be used as an alternative in patients for whom doxycycline is contraindicated. In severe illness, supportive care with specific attention given to cardiopulmonary status, renal function, coagulopathy, and fluid and electrolyte balance is warranted.

**PREVENTION**
Prevention of human leptospirosis infection is facilitated by instituting rodent control measures and avoiding contaminated water and soil. Immunization of livestock and domestic dogs is recommended as a means of reducing animal reservoirs. Attempts at a human vaccine have been challenging, and the diversity of *Leptospira* serovars and their geographic distributions are important considerations in vaccine design. Protective clothing (i.e., boots, gloves, and goggles) should be worn by persons at risk for occupational exposure to, or handling of infected urine. Leptospirosis was successfully prevented in American soldiers stationed in the tropics by administering prophylactic doxycycline (200 mg PO once a week). This approach may be similarly effective for travelers to highly endemic areas for short periods; however, there are no specific pediatric data to support any prophylaxis regimen.

*Bibliography is available at Expert Consult.*
**Bibliography**


Relapsing fever is characterized by recurring fevers and "flu-like symptoms" such as headaches, myalgia, arthralgia, and rigors.

**ETIOLOGY**

It is an arthropod (lice or ticks)-transmitted infection caused by spirochetes of the genus *Borrelia*.

**Louse-borne (epidemic) relapsing fever** is caused by *Borrelia recurrentis* and is transmitted from person to person by *Pediculus humanus*, the human body louse. Human infection occurs as a result of crushing lice during scratching, facilitating entry of infected hemolymph through abraded or normal skin or mucous membranes.

**Tick-borne (endemic) relapsing fever** is caused by several species of *Borrelia* and is transmitted to humans by *Ornithodoros* ticks. *Borrelia hermsii* and *Borrelia turicatae* are the common species in the western United States, while *Borrelia dugeisi* is the major cause of disease in Mexico and Central America. Human infection occurs when saliva, coxal fluid, or excrement is released by the tick during feeding, thereby permitting spirochetes to penetrate the skin and mucous membranes.

**EPIDEMIOLOGY**

Louse-borne relapsing fever tends to occur in epidemics associated with war, poverty, famine, and poor personal hygiene, often in association with typhus. This form of relapsing fever is no longer seen in the United States but is endemic in parts of East Africa. Up to 20.5% of all unexplained fever in the horn of Africa, including northwestern Morocco where the population traditionally lives in mud huts, is caused by tickborne relapsing fever using 16sRNA polymerase chain reaction assays for molecular detection, making this the most common cause of bacterial infections.

*Ornithodoros* ticks, which transmit endemic relapsing fever and are distributed worldwide, including in the western United States, prefer warm, humid environments and high altitudes, and are found in rodent burrows, caves, and other nesting sites (Fig. 221-1). Rodents (e.g., squirrels and chipmunks) are the principal reservoirs. Infected ticks gain access to human dwellings on the rodent host. Human contact is often unnoticed because these soft ticks have a painless bite, and detach immediately after a short blood meal.

**PATHOLOGY AND PATHOGENESIS**

Relapsing fever is cyclical because the *Borrelia* organisms undergo antigenic (phase) variation. Multiple variants evolve simultaneously during the first relapse, with 1 type becoming predominant. Spirochetes isolated during the primary febrile episode differ antigenically from those recovered during a subsequent relapse. During febrile episodes, spirochetes enter the bloodstream, induce the development of specific immunoglobulins M and G antibodies, and undergo
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Cases of Tick-borne Relapsing Fever - United States, 1990-2011

![Cases of Tick-borne Relapsing Fever - United States, 1990-2011](image)

- Each dot, placed randomly within the county of exposure (where known), represents one case.
- Each dot, placed randomly within the county of residence, represents one case.

**Figure 221-1** Cases of tickborne relapsing fever—United States, 1990-2011. During the years 1990-2011, 483 cases of tickborne relapsing fever were reported in the western United States, with infections being transmitted most frequently in California, Washington, and Colorado. (From Centers for Disease Control and Prevention [CDC]: Tick-borne relapsing fever: distribution. Available at: http://www.cdc.gov/relapsing-fever/distribution)

Agglutination, immobilization, lysis, and phagocytosis. During remission, *Borrelia* spirochetes may remain in the bloodstream, but spirochetemia is insufficient to produce symptoms. The number of relapses in untreated patients depends on the number of antigenic variants of the infecting strain.

**CLINICAL MANIFESTATIONS**

Relapsing fever is characterized by febrile episodes lasting 2-9 days, separated by afebrile intervals of 2-7 days. Louse-borne disease has an incubation period of 2-14 days, longer periods of pyrexia, fewer relapses, and longer remission periods than tickborne disease. The incubation period of tickborne disease is usually 7 days (range: 2-9 days). Each form of relapsing fever is characterized by sudden onset of high fever, lethargy, headache, photophobia, nausea, vomiting, myalgia, and arthralgia. Additional symptoms may appear later and include abdominal pain, a productive cough, mild respiratory distress and bleeding manifestations, including epistaxis, hemoptysis, hematuria, and hematemesis. During the end of the primary febrile episode, a diffuse, erythematous, macular, or petechial rash lasting up to 2 days may develop over the trunk and shoulders. There may also be lymphadenopathy, pneumonia, and splenomegaly. Hepatic tenderness associated with hepatomegaly is a common sign, with jaundice in half of affected children. Central nervous system manifestations include lethargy, stupor, meningoencephalitis, and cranial nerve paralysis and may be the principal feature of late relapses in tickborne disease. Severe manifestations include myocarditis, hepatic failure, and disseminated intravascular coagulopathy.

The initial symptomatic period characteristically ends with a crisis in 2-9 days, marked by abrupt diaphoresis, hypothermia, hypotension, bradycardia, profound muscle weakness, and prostration. In untreated patients, the first relapse occurs within 1 wk, followed by usually 3 but up to 10 relapses, with symptoms during each relapse becoming milder and shorter as the afebrile remission period lengthens.

**DIAGNOSIS**

Diagnosis depends on demonstration of spirochetes by darkfield microscopy or in thin or thick blood smears stained with Giemsa or Wright stain and by blood culture (Fig. 221-2). During afebrile remissions, spirochetes are not found in the blood. Serologic tests have not been standardized, are generally not available, and produce crossreactions with other spirochetes, including *Borrelia burgdorferi*, the agent of Lyme disease. Molecular methods, including nested polymerase chain reaction or 16sRNA polymerase chain reaction assays, have been used for detection of tickborne and louse-borne recurrent fever and have been found to have improved sensitivity and specificity compared to blood smears. However, these assays are not yet routinely available for commercial use.

**TREATMENT**

Oral or parenteral tetracycline or doxycycline is the drug of choice for louse-borne and tickborne relapsing fever. For children older than 8 yr of age and young adults, tetracycline 500 mg PO every 6 hr or doxycycline 100 mg PO every 12 hr for 10 days is effective. Single-dose treatment with tetracycline (500 mg PO) or erythromycin is efficacious in adults, but experience in children is limited. In children younger than 8 yr of age, erythromycin (50 mg/kg/day divided every 6 hr PO) for a total of 10 days is recommended. Penicillin and chloramphenicol are also effective.

Resolution of each febrile episode either by natural crisis or as a result of antimicrobial treatment is often accompanied by the Jarisch-Herxheimer reaction, which is caused by massive antigen release. Corticosteroid or antipyretic pretreatment do not prevent the reaction.

**PROGNOSIS**

With adequate therapy, the mortality rate for relapsing fever is <5%. A majority of patients recover from their illness with or without treatment after the appearance of anti-*Borrelia* antibodies, which agglutinate, kill, or opsonize the spirochete. However, pregnant women and their neonates are at increased risk for tickborne recurrent fever-associated complications, including adult respiratory distress syndrome, Jarisch-Herxheimer reaction, and precipitous or premature delivery. Neonates have up to a 33% case-fatality rate.

**PREVENTION**

No vaccine is available. Disease control requires avoidance or elimination of the arthropod vectors. In epidemics of louse-borne disease, good personal hygiene and delousing of persons, dwellings, and clothing with commercially available insecticides can prevent dissemination. The risk for tickborne disease can be minimized in endemic areas by maintaining rodent-free dwellings. Giving prophylactic doxycycline for 4 days after a tick bite may prevent tickborne relapsing fever caused by *Borrelia persica*.

Bibliography is available at Expert Consult.
Bibliography


Lyme disease is the most common vector-borne disease in the United States and is an important public health problem.

**ETIOLOGY**
Lyme disease is caused by the spirochete *Borrelia burgdorferi* sensu lato (broad sense). In North America, *B. burgdorferi* sensu stricto (strict sense) causes virtually all cases, and in Europe, the species *Borrelia afzelii* and *Borrelia garinii* also cause disease. The 3 major outer-surface proteins, called OspA, OspB, and OspC (which are highly charged basic proteins of molecular weights of about 31, 34, and 23 kDa, respectively), and the 41 kDa flagellar protein are important targets for the immune response. Differences in the molecular structure of the different species are associated with differences in the clinical manifestations of Lyme borreliosis in Europe and the United States. These differences include the greater incidence of radiculoneuritis in Europe.

**EPIDEMIOLOGY**
Lyme disease has been reported from more than 50 countries. In the United States, more than 30,000 cases were reported in 2011; however, because of incomplete reporting of cases, it is estimated that the actual number of cases is much higher. In 2011, 93% of cases occurred in 13 states: Connecticut, Delaware, Maine, Maryland, Massachusetts, Minnesota, New Hampshire, New Jersey, New York, Pennsylvania, Vermont, Virginia, and Wisconsin (Fig. 222-1). In endemic areas, the reported annual incidence ranges from 20-100 cases per 100,000 population, although this figure may be as high as 600 cases per 100,000 population in hyperendemic areas. In Europe, most cases occur in the Scandinavian countries and in central Europe, especially Germany, Austria, and Switzerland. The reported incidence is highest among children 5-9 yr of age, with a second peak of disease activity in middle-age adults. In the United States, Lyme disease is diagnosed in boys slightly more often than in girls, and 94% of patients are of European descent. Early Lyme disease (described later) usually occurs from spring to early fall, corresponding to deer tick activity. Late disease (chiefly arthritis) occurs year round. Among adults, outdoor occupation and leisure activities are risk factors; for children, location of residence in an endemic area is the most important risk for infection.

**TRANSMISSION**
Lyme disease is a zoonosis caused by the transmission of *B. burgdorferi* to humans through the bite of an infected tick of the *Ixodes* genus. In the eastern and midwestern United States, the vector is *Ixodes scapularis*, the black-legged tick that is commonly known as the deer tick, which is responsible for most cases of Lyme disease in the United States. The vector on the Pacific Coast is *Ixodes pacificus*, the western black-legged tick. *Ixodes* ticks have a 2 yr, 3 stage life cycle. The larvae hatch in the early summer and are usually uninfected with *B. burgdorferi*. The tick can become infected at any stage of its life cycle by feeding on a host, usually a small mammal such as the white-footed mouse (*Peromyscus leucopus*), which is a natural reservoir for *B. burgdorferi*. The larvae overwinter and emerge the following spring in the nymphal stage, which is the stage of the tick most likely to transmit the infection. The nymphs molt to adults in the fall, and then adults spend the second winter attached to white-tailed deer (*Odocoileus virginianus*). The females lay their eggs the following spring before they die, and the 2 yr life cycle begins again.

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**Figure 222-1** The approximate distribution of predicted risk for Lyme disease in the United States. The risk varies by the distribution of *Ixodes scapularis* and *Ixodes pacificus*, the proportion of ticks that are infected at each stage of the tick’s life cycle, and the presence of grassy or wooded locations favored by white-tailed deer. (From the Centers for Disease Control and Prevention [CDC]: Reported cases of Lyme disease—United States, 2011. Available at: [http://www.cdc.gov/lyme/stats/maps/map2011.html](http://www.cdc.gov/lyme/stats/maps/map2011.html))
Several factors are associated with increased risk for transmission of *B. burgdorferi* from ticks to humans. The proportion of infected ticks varies by geographic area and by stage of the tick’s life cycle. In endemic areas in the northeastern and midwestern United States, 15-25% of nymphal ticks and 35-50% of adult ticks are infected with *B. burgdorferi*. By contrast, *I. pacificus* often feeds on lizards, which are not a competent reservoir for *B. burgdorferi*, reducing the chance that these ticks will be infected. The risk for transmission of *B. burgdorferi* from infected *Ixodes* ticks is related to the duration of feeding. Experiments in animals show that infected nymphal ticks must feed for 36-48 hr, and infected adults must feed for 48-72 hr, before the risk for transmission of *B. burgdorferi* becomes substantial. If the tick is recognized and removed promptly, transmission of *B. burgdorferi* will not occur.

*I. scapularis* also transmits other microorganisms, namely *Anaplasma phagocytophilum* and *Babesia microti*. Simultaneous transmission can result in coinfections with these organisms and *B. burgdorferi*.

**PATHOLOGY AND PATHOGENESIS**

Similar to other spirochetal infections, untreated Lyme disease is characterized by asymptomatic infection, clinical disease that can occur in stages, and a propensity for cutaneous and neurologic manifestations.

The skin is the initial site of infection by *B. burgdorferi*. Inflammation induced by *B. burgdorferi* leads to the development of the characteristic rash, erythema migrans. Early disseminated Lyme disease results from the spread of spirochetes through the bloodstream to tissues throughout the body. The spirochete adheres to the surfaces of a wide variety of different types of cells, but the principal target organs are skin, central and peripheral nervous system, joints, heart, and eyes. Because the organism can persist in tissues for prolonged periods, symptoms can appear very late after initial infection.

The symptoms of early disseminated and late Lyme disease are a result of inflammation mediated by interleukin-1 and other lymphokines in response to the presence of the organism. It is likely that relatively few organisms actually invade the host, but cytokines serve to amplify the inflammatory response and lead to much of the tissue damage. Lyme disease is characterized by inflammatory lesions that contain both T and B lymphocytes, macrophages, plasma cells, and mast cells. The refractory symptoms of late Lyme disease can have an immunogenetic basis. Persons with certain HLA-DR allotypes may be genetically predisposed to develop chronic Lyme arthritis. An autoinflammatory response in the synovium can result in clinical symptoms long after the bacteria have been killed by antibiotics.

**CLINICAL MANIFESTATIONS**
The clinical manifestations of Lyme disease are divided into early and late stages (Table 222-1). Early Lyme disease is further classified as early localized or early disseminated disease. Untreated patients can progressively develop clinical symptoms of each stage of the disease, or they can present with early disseminated or with late disease without apparently having had any symptoms of the earlier stages of Lyme disease.

**Early Localized Disease**
The first clinical manifestation of Lyme disease in most patients is erythema migrans (Fig. 222-2). Although it usually occurs 7-14 days after a tick bite, it can occur as late as 30 days after the bite. The rash is usually annular, with a central clearing. It can be multiform, including a central clearing, a satellite rash, and a bull’s eye rash. The rash is usually not pruritic and is often seen on the extremities or trunk. The rash may be associated with constitutional symptoms such as fever, malaise, and headache.

**Table 222-1**

<table>
<thead>
<tr>
<th>DISEASE STAGE</th>
<th>TIMING AFTER TICK BITE</th>
<th>TYPICAL CLINICAL MANIFESTATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early localized</td>
<td>3-30 days</td>
<td>Erythema migrans (single), variable constitutional symptoms (headache, fever, myalgia, arthralgia, fatigue)</td>
</tr>
<tr>
<td>Early disseminated</td>
<td>3-12 wk</td>
<td>Erythema migrans (single or multiple), worse constitutional symptoms, cranial neuritis, meningitis, carditis, ocular disease</td>
</tr>
<tr>
<td>Late</td>
<td>&gt;2 mo</td>
<td>Arthritis</td>
</tr>
</tbody>
</table>

**Figure 222-2** Skin manifestations of Lyme borreliosis. A, Erythema migrans on the upper leg, showing central clearing. B, Erythema migrans of the arm showing “bulls-eye” appearance. (A from Stanek G, Strle F: Lyme borreliosis. Lancet 362:1639–1647, 2003).
after the bite, the onset of the rash has been reported from 3-30 days later. The initial lesion occurs at the site of the bite. The rash is generally either uniformly erythematous or a target lesion with central clearing; rarely, there are vesicular or necrotic areas in the center of the rash. Occasionally the rash is itchy or painful, although usually it is asymptomatic. The lesion can occur anywhere on the body, although the most common locations are the axilla, periumbilical area, thigh, and groin. It is not unusual for the rash to occur on the neck or face, especially in young children. Without treatment, the rash gradually expands (hence the name migrans) to an average diameter of 15 cm and typically remains present for 1-2 wk. Erythema migrans may be associated with systemic features, including fever, myalgia, headache, or malaise. Coinfection with B. microti or A. phagocytophilum during early infection with B. burgdorferi is associated with more severe systemic symptoms. Powassan virus, Borrelia miyamotoi, and Wisconsin Ehrlichia species are also possible coinfections. Coinfections should be suspected with unusual features of Lyme disease, poor response to treatment, and prolonged fever, anemia, leukopenia, or thrombocytopenia.

Early Disseminated Disease
In the United States, approximately 20% of patients with acute B. burgdorferi infection develop secondary (multiple) erythema migrans lesions, a common manifestation of early disseminated Lyme disease, caused by hematogenous spread of the organisms to multiple skin sites (Fig. 222-3). The secondary lesions, which can develop several days or weeks after the first lesion, are usually smaller than the primary lesion, and are often accompanied by more severe constitutional symptoms. The most common early neurologic manifestations are peripheral facial nerve palsy and meningitis. Lyme meningitis usually has an indolent onset with days to weeks of symptoms that can include headache, neck pain and stiffness, and fatigue. Fever is variably present. The clinical findings of optic neuritis, cranial neuropathy (especially cranial nerve VII), and erythema migrans, which are present individually or together in 90% of cases, help differentiate Lyme from viral meningitis, in which these findings are rarely present. Lyme aseptic meningitis can be accompanied by significant elevations of intracranial pressure, which can sometimes last weeks or even months. All of the cranial nerves except the olfactory have been reported to be involved with Lyme disease, but the most common are VI and especially VII. In endemic areas, Lyme disease is the leading cause of peripheral facial nerve palsy. It is often the initial or the only manifestation of Lyme disease and is sometimes bilateral. Cerebrospinal fluid findings indicating meningitis are present in more than half of the cases of peripheral facial nerve palsy. The facial paralisis usually lasts 2-8 wk and resolves completely in most cases. Radiculoneuritis and other peripheral neuropathies can occur but are more common in Europe.

Cardiac involvement occurs in 5-15% of early disseminated Lyme disease and usually takes the form of heart block, which can be 1st, 2nd, or 3rd degree, and the rhythm can fluctuate rapidly. Rarely, myocardial dysfunction can occur. Patients presenting with suspected or proven early disseminated Lyme disease should have a careful cardiac examination, and electrocardiography should be strongly considered. Lyme carditis is a treatable condition and is the only manifestation of Lyme disease that has been fatal.

Of the ocular conditions reported in Lyme disease, papilledema and uveitis are most common.

Late Disease
Arthritis is the usual manifestation of late Lyme disease and begins weeks to months after the initial infection. Arthritis typically involves the large joints, especially the knee, which is affected in 90% of cases; involvement is usually monoarticular. The hallmark of Lyme arthritis is joint swelling, which is a result of synovial effusion and sometimes synovial hypertrophy. The swollen joint may be only mildly symptomatic or it may be painful and tender, although patients usually do not experience the severe pain and systemic toxicity that are common in pyogenic arthritis. If untreated, the arthritis can last several weeks, resolve, and then be followed by recurrent attacks in the same or other joints.

Late manifestations of Lyme disease involving the central nervous system, sometimes termed late neuroborreliosis, are rarely reported in children. In adults, chronic encephalitis and polyneuritis have been attributed to Lyme disease. The term Lyme encephalopathy has been used to describe chronic encephalitis (demonstrable by objective measures), but other literature has also used this term in reference to memory loss and other cognitive sequelae after Lyme disease has been treated. At times, the vague term chronic Lyme disease has been used to describe symptomatology in persons who might have never had well-documented infection with B. burgdorferi at all, have serologic evidence of prior infection but current symptoms not consistent with Lyme disease, or have persistent symptoms after having received appropriate antibiotic therapy. Post–Lyme disease syndrome is now the preferred term for this last group.

Congenital Lyme Disease
In endemic areas, infection can occur during pregnancy, although congenital infection appears to be a rare event. B. burgdorferi has been identified from several abortuses and from a few liveborn children with congenital anomalies; however, the tissues in which the spirochete has been identified usually have not shown histologic evidence of inflammation. Severe skin and cardiac manifestations have been described in a few cases, but no consistent pattern of fetal damage has been identified to suggest a clinical syndrome of congenital infection. Furthermore, studies conducted in endemic areas have indicated that there is no difference in the prevalence of congenital malformations among the offspring of women with serum antibodies against B. burgdorferi and the offspring of those without such antibodies.

LABORATORY FINDINGS
Standard laboratory tests rarely are helpful in diagnosing Lyme disease because any associated laboratory abnormalities usually are nonspecific. The peripheral white blood cell count may be either normal or elevated. The erythrocyte sedimentation rate may be mildly elevated. Liver transaminases are occasionally mildly elevated. In Lyme arthritis, the white blood cell count in joint fluid can range from 25,000 to 100,000/mL, often with a preponderance of polymorphonuclear cells. A lower erythrocyte sedimentation rate and a peripheral blood absolute neutrophil count of less than 10,000 may help to differentiate Lyme from septic arthritis. When meningitis is present, there usually is a low-grade pleocytosis with a lymphocytic and monocyctic predominance. The cerebrospinal fluid (CSF) protein level may be elevated, but the glucose concentration usually is normal. Gram stain and routine bacterial cultures are negative. Imaging of the central nervous system

Figure 222-3 Multiple erythema migrans in a boy with early disseminated Lyme disease.
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(e.g., MRI and single-photon emission computed tomography) occasionally reveals abnormalities, but there is no definitive pattern in Lyme disease. The main role of imaging is to exclude other diagnoses.

DIAGNOSIS

In the appropriate epidemiologic setting, typical erythema migrans is virtually pathognomonic. Occasionally, the diagnosis of erythema migrans may be difficult because the rash initially can be confused with nummular eczema, tinea corporis, granuloma annulare, an insect bite, southern tick-associated rash illness, or cellulitis. The relatively rapid expansion of erythema migrans helps distinguish it from these other skin lesions. The other clinical manifestations of Lyme disease are less specific and may be confused with other conditions; the monoarticular or pauciarticular arthritis sometimes is confused with a septic joint or other causes of arthritis in children, such as juvenile rheumatoid arthritis or rheumatic fever; the facial nerve palsy caused by Lyme disease is clinically indistinguishable from idiopathic Bell palsy, although bilateral involvement is much more common with Lyme disease; Lyme meningitis generally occurs in the warmer months, the same period that enteroviral meningitis is prevalent. Therefore, for all disease manifestations other than erythema migrans, it is recommended to have laboratory confirmation of infection with *B. burgdorferi*.

Although *B. burgdorferi* has been isolated from blood, skin, CSF, myocardium, and the synovium of patients with Lyme disease, the organism is difficult to isolate in culture (cultivation is largely relegated to research laboratories). Infection is usually identified by the detection of antibody in serum. Although some laboratories offer polymerase chain reaction as a diagnostic test for Lyme disease, its sensitivity may be poor because of the low concentrations of bacteria in many sites, especially CSF. Other antigen-based tests, including a test for *B. burgdorferi* antigens in urine, are unreliable. Clinicians should be aware that some laboratories use alternative diagnostic tests and/or alternative interpretive criteria that are not evidence based, leading to a false diagnosis of Lyme disease.

Serology

Following the transmission of *B. burgdorferi* from a tick bite, specific immunoglobulin (Ig) M antibodies appear first, usually within 2 wk, peak at 6-8 wk, and subsequently decline. Sometimes a prolonged elevation of IgM antibodies occurs despite effective antimicrobial treatment. (For that reason, the results of tests for specific IgM antibodies alone should not be used as a reliable indicator of either active or recent infection.) Specific IgG antibodies usually appear between 2 and 6 wk, peak after 4-6 mo, and can remain elevated for years, particularly in patients with arthritis. The antibody response to *B. burgdorferi* may be blunted in patients with early Lyme disease who are treated promptly. Serodiagnosis during the 1st wk of infection is not sensitive and may need to be repeated.

By far the most common method used to detect IgG and IgM antibodies is the enzyme-linked immunosorbent assay (ELISA). This method is sensitive but not optimally specific. The ELISA sometimes produces false-positive results because of antibodies that crossreact with other spirochetal infections (e.g., syphilis, leptospirosis, or relapsing fever), or certain viral infections (e.g., Epstein-Barr virus or parvovirus B19), or that occur in certain autoimmune diseases (e.g., systemic lupus erythematosus). The positive predictive value of the ELISA result depends primarily on the plausibility that the patient has Lyme disease based on the clinical and epidemiologic history and the physical examination (the pretest probability). For patients who have been in endemic areas with opportunities for *Ixodes* tick exposure and who have typical clinical manifestations of Lyme disease, the pretest probability is high and positive ELISA results are usually true positives. For patients who are from nonendemic areas and/or who have little risk for *Ixodes* tick exposures and/or have nonspecific symptoms (low pretest probability), rates of false-positive results are high.

Western immunoblotting is well standardized, and there are accepted criteria for interpretation. Five of 10 IgG bands and 2 of 3 IgM bands are considered reactive. The Western blot is not as sensitive as ELISA, especially in early infection, but it is highly specific. Any positive or equivocal ELISA should be confirmed with Western blotting. This 2-tier testing is the recommended laboratory evaluation of most cases of Lyme disease and is associated with a high degree of sensitivity and specificity when used appropriately.

Clinicians should be aware that Lyme disease might not be the cause of a patient's symptoms despite the presence of antibodies to *B. burgdorferi*. The test result may be falsely positive (as described for ELISA), or the patient might have been infected previously. Antibodies to *B. burgdorferi* that develop with infection can persist for many years despite adequate treatment and clinical cure of the disease. In addition, because some people who become infected with *B. burgdorferi* are asymptomatic, the background rate of seropositivity among patients who have never had clinically apparent Lyme disease may be substantial in endemic areas. Finally, because antibodies against *B. burgdorferi* persist after successful treatment, there is no reason to obtain follow-up serologic tests.

TREATMENT

Table 222-2 provides treatment recommendations. Most patients can be treated with an oral regimen of antibiotic therapy. Young children are generally treated with amoxicillin. Doxycycline has the advantages of good central nervous system penetration and activity against *A. phagocytophilum*, which may be transmitted at the same time as *B. burgdorferi* in certain geographic areas. In general, children younger than 8 yr of age should not be treated with doxycycline because of the risk of permanent staining of the teeth (although courses of ≤2 wk are usually safe in this regard). Patients who are treated with doxycycline should be alerted to the risk for developing photosensitivity in sun-exposed areas while taking the medication; long sleeves, long pants, and hat are recommended for activities in direct sunlight. The only oral cephalosporin proved to be effective for the treatment of Lyme disease is cefuroxime axetil, which is an alternative for persons who cannot take doxycycline or who are allergic to penicillin. Macrolide antibiotics, including azithromycin, appear to have limited activity.

### Table 222-2 Recommended Treatment of Lyme Disease

<table>
<thead>
<tr>
<th>DRUG</th>
<th>PEDIATRIC DOSING</th>
<th>RECOMMENDED THERAPY BASED ON CLINICAL MANIFESTATION</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A.</strong></td>
<td><strong>Dosage</strong></td>
<td><strong>Manifetstion</strong></td>
</tr>
<tr>
<td><strong>Amoxicillin</strong></td>
<td>50 mg/kg/day in 3 divided doses (max: 1,500 mg/day)</td>
<td>Oral regimen, 14-21 days</td>
</tr>
<tr>
<td><strong>Doxycycline</strong></td>
<td>4 mg/kg/day in 2 divided doses (max: 200 mg/day) (see text regarding doxycycline use in children)</td>
<td>Oral regimen, 14-21 days (see text regarding possible need for lumbar puncture)</td>
</tr>
<tr>
<td><strong>Cefuroxime axetil</strong></td>
<td>30 mg/kg/day in 2 divided doses (max: 1,000 mg/day)</td>
<td>Oral regimen or ceftriaxone, 14-21 days (see text for specifics)</td>
</tr>
<tr>
<td><strong>Ceftriaxone (IV)</strong></td>
<td>50-75 mg/kg/day once daily (max: 2,000 mg/day)</td>
<td>Oral regimen, 28 days</td>
</tr>
<tr>
<td><strong>Arthritis</strong></td>
<td>Oral regimen or ceftriaxone, 14-28 days</td>
<td>Late neurologic disease</td>
</tr>
</tbody>
</table>

*Cefotaxime and penicillin G are alternative parenteral agents.
Doses of 100 mg/kg/day should be used for meningitis.
Persistent arthritis can be treated with a second oral regimen or ceftriaxone.
Parenteral therapy is recommended for patients with central nervous system infection and higher degrees of heart block. Patients with arthritis that fails to resolve after an initial course of oral therapy can be retreated with an oral regimen or can receive intravenous antibiotic therapy. Ceftriaxone is usually favored because of its excellent anti-
Borrelia activity, tolerability, and once-daily dosing regimen, which can usually be done on an outpatient basis.

Peripheral facial nerve palsy can be treated using an oral antibiotic. However, many of these patients have concomitant meningitis; patients with meningitis should receive a parenteral antibiotic. Experts are divided on whether every patient with Lyme-associated facial palsy should have a CSF analysis, but clinicians should consider lumbar puncture for patients with significant headache, neck pain or stiffness, or papilledema.

Patients with symptomatic cardiac disease, 2nd- or 3rd-degree heart block, or significantly prolonged PR interval should be hospitalized and monitored closely. These patients should receive a parenteral antibiotic. Patients with mild 1st-degree heart block can be treated with an oral antibiotic.

Some patients develop a Jarisch-Herxheimer reaction soon after treatment is initiated; this results from lysis of the Borrelia. The manifestations of this reaction are low-grade fever and achiness. These symptoms resolve spontaneously within 24–48 hr, although administration of nonsteroidal antiinflammatory drugs is often beneficial. Nonsteroidal antiinflammatory drugs also may be useful in treating symptoms of early Lyme disease and of Lyme arthritis. Coinfections with other pathogens transmitted by Ixodes ticks should be treated according to standard recommendations.

Criteria for the post–Lyme disease syndrome have been proposed by the Infectious Disease Society of America. There is no clear evidence that this condition is related to persistence of the organism. Studies in adults show little benefit associated with prolonged or repeated treatment with oral or parenteral antibiotics.

**PROGNOSIS**

There is a widespread misconception that Lyme disease is difficult to cure and that chronic symptoms and clinical recurrences are common. The most likely reason for apparent treatment failure is an incorrect diagnosis of Lyme disease.

The prognosis for children treated for Lyme disease is excellent. Children treated for erythema migrans rarely progress to late Lyme disease. The long-term prognosis for patients who are treated beginning in the later stages of Lyme disease also is excellent. Although chronic and recurrent arthritis does occur rarely, especially among patients with certain human leukocyte antigen allotypes (an autoimmune process), most children who are treated for Lyme arthritis are cured and have no sequelae. Although there are rare reports of adults who have developed late neuroborreliosis, usually among persons with Lyme disease in whom treatment was delayed for months or years; similar cases in children are rare.

**PREVENTION**

The best way to avoid Lyme disease is to avoid tick-infested areas. Children should be examined for deer ticks after known or potential exposure (although many people are not able to identify the species or the stage of the tick). If a tick attachment is noted, the tick should be grasped at the mouthparts with a forceps or tweezers; if these are not available, the tick should be covered with a tissue. The recommended method of tick removal is to pull directly outward without twisting; infection is usually preventable if the tick is removed before 48 hr of attachment. The overall risk for acquiring Lyme disease after a tick bite is low (1–3%) in most endemic areas. Patients and families can be advised to watch the area for development of erythema migrans and to seek medical attention if the rash or constitutional symptoms occur. If infection develops, early treatment of the infection is highly effective. Although a study of prophylaxis after a tick bite found that a single dose of doxycycline in adults (200 mg PO) was 87% effective in preventing Lyme disease, data in children using this strategy are lacking. For these various reasons, routine administration of antimicrobial prophylaxis is not recommended. The routine testing of ticks that have been removed from humans for evidence of B. burgdorferi is not recommended, because the value of a positive test result for predicting infection in the human host is unknown.

Personal protective measures that may be effective in reducing the chance of tick bites include wearing protective clothing (long pants tucked into socks, long-sleeved shirts) when entering tick-infested areas, checking for and promptly removing ticks, and using tick repellents such as N,N-diethyl-3-methylbenzamide (DEET). This chemical can safely be used on pants, socks, and shoes; care must be used with heavy or repeated application on skin, particularly in infants, because of the risk of systemic absorption and toxicity.

*Bibliography is available at Expert Consult.*
Bibliography


Among the 7 Mycoplasma species isolated from the human respiratory tract, *Mycoplasma pneumoniae* remains the most common species causing respiratory infections in school-age children and young adults.

**THE ORGANISM**

Mycoplasmas are the smallest self-replicating prokaryotes known to cause disease in humans. Their size of 150-250 nm is more on the order of viruses than bacteria. *M. pneumoniae* is a fastidious double-stranded DNA bacterium that is distinguished by a small genome (800,000 base pairs) and a long doubling time, which makes culturing of *Mycoplasma* a slow process (5-20 days) compared to other bacteria. Like other mycoplasmas, *M. pneumoniae* is distinguished by the complete absence of a cell wall that results (1) in their dependence to host cells for obtaining essential nutrients, (2) the intrinsic resistance to β-lactam agents, and (3) their pleomorphic shape and lack of visibility on Gram staining.

**EPIDEMIOLOGY**

*M. pneumoniae* infections occur worldwide and throughout the year. This organism is a frequent cause of community-acquired pneumonia (CAP) in school-age children and adults, accounting for 7-40% of all CAP in children 3-15 yr of age.

In contrast to the acute, short-lived epidemics of some respiratory viruses, *M. pneumoniae* infection is endemic in larger communities, with epidemic outbreaks occurring every 4-7 yr, usually beginning in the fall. Infection occurs through the respiratory route by large droplet spread during close contact with a symptomatic person. Community outbreaks have been described in closed settings (colleges, summer camps, military bases) and can spread largely through school contacts. High transmission rates have been documented within families with up to 40% of household contacts developing mycoplasma lower respiratory tract infection. In contrast to many other respiratory infections the incubation period is 2-3 wk; hence, the course of infection in a specific population (family) may last several weeks.

The occurrence of mycoplasmal illness is related, in part, to age and preexposure immunity. Overt illness is less common before 3 yr of age but can occur. Children younger than 5 yr of age appear to have mild
illness associated with upper respiratory tract involvement, vomiting, and diarrhea. Immunity after infection is not long lasting. Recurrent infections occur infrequently but are well documented in adults at intervals of 4-7 yr. Asymptomatic carriage after infection can last up to 4 mo despite antibiotic therapy and may contribute to prolonged outbreaks.

**PATHOLOGY AND PATHOGENESIS**

The pathogenicity of *M. pneumoniae* is dependent upon its extracellular attachment and the initiation of the host cell immune response. Cells of the ciliated respiratory epithelium are the target cells of *M. pneumoniae* infection. The organism is an elongated snake-like structure with a one-end organelle, which mediates the attachment to the ciliary membrane through different adherence-accessory proteins (P1, P30, P65, P116, and HMW1-3). *M. pneumoniae* rarely invades beyond the respiratory tract basement membrane. Virulent organisms attach to ciliated respiratory epithelial cell surfaces located in the bronchi, bronchioles, alveoli, and possibly upper respiratory tract and burrow down between cells, resulting in ciliostasis and eventual sloughing of the cells. In addition, *M. pneumoniae* causes cytolytic injury to the host cells in part by the production of hydrogen peroxide and possibly through an adenosine diphosphate–ribosylating and vacuolating toxin termed CARDS: community-acquired respiratory distress syndrome. This toxin is associated with more severe or even fatal disease.

Once *M. pneumoniae* reaches the lower respiratory tract, promotes the polyclonal activation of B-lymphocytes and CD4+ T-cells, and amplifies the immune response with the production of various proinflammatory and antiinflammatory cytokines and chemokines such as tumor necrosis factor-α, interferon-γ, and granulocyte-macrophage colony-stimulating factor.

Although it is well documented that specific cell-mediated immunity and antibody titers against *M. pneumoniae* increase with age (and therefore probably follow repeated infections), the immune mechanisms that protect against or clear the infection are not well defined. The high prevalence of infection in children, adolescents, and young adults, but the frequently mild disease in young children suggests the possible role of immune-mediated mechanisms associated with reinfections causing disease in older patients. Patients with congenital immunodeficiencies such as hypogammaglobulinemia as well as those with sickle cell disease or sickle-related hemoglobinopathies can have more severe forms of *Mycoplasma* pneumonia. *M. pneumoniae* is a common infectious cause of acute chest syndrome in sickle cell disease, and in patients with hypogammaglobulinemia it can persist for years in the respiratory tract despite multiple courses of antibiotics. On the other hand, *M. pneumoniae* does not seem to be a common opportunistic agent in patients with AIDS.

*M. pneumoniae* has been detected by polymerase chain reaction (PCR) in many nonrespiratory sites. The mechanisms of extrapulmonary disease associated with *M. pneumoniae* are unclear. The identification of *M. pneumoniae* PCR from blood, pleural fluid, cerebrospinal fluid, or synovial fluid in some cases indicates that direct dissemination rather than an immune-mediated mechanism may occur.

**CLINICAL MANIFESTATIONS**

**Respiratory Tract Disease**

Tracheobronchitis and pneumonia are the most commonly recognized clinical syndromes associated with *M. pneumoniae* infection. This agent is responsible for up to 20% of all cases of pneumonia. Although the onset of illness may be abrupt, it is usually characterized by gradual onset of headache, malaise, fever, and sore throat, followed by progression of lower respiratory symptoms, including hoarseness and nonproductive cough. Coryza or gastrointestinal complaints are unusual with *M. pneumoniae* pneumonia and usually suggest a viral etiology. Although the clinical course in untreated patients is variable, cough, the clinical hallmark of *M. pneumoniae* infection, usually worsens during the 1st wk of illness, and symptoms generally resolve within 2 wk. Cough can last up to 4 wk and may be accompanied by wheezing. Patients generally recover without complications.

Chest exam is often unrevealing, even in patients with severe cough. There may be no auscultative or percussion findings or only minimum dry rales. Clinical findings are often less severe than suggested by the patient chest radiograph, explaining why the term “walking pneumonia” is often used to describe CAP caused by *M. pneumoniae*. Radiographic findings are variable and nonspecific, not allowing differentiation from viral or bacterial pathogens. Pneumonia is usually described as interstitial or bronchopneumonic, and involvement is most common in the lower lobes. Bilateral diffuse infiltrates, lobar pneumonia or hilar lymphadenopathy can occur in up to 30% of patients. Although unusual, large pleural effusions associated with lobar infiltrates and necrotizing pneumonia have been described in patients with sicker cell disease, immunodeficiencies, Down syndrome, and chronic cardiopulmonary disease. The white blood cell and differential counts are usually normal, whereas the erythrocyte sedimentation rate is often elevated.

Other respiratory illnesses caused occasionally by *M. pneumoniae* include undifferentiated upper respiratory tract infections, pharyngitis (usually without marked cervical lymphadenopathy), sinusitis, croup, and bronchiolitis. *M. pneumoniae* is a common trigger of wheezing in asthmatic children and can cause chronic colonization in the airways, resulting in lung dysfunction in adolescents and adult asthmatic patients. Otitis media and bullous myringitis, which also occur with other viral and bacterial infections, have been described but are rare, and their absence should not rule out the diagnosis of *M. pneumoniae*.

**Extrapulmonary Disease**

Despite the reportedly rare isolation of *M. pneumoniae* from nonrespiratory sites, the improved sensitivity of PCR for *M. pneumoniae* DNA detection has led to increasing identification of *M. pneumoniae* in nonrespiratory sites, particularly the central nervous system (CNS). Patients with or without respiratory symptoms can have involvement of the skin, CNS, blood, heart, gastrointestinal tract, and joints. Nonrespiratory manifestations of *M. pneumoniae* include:

1. **CNS disease**, which may be the most common extrapulmonary site associated with *M. pneumoniae* infection and includes encephalitis, transverse myelitis, aseptic meningitis, Guillain-Barré syndrome, ataxia, Bell palsy, postinfectious demyelination, peripheral neuropathy, and acute disseminated encephalomyelitis. CNS disease manifestations occur 3-23 days (mean: 10 days) after onset of respiratory illness but may not be preceded by any signs of respiratory infection in up to 20% of cases. Encephalitis occurring within 5 days of the onset of prodromal symptoms may be caused by direct invasion of *M. pneumoniae* in the CNS, although cerebrospinal fluid (CSF) PCR is positive in <5% of cases. Encephalitis occurring more than 7 days after onset of prodromal symptoms is more likely to be caused by an autoimmune response to *M. pneumoniae* and accounts for up to 5-15% of all forms of childhood encephalitis. Involvement of the brainstem can result in severe dystonia and movement disorders. Concomitant infection with other pathogens such as enteroviruses or respiratory viruses is found in approximately 10% of children. The CSF may be normal or have mild mononuclear pleocytosis. Diagnosis is confirmed with positive CSF PCR, positive PCR from a throat swab, or the presence of definitive serum antibody titers. Findings on MRI include focal ischemic changes, ventriculomegaly, diffuse edema, or multifocal white matter inflammatory lesions consistent with postinfectious demyelinating encephalomyelitis. Long-term sequelae are not uncommon and have been reported in 23-64% of cases.

2. **Dermatologic disease**, which includes a variety of exanthemas, most notably maculopapular rash urticaria, and erythema multiforme or Stevens-Johnson syndrome (SJS). Gianotti-Crosti syndrome and erythema nodosum are also associated with *M. pneumoniae* infections. Approximately 10% of children with *M. pneumoniae* CAP will exhibit a maculopapular rash. *M. pneumoniae* is the most common infectious agent associated with SJS and has a male predominance. SJS usually develops
3-21 days after initial respiratory symptoms, lasts less than 14 days, and is rarely associated with severe complications (Figs. 223-1 and 223-2). *M. pneumoniae* is linked to atypical SJS with oral mucositis but absence of rash.

3. **Hematologic abnormalities**, which include mild degrees of hemolysis with a positive Coombs test and minor reticulocytosis 2-3 wk after the onset of illness. Severe hemolysis is associated with high titer of cold hemagglutinins (>1:512) and occurs rarely. Thrombocytopenia, aplastic anemia, and coagulation defects occur occasionally.

4. **Arthritis**, which appears to be less common in children than adults, but monoarthritis, polyarthritis, and migratory arthritis have been described.

5. **Other conditions**, such as mild hepatitis, pancreatitis, acute glomerulonephritis, and cardiac complication (pericarditis, myocarditis, and rheumatic fever-like syndrome, most commonly seen in adults), are also described. Fatal *M. pneumoniae* infections are rare.

**DIAGNOSIS**

No specific clinical, epidemiologic, or laboratory parameters allow for a definite diagnosis of *M. pneumoniae* infection early in the clinical course. Nevertheless, pneumonia in school-age children and young adults with cough as a prominent finding suggests *M. pneumoniae* infection. The best method of diagnosis is a combination of PCR from respiratory samples and serology (acute and convalescent).

**Cultures** on special media (SP4 agar media) of the throat or sputum might demonstrate the classic *M. pneumoniae* “mulberry” colonies, but growth generally requires incubation for 1-3 wk, and few commercial laboratories maintain the capability of culturing *M. pneumoniae*. The fastidious nutritional requirements of Mycoplasma make cultures slow and impractical.

**Serologic tests** (immunofluorescence tests or enzyme-linked immune assays) to detect serum immunoglobulin (Ig) M and IgG antibodies against *M. pneumoniae* are commercially available. IgM antibodies have a high rate of false-positive and false-negative results. In most cases, IgM antibodies are not detected within the 1st wk after onset of symptoms or in children with recurrent infections and may be positive for up to 6-12 mo after infection. A 4-fold or greater increase in IgG antibody titers against *M. pneumoniae* between acute and convalescent sera obtained 10 days to 3 wk apart is diagnostic.

**Cold hemagglutinins** (cold-reacting antibodies against red blood cells) can be detected in approximately 50% of patients with *M. pneumoniae* atypical pneumonia. These antibodies are nonspecific, especially at titers <1:64, as modest increases in cold hemagglutinin can be observed in other viral infections. Cold agglutinin antibodies should not be used for the diagnosis of *M. pneumoniae* infections if other methods are available. Nonetheless the PCR may be positive in some asymptomatic patients.

**PCR-based tests** for *M. pneumoniae* have replaced other diagnostic tests. PCR of a nasopharyngeal or throat swab (doing both increases sensitivity) for *M. pneumoniae* DNA carries a sensitivity and a specificity of 80% to >97%. Different primers have been used to identify gene sequences of the P1 cytoadhesin protein or the ribosomal (r)RNA. PCR allows a more rapid diagnosis in acutely ill patients and can be positive earlier in the course of infection than serologic tests. Identification of *M. pneumoniae* by PCR (or culture) from a patient with compatible clinical manifestations suggests causation.

The diagnosis of extrapulmonary disease associated with *M. pneumoniae* is challenging. Although small case series identified *M. pneumoniae* by PCR in the CSF of children with encephalitis, there are currently no reliable tests for the diagnosis of CNS or other nonrespiratory sites associated with *M. pneumoniae*.

**TREATMENT**

*M. pneumoniae* illness is usually mild, and most cases of pneumonia can be managed without the need for hospitalization. Because mycoplasmas lack a cell wall, they inherently are resistant to β-lactam agents that act by inhibiting the cell wall synthesis.

**Antimicrobial Therapy**

*M. pneumoniae* is typically sensitive to macrolides (erythromycin, clarithromycin, azithromycin), the tetracyclines, and quinolones in vitro. Data from observational studies showed that macrolide treatment of children with *M. pneumoniae* CAP markedly shortened the course of illness. Treatment may be more effective when started within 3-4 days of illness onset. Although macrolides do not have bactericidal activity, they are preferred in children younger than 8 yr of age. Two multicenter studies of pediatric CAP demonstrated comparable clinical and bacteriologic success rates between erythromycin and clarithromycin or azithromycin. However, the newer macrolides were better tolerated. The recommended treatment is clarithromycin (15 mg/kg/day divided into 2 doses PO for 10 days) or azithromycin (10 mg/kg once PO on day 1 and 5 mg/kg once daily PO on days 2-5). In addition to the antibacterial effect, macrolides have immunomodulatory properties, but the relevance of the anti-inflammatory properties of macrolides for the treatment of *M. pneumoniae* CAP is not known. Tetracyclines (doxycycline 100 mg twice a day for 7-14 days) are also effective and may be used for children older than 8 yr of age. Fluoroquinolones such as levofloxacin (500 mg once a day for 7-14 days) are effective but are less active than macrolides and are not recommended as a first-line therapy in children.
Macrolide-resistant strains, mostly associated with mutations in the 23S rRNA, have been reported in Asia (>40% in Japan and 80-90% in China) and are also present in Europe and the United States (with rates ranging from 8-20%). Although not routinely done at commercial laboratories, identification of macrolide-resistant strains can be performed by sequencing and identification of specific mutations at the 23S rRNA gene. The tetracycline minocycline (for children > 8 yr) and the quinolone tosufloxacin (for children < 8 yr) are approved in Japan for pediatric use to treat macrolide-resistant *M. pneumoniae* infections. For patients with severe mycoplasma pneumonia not responding to macrolide therapy, the possibility of macrolide-resistant *M. pneumoniae* strains should be considered, and switching to a nonmacrolide antimicrobial agent might be prudent.

**Adjunctive Therapy**

There is no evidence that treatment of upper respiratory tract or non-respiratory tract disease with antimicrobial agents alters the course of illness. However, patients with severe manifestations of extrapulmonary disease may benefit from antimicrobial treatment combined with immunotherapy. In this regard, corticosteroids with or without intravenous immunoglobulin are the most commonly used agents in the management of severe *M. pneumoniae* extrapulmonary manifestations, particularly with CNS involvement. Although definitive data are lacking, case studies suggest associated clinical benefit of steroids used in the management of severe lung disease, SJS, and hemolytic anemia.

**PREVENTION**

Trials with inactivated and live attenuated vaccines for *M. pneumoniae* have been conducted with disappointing results. In hospitalized patients standard and droplet precautions are recommended for the duration of symptoms. It is important to emphasize that *Mycoplasma* infection remains contagious as long as cough persists and despite successful antibiotic therapy. Prophylaxis with tetracyclines or azithromycin substantially reduces the secondary attack rates in institutional outbreaks and family close contacts. Antimicrobial prophylaxis is not recommended routinely; however, it can be considered in patients at high risk for severe disease, such as children with sickle cell disease.

*Bibliography is available at Expert Consult.*
Bibliography

Chapter 224
Genital Mycoplasmas
(Mycoplasma Hominis, Mycoplasma Genitalium, and Ureaplasma Urealyticum)
Rebecca Wallihan and Asuncion Mejias

ETIOLOGY
Mycoplasma species are small pleomorphic bacteria that typically lack a cell wall. These ubiquitous organisms are difficult to cultivate and belong to the family Mycoplasmataceae in the class Mollicutes and represent the smallest self-replicating organisms known to date. The family Mycoplasmataceae is composed of 2 genera responsible for human infection: Mycoplasma and Ureaplasma. Of those, Mycoplasma hominis, Mycoplasma genitalium, and Ureaplasma spp., which includes Ureaplasma urealyticum (biovar 2) and Ureaplasma parvum (biovar 1), are considered human urogenital pathogens and are reviewed in this chapter. Genital mycoplasmas are often associated with sexually transmitted infections such as cervicitis and nongonococcal urethritis (NGU) or with puerperal infections such as endometritis. M. hominis and Ureaplasma spp. commonly colonize the female genital tract and can cause chorioamnionitis, colonization of neonates, and perinatal infections. Two other genital Mycoplasma species, Mycoplasma fermentans and Mycoplasma penetrans, have been identified in respiratory or genitourinary secretions primarily in HIV-infected patients.

EPIDEMIOLOGY
M. hominis and Ureaplasma spp. are commensal organisms in the lower genital and urinary tracts of postpubertal women and men. Colonization rates are directly related to sexual activity and are highest among individuals with multiple sexual partners. Female colonization is maximal in the vagina and less in the endocervix, urethra, and endometrium, with rates varying from 40-80% for Ureaplasma spp. and 21-70% for M. hominis among sexually active asymptomatic women. Male colonization is less common and occurs primarily in the urethra. Among prepubertal children and sexually inactive adults, colonization rates are <10%. M. genitalium is implicated in approximately 25% of NGU cases in men and plays a role in cervicitis and pelvic inflammatory disease in women. Studies using polymerase chain reaction (PCR) show that colonization of the female lower urogenital tract with M. genitalium is less common than with M. hominis or Ureaplasma spp.

TRANSMISSION
Genital mycoplasmas are transmitted by sexual contact or by vertical transmission from mother to infant. As with other perinatal infections, vertical transmission can occur through ascending intrauterine infection, hematogenous spread from placental infection, or through a colonized birth canal at the time of delivery. Transmission rates among neonates born to women colonized with Ureaplasma spp. range from 18-88%. Neonatal colonization rates are higher among infants who weigh <1,000 g, are born in the presence of chorioamnionitis, or are born to mothers of lower socioeconomic status. Organisms may be recovered from the newborn’s throat, vagina, rectum, and, occasionally, conjunctiva for as long as 3 mo after birth.

PATHOLOGY AND PATHOGENESIS
Genital mycoplasmas can cause chronic inflammation of the genitourinary tract and amniotic membranes. Ureaplasma spp. can infect the amniotic sac early in gestation without rupturing the amniotic membranes, resulting in a clinically silent, chronic chorioamnionitis characterized by an intense inflammatory response. Attachment to fetal human tracheal epithelium can cause ciliary disarray, clumping, and loss of epithelial cells. In vitro studies show that Ureaplasma spp. stimulates macrophage production of interleukin-6 and tumor necrosis factor-α. In addition, high concentrations of proinflammatory cytokines possibly associated with development of chronic lung disease (CLD) of prematurity, such as monocyte chemoattractant protein-1 and interleukin-8, have been found in tracheal secretions from very-low-birthweight infants colonized with Ureaplasma spp. Immunity appears to require serotype-specific antibody. Thus, lack of maternal antibodies might account for a higher disease risk in premature newborns.

CLINICAL MANIFESTATIONS
Intrauterine and Neonatal Infections
Genital mycoplasmas are associated with a variety of fetal and neonatal infections. Ureaplasma spp. can cause clinically inapparent chorioamnionitis resulting in spontaneous abortion, increased fetal death, or premature delivery. Ureaplasma spp. can also be recovered from tracheal, blood, cerebrospinal fluid (CSF), or lung biopsy specimens in up
to 50% of sick infants younger than 34 wk of gestational age. In a study of 351 preterm infants born between 23 and 32 wk of gestational age, isolation of Ureaplasma spp. or M. hominis from cord blood correlated with the development of systemic inflammatory response syndrome. The role of these organisms causing severe respiratory insufficiency, the need for mechanical ventilation, the development of CLD, or death remains controversial. Meta-analyses of published studies have identified respiratory colonization with Ureaplasma spp. as an independent risk factor for the development of CLD. However, trials of erythromycin therapy in high-risk preterm infants with tracheobronchial colonization of U. urealyticum have failed to show any difference in the development of CLD in treated vs nontreated infants. M. hominis and Ureaplasma spp. have been isolated from the CSF of premature and, less commonly, full-term infants. However, the clinical significance of recovering these bacteria from the CSF is uncertain. Simultaneous isolation of other pathogens is unusual, and most infants have no overt signs of central nervous system (CNS) disease. Overall, CSF pleocytosis is not consistent, and spontaneous clearance of mycoplasmas has been documented without specific therapy. Ureaplasma spp. meningitis has been associated with intraventricular hemorrhage and hydrocephalus. Limited data suggest that meningitis caused by M. hominis can be associated with significant morbidity and mortality. In a review of 29 reported neonatal cases with M. hominis meningitis, 8 (28%) neonates died and 8 (28%) developed neurologic sequelae. The age of onset of meningitis ranges from 1 to 196 days of life, and organisms can persist in the CSF without therapy for days to weeks. Pachymeningitis may be evident on MRI scans. M. hominis and Ureaplasma spp. have also been associated with neonatal conjunctivitis, lymphadenitis, pharyngitis, pneumonitis, osteomyelitis, brain abscess, pericarditis, meningoencephalitis, and scalp abscess.

Genitourinary Infections
In sexually active adolescents and adults, genital mycoplasmas are associated with sexually transmitted diseases and are rarely associated with focal infections outside the genital tract. Ureaplasma spp. and M. genitalium are recognized etiologic agents of NGU. Approximately 30% of NGU in males may be caused by these organisms either alone or associated with Chlamydia trachomatis (see Chapter 226). Ureaplasma spp. are also associated with the development of urinary calculi. Disease is most common in young adults but is also prevalent in sexually active adolescents. The average incubation period is 2-3 wk, with symptoms typically consisting of scant mucoid-white urethral discharge, dysuria, and penile discomfort. The discharge is often evident only in the morning or after the urethra is stripped. Rare complications of NGU include epididymitis and proctitis. Approximately 20-60% of patients with M. genitalium NGU develop recurrent or chronic urethritis despite 1-2 wk of treatment with doxycycline.

Nongenital Infections
Extragenital Ureaplasma spp. infections are rarely described but include pneumonia, osteomyelitis, arthritis, meningitis, mediastinitis, infection of aortic grafts, and postcesarean wound infections. Patients with hypogammaglobulinemia appear to be at higher risk for chronic arthritis caused by various Mycoplasma spp. On the other hand, M. hominis is associated with septicemia, endocarditis, wound infections, osteomyelitis, lymphadenitis, pneumonia, meningitis, brain abscesses, arthritis, amnionitis, and postpartum fever. There are reports of life-threatening mediastinitis, sternal wound infections, pleuritis, peritonitis, and pericarditis with high mortality rates in patients following organ transplantation.

DIAGNOSIS
All Mollicutes lack a cell wall and are therefore not visible on Gram stain. M. hominis and Ureaplasma spp. can grow in cell-free media and require sterols for growth, producing characteristic colonies on agar. Colonies of M. hominis are 200-300 μm in diameter with a “fried-egg” appearance, while colonies of Ureaplasma spp. are smaller (16-60 μm in diameter). Although these organisms can grow in culture, PCR assays have a greater sensitivity. Assays for both Ureaplasma spp. and M. hominis are available at research and reference laboratories in the United States. M. genitalium is a fastidious organism and can be isolated with difficulty in cell culture systems; however, PCR provides a more practical method for detection.

Genital Tract Infection
Confirmation of genital tract infection is challenging because of the high colonization rates in the vagina and urethra. NGU is typically defined as new-onset urethral discharge or dysuria with Gram stain of urethral discharge showing ≥25 polymorphonuclear leukocytes per oil-immersion field in the absence of Gram-negative diplococci (i.e., Neisseria gonorrhoeae). A urethral swab or exudate can be cultured for C. trachomatis and Ureaplasma spp. Detection of Ureaplasma spp. or M. hominis by PCR is available for a variety of specimens, including urine, amniotic fluid, placental tissue, respiratory specimens, synovial fluid, and swabs of the cervix, urethra, and vagina. M. genitalium is often identified by PCR testing of first-void urine specimens in men and vaginal swabs in women.

Neonates
Ureaplasma spp. and M. hominis have been isolated from urine, blood, CSF, tracheal aspirates, pleural fluid, abscesses, and lung tissue. Premature neonates who are clinically ill with pneumonitis, focal abscesses, or CNS disease (particularly progressive hydrocephalus with or without pleocytosis) for whom bacterial cultures are negative or in whom there is no improvement with standard antibiotic therapy warrant cultures/PCR for genital mycoplasmas. Isolation requires special media, and clinical specimens must be cultured immediately or frozen at −70°C (−94°F) to prevent loss of organisms. When inoculated into broth containing arginine (for M. hominis) or urea (for Ureaplasma spp.), growth is indicated by an alkaline pH. Identification of Ureaplasma spp. on agar requires 1-2 days of growth and visualization with the dissecting microscope, whereas M. hominis is apparent to the eye but can require 1 wk to grow. Cultures from the upper respiratory tract may be less specific owing to high colonization rates. Cultures of the lower respiratory tract through endotracheal aspirate or biopsy are essential.

TREATMENT
These organisms lack a cell wall, and thus β-lactam agents are not effective. These bacteria are also resistant to sulfonamides and tetracyclines because they do not produce folic acid. Rifampicins do not have activity against Mollicutes. M. hominis is resistant to macrolides but generally susceptible to clindamycin and quinolones. Most Ureaplasma spp. are susceptible to macrolides and advanced generation quinolones, such as moxicillin, but often resistant to ciprofloxacin and clindamycin. Susceptibility to tetracyclines is variable for both organisms, with increasing resistance being reported. M. genitalium is typically susceptible to macrolides and moxicillin, with variable resistance to tetracyclines and clindamycin.

Adolescents and Adults
Recommended treatment for NGU in males is azithromycin (1 g PO as a single dose) and doxycycline (100 mg PO twice daily for 7 days). Recurrent NGU after completion of treatment suggests the presence of azithromycin-resistant M. genitalium. Treatment with moxifloxacin may be most effective. Sexual partners should also be treated to avoid recurrent disease in the index case. Nongenital mycoplasmal infections may require surgical drainage and prolonged antibiotic therapy.

Neonates
Therapy for neonates with genital mycoplasma infections is indicated if infections are associated with pure growth of the organism or if the organism is detected by PCR from a normally sterile site in conjunction with compatible disease manifestations to assure the treatment of an infectious process rather than merely colonization. The role of preventive therapy for the possible role of genital mycoplasmas in the genesis of CLD in very-low-birthweight infants awaits results of further studies. Treatment is based on predictable antimicrobial sensitivities,
because susceptibility testing is not readily available for individual isolates. For infants with symptomatic CNS infection, cures have been described with chloramphenicol, doxycycline, and moxifloxacin. The long-term consequences of asymptomatic CNS infection associated with genital mycoplasmas, especially in the absence of pleocytosis, are unknown. Because mycoplasmas can spontaneously clear from the CSF, therapy should involve minimal risks.

_Bibliography is available at Expert Consult._
Bibliography
Chlamydia pneumoniae is a common cause of lower respiratory tract diseases, including pneumonia in children and bronchitis and pneumonia in adults.

**ETIOLOGY**

Chlamydiae are obligate intracellular pathogens that have established a unique niche in host cells. Chlamydiae cause a variety of diseases in animal species at virtually all phylogenic levels. The most significant human pathogens are *C. pneumoniae* and *Chlamydia trachomatis* (see Chapter 226). *Chlamydia psittaci* is the cause of psittacosis, an important zoonosis (see Chapter 227).

Chlamydiae have a Gram-negative envelope without detectable peptidoglycan, although recent genomic analysis has revealed that both *C. pneumoniae* and *C. trachomatis* encode proteins forming a nearly complete pathway for synthesis of peptidoglycan, including penicillin-binding proteins. Chlamydiae also share a group-specific lipopolysaccharide antigen and use host adenosine triphosphate for the synthesis of chlamydial proteins. Although chlamydiae are auxotrophic for 3 of 4 nucleoside triphosphates, they encode functional glucose-catabolizing enzymes that can be used to generate adenosine triphosphate. As with peptidoglycan synthesis, for some reason these genes are turned off. All chlamydiae also encode an abundant surface exposed protein called the major outer membrane protein. The major outer membrane protein is the major determinant of the serologic classification of *C. trachomatis* and *C. psittaci* isolates.

**EPIDEMIOLOGY**

*C. pneumoniae* is primarily a human respiratory pathogen. The organism has also been isolated from nonhuman species, including horses, koalas, reptiles, and amphibians, where it also causes respiratory infection, although the role that these infections might play in transmission to humans is unknown. *C. pneumoniae* appears to affect individuals of all ages. The proportion of community-acquired pneumonias associated with *C. pneumoniae* infection is 2-19%, varying with geographic location, the age group examined, and the diagnostic methods used. Several studies of the role of *C. pneumoniae* in lower respiratory tract infection in pediatric populations have found evidence of infection in 0-18% of patients based on serology or culture for diagnosis. In 1 study, almost 20% of the children with *C. pneumoniae* infection were coinfected with *Mycoplasma pneumoniae*. *C. pneumoniae* may also be responsible for 10-20% of episodes of acute chest syndrome in children with sickle cell disease, up to 10% of asthma exacerbations, 10% of episodes of bronchitis, and 5-10% episodes of pharyngitis in children. Asymptomatic infection appears to be common based on epidemiologic studies.

Transmission probably occurs from person to person through respiratory droplets. Spread of the infection appears to be enhanced by close proximity, as is evident from localized outbreaks in enclosed populations, such as military recruits and in nursing homes.

**PATHOGENESIS**

Chlamydiae are characterized by a unique developmental cycle (Fig. 225-1) with morphologically distinct infectious and reproductive forms: the elementary body (EB) and reticulate body (RB). Following infection, the infectious EBs, which are 200-400 μm in diameter, attach to the host cell by a process of electrostatic binding and are taken into the cell by endocytosis that does not depend on the microtubule system. Within the host cell, the EB remains within a membrane-lined phagosome. The phagosome does not fuse with the host cell lysosome. The inclusion membrane is devoid of host cell markers, but lipid markers traffic to the inclusion, which suggests a functional interaction with the Golgi apparatus. The EBs then differentiate into RBs that undergo binary fission. After approximately 36 hr, the RBs differentiate into EBs. At approximately 48 hr, release can occur by cytolysis or by a process of exocytosis or extrusion of the whole inclusion, leaving the host cell intact. Chlamydiae can also enter a persistent state after treatment with certain cytokines such as interferon-γ treatment with antibiotics, or restriction of certain nutrients. While chlamydiae are in the persistent state, metabolic activity is reduced. The ability to cause prolonged, often subclinical, infection is one of the major characteristics of chlamydiae.

**CLINICAL MANIFESTATIONS**

Infections caused by *C. pneumoniae* cannot be readily differentiated from those caused by other respiratory pathogens, especially *M. pneumoniae*. The pneumonia usually occurs as a classic atypical (or non-bacterial) pneumonia characterized by mild to moderate constitutional symptoms, including fever, malaise, headache, cough, and often pharyngitis. Severe pneumonia with pleural effusions and empyema has
been described. Milder respiratory infections have been described, which can manifest as a pertussis-like illness.

*C. pneumoniae* can serve as an infectious trigger for asthma, can cause pulmonary exacerbations in patients with cystic fibrosis, and produce acute chest syndrome in patients with sickle cell anemia. *C. pneumoniae* has been isolated from middle ear aspirates of children with acute otitis media, most of the time as co-infection with other bacteria. Asymptomatic respiratory infection has been documented in 2-5% of adults and children and can persist for 1 yr or longer.

**DIAGNOSIS**

It is not possible to differentiate *C. pneumoniae* from other causes of atypical pneumonia on the basis of clinical findings. Auscultation reveals the presence of rales and often wheezing. The chest radiograph often appears worse than the patient's clinical status would indicate and can show mild, diffuse involvement or lobar infiltrates with small pleural effusions. The complete blood count may be elevated with a left shift but is usually unremarkable.

Specific diagnosis of *C. pneumoniae* infection is based on isolation of the organism in tissue culture. *C. pneumoniae* grows best in cycloheximide-treated HEP-2 and HL cells. The optimum site for culture is the posterior nasopharynx; the specimen is collected with wire-shafted swabs in the same manner as that used for *C. trachomatis*. The organism can be isolated from sputum, throat cultures, bronchoalveolar lavage fluid, and pleural fluid, but few laboratories perform such cultures because of technical difficulties. BioFire Technologies (formerly Idaho Technologies) has a nucleic acid amplification testing assay (Film Array) for the detection of 17 viruses and some of the atypical agents of pneumonia, including *C. pneumoniae, M. pneumoniae*, and *Bordetella pertussis*. This assay received FDA clearance in July 2012. The Film Array system combines nucleic acid extraction, nested polymerase chain reaction, detection, and data analysis.

Serologic diagnosis can be accomplished using the microimmunofluorescence (MIF) or the complement fixation tests. The complement fixation test is genus specific and is also used for diagnosis of lymphogranuloma venereum (see Chapter 226.4) and psittacosis (see Chapter 227). Its sensitivity in hospitalized patients with *C. pneumoniae* infection and children is variable. The Centers for Disease Control and Prevention (CDC) has proposed modifications in the serologic criteria for diagnosis. Although the MIF test was considered to be the only currently acceptable serologic test, the criteria were made significantly more stringent. Acute infection, using the MIF test, was defined by a 4-fold increase in immunoglobulin (Ig) G titer or an IgM titer of ≥16; use of a single elevated IgG titer was discouraged. An IgG titer of ≥16 was thought to indicate past exposure, but neither elevated IgA titers nor any other serologic marker was thought to be a valid indicator of persistent or chronic infection. Because diagnosis would require paired sera, this would be a retrospective diagnosis. The CDC did not recommend the use of any enzyme-linked immune assay for detection of antibody to *C. pneumoniae* because of concern about the inconsistent correlation of these results with culture results. Studies of *C. pneumoniae* infection in children with pneumonia and asthma show that more than 50% of children with culture-documented infection have no detectable MIF antibody.

**TREATMENT**

The optimum dose and duration of antimicrobial therapy for *C. pneumoniae* infections remain uncertain. Most treatment studies have used only serology for diagnosis, and thus microbiologic efficacy cannot be assessed. Prolonged therapy for 2 wk or longer is required for some patients, because recrudescent symptoms and persistent positive cultures have been described following 2 wk of erythromycin and 30 days of tetracycline or doxycycline.

Tetracyclines, erythromycin, the macrolides (azithromycin and clarithromycin), and quinolones show in vitro activity. Like *C. psittaci*, *C. pneumoniae* is resistant to sulfonamides. The results of treatment studies have shown that erythromycin (40 mg/kg/day PO divided twice a day for 10 days), clarithromycin (15 mg/kg/day PO divided twice a day for 10 days), and azithromycin (10 mg/kg PO on day 1, and then 5 mg/kg/day PO on days 2-5) are effective for eradication of *C. pneumoniae* from the nasopharynx of children with pneumonia in approximately 80% of cases.

**PROGNOSIS**

Clinical response to antibiotic therapy varies. Coughing often persists for several weeks even after therapy.

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Bibliography


Chlamydia trachomatis is subdivided into 2 biovars: lymphogranuloma venereum (LGV) and trachoma, which is the agent of human oculo-genital diseases other than LGV. Although the strains of both biovars have almost complete DNA homology, they differ in growth characteristics and virulence in tissue culture and animals. In developed countries, C. trachomatis is the most prevalent sexually transmitted disease, causing urethritis in men, cervicitis and salpingitis in women, and conjunctivitis and pneumonia in infants.

226.1 Trachoma

Trachoma is the most important preventable cause of blindness in the world. It is caused primarily by the A, B, Ba, and C serotypes of C. trachomatis. It is endemic in the Middle East and Southeast Asia and among Navajo Indians in the southwestern United States. In areas that are endemic for trachoma, such as Egypt, genital chlamydial infection is caused by the serotypes responsible for oculogenital disease: D, E, F, G, H, I, J, and K. The disease is spread from eye to eye. Flies are a common vector.

Trachoma begins as a follicular conjunctivitis, usually in early childhood. The follicles heal, leading to conjunctival scarring that can result in an entropion, with the eyelid turning inward so that the lashes abrade the cornea. It is the corneal ulceration secondary to the constant trauma that leads to scarring and blindness. Bacterial superinfection can also contribute to scarring. Blindness occurs years after the active disease.

Trachoma can be diagnosed clinically. The World Health Organization suggests that at least 2 of 4 criteria must be present for a diagnosis of trachoma: lymphoid follicles on the upper tarsal conjunctivae, typical conjunctival scarring, vascular pannus, and limbal follicles. The diagnosis is confirmed by culture or staining tests for C. trachomatis performed during the active stage of disease. Serologic tests are not helpful clinically because of the long duration of the disease and the high seroprevalence in endemic populations.

Poverty and lack of sanitation are important factors in the spread of trachoma. As socioeconomic conditions improve, the incidence of the disease decreases substantially. Endemic trachoma has been controlled in most instances by administering topical tetracyclines (or, rarely, erythromycin ointment) daily for periods of 6-10 wk or intermittently over a 6 mo period. Oral doxycycline is effective but is contraindicated in children younger than 8 yr of age. Oral erythromycin requires frequent dosing, which is impractical in the control of endemic trachoma.
Several studies have reported that 1-6 doses of oral azithromycin are equivalent to 30 days of treatment with topical oxytetracycline/ polymyxin ointment. The World Health Organization recommends single-dose azithromycin (20 mg/kg; maximum: 1 g) for the treatment of trachoma in children. Mass treatment with a single dose of azithromycin to all the residents of a village dramatically reduced the prevalence and intensity of infection. This effect continued for 2 yr after treatment, probably by interrupting the transmission of ocular *C. trachomatis* infection.

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### 226.2 Genital Tract Infections

**Margaret R. Hammerschlag**

**EPIDEMIOLOGY**

There are an estimated 3 million new cases of chlamydial sexually transmitted infections each year in the United States. *C. trachomatis* is a major cause of epididymitis and is the cause of 23-55% of all cases of nongonococcal urethritis, although the proportion of chlamydial nongonococcal urethritis has been gradually declining. As many as 50% of men with gonorrhea may be coinfected with *C. trachomatis*. The prevalence of chlamydial cervicitis among sexually active women is 2-35%. Rates of infection among girls 15-19 yr of age exceed 20% in many urban populations but can be as high as 15% in suburban populations as well.

Children who have been sexually abused can acquire anogenital *C. trachomatis* infection, which is usually asymptomatic. However, because perinatally acquired rectal and vaginal *C. trachomatis* infections can persist for 3 yr or longer, the detection of *C. trachomatis* in the vagina or rectum of a young child is not absolute evidence of sexual abuse.

**CLINICAL MANIFESTATIONS**

The trachoma biovar of *C. trachomatis* causes a spectrum of disease in sexually active adolescents and adults. Up to 75% of women with *C. trachomatis* have no symptoms of infection. *C. trachomatis* can cause urethritis (acute urethral syndrome), epididymitis, cervicitis, salpingitis, proctitis, and pelvic inflammatory disease. The symptoms of chlamydial genital tract infections are less acute than those of gonorrhea, consisting of a discharge that is usually mucoid rather than purulent. Asymptomatic urethral infection is common in sexually active men. Autoinoculation from the genital tract to the eyes can lead to conjunctival inclusion conjunctivitis.

**DIAGNOSIS**

Definitive diagnosis of genital chlamydial infection is accomplished by isolation of the organism in tissue culture and confirmed by microscopic identification of the characteristic inclusions using fluorescent antibody staining in culture specimens obtained from the urethra in men and the endocervix in women. Care should be taken to obtain epithelial cells, not only discharge. *C. trachomatis* can be cultured in cycloheximide-treated HeLa, McCoy, and HEP-2 cells. Chlamydia culture has been further defined by the Centers for Disease Control and Prevention (CDC) as isolation of the organism in tissue culture and as confirmation of the characteristic intracytoplasmic inclusions by fluorescent antibody staining.

Alternatively, a nonculture method, specifically a nucleic acid amplification test (NAAT) can be used. These tests have high sensitivity, perhaps even detecting 10-20% greater than culture, while retaining high specificity. Currently, 4 FDA-approved NAATs are commercially available for detection *C. trachomatis* polymerase chain reaction (PCR; Amplicor Chlamydia test, Roche Molecular Diagnostics, Nutley, NJ), strand displacement amplification (ProbeTec, BD Diagnostic Systems, Sparks, MD), transcription-mediated amplification (AMP CT, Gen Probe, San Diego, CA) and GeneXpert CT/NG assay (Cepheid, Sunnyvale, CA). PCR and strand displacement amplification are DNA amplification tests that use primers that target gene sequences on the cryptogenic *C. trachomatis* plasmid that are present at approximately 10 copies in each infected cell. Transcription-mediated amplification is a ribosomal RNA amplification assay. GeneXpert is an on-demand qualitative real-time PCR. All these assays are also available as coamplification tests for simultaneously detecting *C. trachomatis* and *Neisseria gonorrhoeae*.

The currently available commercial NAATs are FDA approved for cervical swabs from adolescent girls and women, urethral swabs from adolescent boys and men, and urine from adolescents and adults. The latest version of transcription-mediated amplification was approved for use with vaginal swabs in adolescents and adults. Use of urine avoids the necessity for a clinical pelvic examination and can greatly facilitate screening in certain populations, especially adolescents, although several studies have now demonstrated that endocervical specimens and vaginal swabs are superior to urine for NAAT. Self-collected vaginal specimens appear to be as reliable as specimens obtained by a healthcare professional.

Data on use of NAATs for vaginal specimens or urine from children are very limited and insufficient to allow making a recommendation for their use. The CDC recommends that NAATs be used as an alternative to culture only if confirmation is available. Confirmation tests should consist of a second FDA-approved NAAT that targets a different gene sequence from the initial test.

The etiology of most cases of nonchlamydial nongonococcal urethritis is unknown, although *Ureaplasma urealyticum* and possibly *Mycoplasma genitalium* are implicated in up to one-third of cases (see Chapter 224). Proctocolitis may develop in individuals who have a rectal infection with an LGV strain (see Chapter 226.4).

### TREATMENT

The first-line treatment regimens recommended by the CDC for uncomplicated *C. trachomatis* genital infection in men and nonpregnant women include azithromycin (1 g PO as a single dose) and doxycycline (100 mg PO twice a day for 7 days). Alternative regimens are erythromycin base (500 mg PO 4 times a day for 7 days), erythromycin ethylsuccinate (800 mg PO 4 times a day for 7 days), ofloxacin (300 mg PO twice a day for 7 days), and levofloxacin (500 mg PO once daily for 7 days). The high erythromycin dosages might not be well tolerated. Doxycycline and quinolones are contraindicated in pregnant women, and quinolones are contraindicated in persons younger than 18 yr. For pregnant women, the recommended treatment regimen is azithromycin (1 g PO as a single dose) or amoxicillin (500 mg PO 3 times a day for 7 days). Alternative regimens for pregnant women are erythromycin base (250 mg PO 4 times a day for 14 days), and erythromycin ethylsuccinate (800 mg PO 4 times a day for 7 days or 400 mg PO 4 times a day for 14 days).

**Empirical treatment** without microbiologic diagnosis is recommended only for patients at high risk for infection who are unlikely to return for follow-up evaluation, including adolescents with multiple sex partners. These patients should be treated empirically for both *C. trachomatis* and gonorrhea.

**Sex partners** of patients with nongonococcal urethritis should be treated if they have had sexual contact with the patient during the 60 days preceding the onset of symptoms. The most recent sexual partner should be treated even if the last sexual contact was more than 60 days from onset of symptoms.

### COMPLICATIONS

Complications of genital chlamydial infections in women include pericystitis (Fitz-Hugh–Curtis syndrome) and salpingitis. Of women with untreated chlamydial infection who develop pelvic inflammatory disease, up to 40% will have significant sequelae; approximately 17% will suffer from chronic pelvic pain, approximately 17% will become infertile, and approximately 9% will have an ectopic (tubal) pregnancy. Adolescent girls may be at higher risk for developing complications, especially salpingitis, than older women. Salpingitis in adolescent girls is also more likely to lead to tubal scarring, subsequent obstruction with secondary infertility, and increased risk for ectopic pregnancy. Approximately 50% of neonates born to pregnant women with untreated chlamydial infection will acquire *C. trachomatis* infection.
Bibliography


Chlamydia trachomatis infections should be empirically treated for genital infections. Infants born to mothers with Chlamydia pneumoniae. A distinctive laboratory finding is the presence of peripheral eosinophilia (≥5% of white blood cells). The absence of fever and wheezing helps to distinguish nonbronchopulmonary disease from bronchopulmonary disease. At least 50% of infants with chlamydial conjunctivitis must be differentiated from gonococcal ophthalmia, which is often associated with rectal infection. A rectal examination reveals friable tissue. Chlamydial conjunctivitis can develop infection in the conjunctiva of infants with conjunctivitis. The recommended treatment regimens for C. trachomatis conjunctivitis or pneumonia in infants are erythromycin (base or ethylsuccinate, 50 mg/kg/day divided 4 times a day PO for 14 days) and azithromycin suspension (20 mg/kg/day once daily PO for 3 days). The rationale for using oral therapy for conjunctivitis is that 50% or more of these infants have concomitant nasopharyngeal infection or disease at other sites, and studies demonstrate that topical therapy with sulfonamide drops and erythromycin ointment is not effective. The failure rate with oral erythromycin remains 10-20%, and some infants require a second course of treatment. Mothers (and their sexual contacts) of infants with C. trachomatis infections should be empirically treated for genital infection. An association between treatment with oral erythromycin and infantile hypertrophic pyloric stenosis has been reported in infants younger than 6 wk of age who were given the drug for prophylaxis after nursery exposure to pertussis. The most effective method of controlling perinatal chlamydial infection is screening and treatment of pregnant women. For treatment of C. trachomatis infection in pregnant women, the CDC currently recommends either azithromycin (1 g PO as a single dose) or amoxicillin (500 mg PO 3 times a day for 7 days) as first-line regimens. Erythromycin base (250 mg PO 4 times a day for 14 days) and erythromycin ethylsuccinate (800 mg 4 times a day for 7 days, or 400 mg PO 4 times a day for 14 days) are listed as alternative regimens. Reasons for failure of maternal treatment to prevent infantile chlamydial infection include poor compliance and reinfection from an untreated sexual partner. Neonatal gonococcal prophylaxis with topical erythromycin ointment does not prevent chlamydial ophthalmia or nasopharyngeal colonization with C. trachomatis or chlamydial pneumonia. The most effective method of controlling perinatal chlamydial infection is screening and treatment of pregnant women. For treatment of C. trachomatis infection in pregnant women, the CDC currently recommends either azithromycin (1 g PO as a single dose) or amoxicillin (500 mg PO 3 times a day for 7 days) as first-line regimens. Erythromycin base (250 mg PO 4 times a day for 14 days) and erythromycin ethylsuccinate (800 mg 4 times a day for 7 days, or 400 mg PO 4 times a day for 14 days) are listed as alternative regimens. Reasons for failure of maternal treatment to prevent infantile chlamydial infection include poor compliance and reinfection from an untreated sexual partner. LGV is a systemic sexually transmitted disease caused by the L1, L2, and L3 serotypes of the LGV biovar of C. trachomatis. Unlike strains of the trachoma biovar, LGV strains have a predilection for lymphoid tissue. Less than 1,000 cases are reported in adults in the United States annually. There has been a resurgence of LGV infections among men who have sex with men in Europe and the United States. Many of the men were HIV infected and used illicit drugs, specifically methamphetamine. To our knowledge, cases in the pediatric population have not been reported since the emergence of the new clusters of HIV-associated cases in 2003. We reported a case of a 16yr old boy who presented with LGV proctocolitis after having receptive unprotected anal intercourse with a 30yr old man he met on the Internet. This history was obtained after the boy was found to be HIV-positive.
Bibliography
Bibliography

diagnosis of LGV, particularly when it presents with proctocolitis, relies on a high index of suspicion that would lead to emphasizing certain aspects of the history and ordering the pertinent diagnostic tests. Many pediatricians and pediatric gastroenterologists might not be very familiar with the entity and might not entertain it as a diagnostic consideration in the pediatric patients. The diagnosis can be further suggested by *C. trachomatis* testing: culturing the organism or, more commonly by NAATs. Currently available NAATs will not differentiate LGV from other *C. trachomatis* serovars. NAATs for *C. trachomatis* are also not FDA-cleared for testing rectal specimens. Trying to ascertain the *C. trachomatis* serovar for confirmation of LGV has therapeutic implications as a single-dose of azithromycin is unlikely to eradicate the infection and a 3 wk course of doxycycline is the preferred treatment.

**CLINICAL MANIFESTATIONS**

The 1st stage of LGV is characterized by the appearance of the primary lesion, a painless, usually transient papule on the genitals. The 2nd stage is characterized by usually unilateral femoral or inguinal lymphadenitis with enlarging, painful buboes. The nodes may break down and drain, especially in men. In women, the vulvar lymph drains to the retroperitoneal nodes. Fever, myalgia, and headache are common. The 3rd stage is a genitoanorectal syndrome with rectovaginal fistulas, rectal strictures, and urethral destruction. Among men who have sex with men, rectal infection with LGV can produce a severe, acute proctocolitis, which can be confused with inflammatory bowel disease or malignancy.

**DIAGNOSIS**

LGV can be diagnosed by serologic testing or by culture of *C. trachomatis* or molecular testing for *C. trachomatis* from a specimen aspirated from a bubo. Most patients with LGV have complement-fixing antibody titers of >1:16. Chancroid and herpes simplex virus can be distinguished clinically from LGV by the concurrent presence of painful genital ulcers. Syphilis can be differentiated by serologic tests. However, co-infections can occur.

**TREATMENT**

Doxycycline (100 mg PO bid for 21 days) is the recommended treatment. The alternative regimen is erythromycin base (500 mg PO 4 times/day for 21 days). Azithromycin (1 g PO once weekly for 3 wk) may also be effective but clinical data are lacking. Sex partners of patients with LGV should be treated if they have had sexual contact with the patient during the 30 days preceding the onset of symptoms.

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Psittacosis (Chlamydia psittaci)
Stephan A. Kohlhoff and Margaret R. Hammerschlag

Chlamydia psittaci, the agent of psittacosis (also known as parrot fever and ornithosis), is primarily an animal pathogen and causes human disease uncommonly. In birds, C. psittaci infection is known as avian chlamydiosis.

ETIOLOGY
C. psittaci affects both psittacine birds (e.g., parrots, parakeets, macaws) and nonpsittacine birds (ducks, turkeys); the known host range includes 130 avian species. The life cycle of C. psittaci is the same as for Chlamydia pneumoniae (see Chapter 217). Strains of C. psittaci have been analyzed by patterns of pathogenicity, inclusion morphology in tissue culture, DNA restriction endonuclease analysis, and monoclonal antibodies, which indicate that there are 7 avian serovars. Two of the avian serovars, psittacine and turkey, are of major importance in the avian population of the United States. Each is associated with important host preferences and disease characteristics.

EPIDEMIOLOGY
From 1988-2003 there were 935 reported cases of psittacosis in the United States. Of these, 85% of these cases were associated with exposure to birds, including 70% following exposure to caged pet birds, which were usually psittacine birds, including cockatiels, parakeets, parrots, and macaws. Chlamydiosis among caged nonpsittacine birds occurs most often in pigeons, doves, and mynah birds. Persons at highest risk for acquiring psittacosis include bird fanciers and owners of pet birds (43% of cases) and pet shop employees (10% of cases). Reported cases most likely underestimate the number of actual infections owing to a lack of awareness.

Inhalation of aerosols from feces, fecal dust, and nasal secretions of animals infected with C. psittaci is the primary route of infection. Source birds are either asymptomatic or have anorexia, ruffled feathers, lethargy, and watery green droppings. Psittacosis is uncommon in children, in part because children may be less likely to have close contact with infected birds. One high-risk activity is cleaning the cage. Several major outbreaks of psittacosis have occurred in turkey-processing plants; workers exposed to turkey viscera are at the highest risk for infection.

CLINICAL MANIFESTATIONS
Infection with C. psittaci in humans ranges from clinically inapparent to severe disease, including pneumonia and multiorgan involvement. The mean incubation period is 15 days after exposure, with a range of 5-21 days. Onset of disease is usually abrupt, with fever, cough, headache, myalgia, and malaise. The fever is high and is often associated with rigors and sweats. The headache can be so severe that meningitis is considered. The cough is usually nonproductive. Gastrointestinal symptoms are occasionally reported. Crackles may be heard on auscultation. Chest radiographs are usually abnormal and are characterized by the presence of variable infiltrates, sometimes accompanied by pleural effusions. The white blood cell count is usually normal but is sometimes mildly elevated. Elevated levels of aspartate aminotransferase, alkaline phosphatase, and bilirubin are common.

DIAGNOSIS
Psittacosis can be difficult to diagnose because of the varying clinical presentations. A history of exposure to birds or association with an active case can be important clues, but as many as 20% of patients with psittacosis have no known contact. Person-to-person spread has been suggested but not proved. Other infections that cause pneumonia with high fever, unusually severe headache, and myalgia include routine bacterial and viral respiratory infections as well as Coxiella burnetii infection (Q fever), Mycoplasma pneumoniae infection, C. pneumoniae infection, tularemia, tuberculosis, fungal infections, and Legionnaires disease.

The Centers for Disease Control and Prevention and the Council of State and Territorial Epidemiologists have established national case definitions for epidemiologic surveillance of psittacosis. A patient is considered to have a confirmed case of psittacosis if clinical illness is compatible with psittacosis and the case is laboratory confirmed by either: isolation of C. psittaci from respiratory specimens (e.g., sputum, pleural fluid, or tissue) or blood, or 4-fold or greater increase in antibody (immunoglobulin G) against C. psittaci by complement fixation or microimmunofluorescence between paired acute- and convalescent-phase serum specimens obtained at least 2-4 wk apart. A patient is considered to have a probable case of psittacosis if the
clinical illness is compatible with psittacosis and 1 of the 2 following laboratory results is present: supportive serology (e.g., C. psittaci antibody titer [Immunoglobulin M] of greater \( \geq 32 \) in at least 1 serum specimen obtained after onset of symptoms), or detection of C. psittaci DNA in a respiratory specimen (e.g., sputum, pleural fluid or tissue) via amplification of a specific target by polymerase chain reaction assay.

Although microimmunofluorescence has greater specificity to C. psittaci than complement fixation, crossreactions with other Chlamydia species can occur. Therefore acute- and convalescent-phase serum specimens should be analyzed at the same time in the same laboratory. False-negative microimmunofluorescence results can occur in acutely ill patients. Early treatment of psittacosis with tetracycline can abrogate the antibody response.

Although C. psittaci will grow in the same culture systems used for isolation of Chlamydia trachomatis and C. pneumoniae, very few laboratories culture for C. psittaci, mainly because of the potential biohazard. Real-time polymerase chain reaction assays have been developed for use in the detection of C. psittaci in respiratory specimens. These assays can distinguish C. psittaci from other chlamydial species and identify different C. psittaci genotypes. However, polymerase chain reaction–based tests have not been cleared by the FDA for use as diagnostic tests in humans samples.

**TREATMENT**
Recommended treatment regimens for psittacosis are doxycycline (100 mg PO twice daily) or tetracycline (500 mg PO 4 times a day) for at least 10-14 days after the fever abates. The initial treatment of severely ill patients is doxycycline hyclate (4.4 mg/kg/day divided every 12 hr IV; maximum: 100 mg/dose). Erythromycin (500 mg PO 4 times a day) and azithromycin (10 mg/kg PO day 1, not to exceed 500 mg, followed by 5 mg/kg PO on days 2-5, not to exceed 250 mg) are alternative drugs if tetracyclines are contraindicated (e.g., children <8 yr of age and pregnant women) but may be less effective. Remission is usually evident within 48-72 hr. Initial infection does not appear to be followed by long-term immunity. Reinfection and clinical disease can develop within 2 mo of treatment.

**PROGNOSIS**
The mortality rate of psittacosis is 15-20% with no treatment but is <1% with appropriate treatment. Severe illness leading to respiratory failure and fetal death has been reported among pregnant women.

**PREVENTION**
Several control measures are recommended to prevent transmission of C. psittaci from birds. Bird fanciers should be cognizant of the potential risk. C. psittaci is susceptible to heat and to most disinfectants and detergents but is resistant to acid and alkali. Accurate records of all bird-related transactions aid in identifying sources of infected birds and potentially exposed persons. Newly acquired birds, including birds that have been to shows, exhibitions, fairs, or other events, should be isolated for 30-45 days or tested or treated prophylactically before adding them to a group of birds. Care should be taken to prevent transfer of fecal material, feathers, food, or other materials between birdcages. Birds with signs of avian chlamydiosis (e.g., ocular or nasal discharge, watery green droppings, or low body weight) should be isolated and should not be sold or purchased. Their handlers should wear protective clothing and a disposable surgical cap and use a respirator with an N95 or higher efficiency rating (not a surgical mask) when handling them or cleaning their cages. Infected birds should be isolated until fully treated, which is generally 45 days.

* Bibliography is available at Expert Consult.
Bibliography


Rickettsia species were classically divided into “spotted fever” and “typhus” groups based on serologic reactions and later on the presence or absence of the outer membrane protein A (ompA) gene. Sequencing of at least 45 complete genomes has refined distinctions. However, there is controversy regarding phylogeny and some data suggest that diversity and pathogenicity are the result of gene loss and lateral gene transfer from other prokaryotes or even eukaryotes, which further obscures accurate taxonomic classification. One proposal is to divide existing species into spotted fever and “transitional” groups based on genetic relatedness; both include pathogenic species and species not now known to cause human disease (Table 228-1). Although increasingly more is understood about the molecular basis by which these bacteria cause human illness, an alternative classification system based on pathogenetic mechanisms has not been defined. The list of pathogens and potential pathogens in the spotted fever group has expanded dramatically in recent years. Among them are the tickborne agents Rickettsia rickettsii, the cause of Rocky Mountain or Brazilian spotted fever (RMSF); Rickettsia conorii, the cause of Mediterranean spotted fever (MSF) or boutonneuse fever; Rickettsia sibirica, the cause of North Asian tick typhus; Rickettsia japonica, the cause of Oriental spotted fever; Rickettsia honei, the cause of Flinders Island spotted fever or Thai tick typhus; Rickettsia philippinae, the cause of African tick bite fever; Rickettsia akari, the cause of mite-transmitted rickettsialpox; Rickettsia felis, the cause of cat flea–transmitted typhus; and Rickettsia australis, the cause of tick-transmitted Queensland tick typhus. One proposal creates subspecies of R. conorii, including subsp. conorii (classical MSF), subsp. indica (Indian tick typhus), subsp. caspia (Astrakhan fever), and subsp. israelensis (Israeli spotted fever). The recognition that Rickettsia parkeri and “Rickettsia philippinae” (Rickettsia 364D) both cause mild spotted fever in North America and the association of high seroprevalence for spotted fever group Rickettsia infections in humans where Amblyomma ticks frequently contain Rickettsia amblyommii suggest that the full range of agents that can cause spotted fever is still to be discerned.

Infections with other members of the spotted fever and transitional groups are clinically similar to MSF, with fever, maculopapular rash, and eschar at the site of the tick bite. Israeli spotted fever is generally associated with a more severe course, including death, in children. African tick bite fever is relatively mild, can include a vesicular rash, and often manifests with multiple eschars. New potentially pathogenic rickettsial species have been identified, including Rickettsia slovaca, the cause of tickborne lymphadenopathy or Dermacentor-borne necrosis and lymphadenopathy. Rickettsia aeschlimannii, Rickettsia heilongjiangensis, Rickettsia helvetica, Rickettsia massiliae, and Rickettsia raoultii are all reported to cause mild to moderate illnesses in humans, although few cases have been described. Fortunately, the vast majority of infections respond well to doxycycline treatment if instituted early in illness; however, this is a significant challenge.
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<th>SPOTTED FEVER GROUP</th>
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<th>GEOGRAPHIC DISTRIBUTION</th>
<th>PRESENTING CLINICAL FEATURES*</th>
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<td>Tick bite: <em>Dermacentor</em> species (wood tick, dog tick) <em>Rhipicephalus</em> sanguineus (brown dog tick)</td>
<td>Western hemisphere</td>
<td>Fever, headache, rash,* emesis, diarrhea, myalgias</td>
<td>AST, ALT ↓Na (mild) ↓Platelets ±Leukopenia Left shift</td>
<td>Early: IH, DFA, PCR After 1st wk: IFA</td>
<td>Doxycycline Tetracycline Chloramphenicol</td>
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<tr>
<td><em>Mediterranean spotted fever (Boutonneuse fever)</em> Rickettsia conorii</td>
<td>Tick bite: <em>R. sanguineus</em> (brown dog tick)</td>
<td>Africa, Mediterranean, India, Middle East</td>
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<td>AST, ALT ↓Na (mild) ↓Platelets ±Leukopenia Left shift</td>
<td>Early: IH, DFA, PCR After 1st wk: IFA</td>
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<tr>
<td><em>Tickborne lymphadenopathy (TIBOLA); Dermacentor-borne necrosis and lymphadenopathy (DEBONEL) Rickettsia slovaca</em></td>
<td>Tick bite: <em>Dermacentor</em></td>
<td>Europe</td>
<td>?</td>
<td>?</td>
<td>PCR</td>
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<tr>
<td><em>Rickettsia</em>, 364D genotype &quot;<em>Rickettsia philippinii</em>&quot;</td>
<td><em>Dermacentor occidentalis</em> (Pacific coast tick)</td>
<td>California</td>
<td>Eschar, fever, headache, lymphadenopathy malaise</td>
<td>Unremarkable</td>
<td>PCR</td>
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<td><em>Rickettsia</em> akari</td>
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<td>Mice</td>
<td>North America, Russia, Ukraine, Adriatic, Korea, South Africa</td>
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<td>Early: IH, DFA After 1st wk: IFA</td>
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<tr>
<td><em>Cat flea typhus</em> Rickettsia felis</td>
<td>Flea bite</td>
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<td>Cats, Dogs</td>
<td>Western hemisphere, Europe</td>
<td>Fever, rash,* headache</td>
<td>Early: PCR After 1st wk: IFA</td>
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<th>TYPHUS GROUP</th>
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<td><em>Murine typhus</em> Rickettsia typhi</td>
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<td>Fever, headache, rash,* myalgias, emesis, lymphadenopathy, hepatosplenomegaly</td>
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<tr>
<td><em>Epidemic (louse-borne) typhus (recrudescence form; Brill-Zinsser disease) Rickettsia prowazekii</em></td>
<td>Louse feces</td>
<td>Humans</td>
<td>South America, Central America, Mexico, Africa, Asia, Eastern Europe</td>
<td>Fever, headache, abdominal pain, rash,* CNS involvement</td>
<td>Early: none After 1st wk: IgG/IgM, IFA</td>
<td>Doxycycline Tetracycline Chloramphenicol</td>
</tr>
<tr>
<td><em>Flying squirrel (sylvatic) typhus</em> Rickettsia prowazekii</td>
<td>Louse feces? Flea feces or bite?</td>
<td>Flying squirrels</td>
<td>Eastern United States</td>
<td>Same as above (often milder)</td>
<td>AST, ALT ↓Platelets</td>
<td>Doxycycline Tetracycline Chloramphenicol</td>
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<td><em>Orientia tsutsugamushi</em></td>
<td>Leptotrombidium</td>
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### Ehrlichioses and Anaplasmosis

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<th>Ehrlichia spp.</th>
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<td>Amblyomma americanum (lone star tick)</td>
<td>Deer</td>
<td>United States, Europe</td>
<td>Fever, headache, malaise, myalgias, rash, descending platelets</td>
<td>AST, ALT ↓WBC ↓Platelets ↓Na (mild) AST, ALT ↓WBC ↓ANC ↓Platelets ↓Na (mild)</td>
<td>Doxycycline Tetracycline Chloramphenicol</td>
</tr>
<tr>
<td>Ehrlichia ewingii</td>
<td>Amblyomma americanum (lone star tick)</td>
<td>Dogs</td>
<td>United States (south-central, southeast)</td>
<td>Fever, headache, malaise, myalgias</td>
<td>AST, ALT ↓WBC ↓Platelets ↓Na (mild)</td>
<td>Doxycycline Tetracycline</td>
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### Q Fever

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<th><strong>Bacteria</strong></th>
<th><strong>Clinical Manifestations</strong></th>
<th><strong>Diagnosis</strong></th>
<th><strong>Treatment</strong></th>
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<tr>
<td><em>Coxiella burnetii</em></td>
<td>Fever, headache, arthralgias, myalgias, gastrointestinal symptoms, cough, pneumonia, rash (children)</td>
<td>AST, ALT ↓WBC ↓Platelets Interstitial infiltrate</td>
<td>Doxycycline Tetracycline Fluoroquinolones Trimethoprim-sulfamethoxazole</td>
</tr>
</tbody>
</table>

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* Rash is infrequently present at initial presentation but appears during the 1st wk of illness.
† Preferred treatment is in bold.
‡ Often present in children but not adults.

ALT, alanine aminotransferase; ANC, absolute neutrophil count; AST, aspartate aminotransferase; CNS, central nervous system; DFA, direct fluorescent antibody; IFA, indirect fluorescent antibody; IgG, immunoglobulin G; IgM, immunoglobulin M; IH, immunohistochemistry; PCR, polymerase chain reaction; WBC, white blood cell count.
228.1 Rocky Mountain Spotted Fever (Rickettsia rickettsii)
Megan E. Reller and J. Stephen Dumler

RMSF is the most frequently identified and most severe rickettsial disease in the United States. It is also the most common vector-borne disease in the United States after Lyme disease. Although considered uncommon, RMSF is believed to be greatly underdiagnosed and underreported. RMSF should be considered in the differential diagnosis of fever, headache, and rash in the summer months, especially after tick exposure. Because fulminant disease and death are associated with delays in treatment, patients in whom the illness is clinically suspected should be treated promptly.

ETIOLOGY
RMSF results from systemic infection of endothelial cells by the obligate intracellular bacterium Rickettsia rickettsii.

EPIEDEMILOGY
The term Rocky Mountain spotted fever is historical, because the agent was discovered in the Bitterroot Range of the Rocky Mountains of Montana. Few cases are now reported from this region. Cases have been reported throughout the continental United States (except Vermont and Maine), southwestern Canada, Mexico, Central America, and South America, but not from outside of the Western Hemisphere. In 2010, the Centers for Disease Control and Prevention (CDC) reporting criteria for “Rocky Mountain spotted fever” changed to spotted fever group rickettsiosis because serology often does not distinguish R. rickettsii from infection by other spotted fever group Rickettsia. Additionally, cases detected by enzyme immunoassay were classified as probable. Thus, in 2012, 2,802 confirmed and probable cases of spotted fever rickettsiosis were reported in Morbidity and Mortality Weekly Reports Summary of Notifiable Diseases. Unlike in prior years, most cases were reported from the west south-central states, especially from Arkansas, Oklahoma, and Missouri; high numbers of cases were also reported from North Carolina, Tennessee, Virginia, New Jersey, Georgia, Alabama, as well as Arizona. The incidence of RMSF cycles over 25-35 yr intervals but has generally increased over the past decades. The mean number of cases reported each year to the CDC has steadily increased (515 during 1993-1998, 946 during 1999-2004, and 2,068 cases in 2005-2010). Habitats favored by ticks, including wooded areas or coastal grassland and salt marshes, and, in the Southwestern United States and Mexico, shaded areas where dogs congregate are associated with disease. Foci of intense infection are found both in rural and urban areas. Clustering of cases within families likely reflects shared environmental exposures. In the United States, 90% of cases occur between April and September, months in which humans spend the most time outdoors. The highest age-specific incidence of RMSF among children is seen in those older than 5 yr of age, with boys outnumbering girls.

TRANSMISSION
Ticks are the natural hosts, reservoirs, and vectors of R. rickettsii and maintain the infection in nature by transovarial transmission (passage of the organism from infected ticks to their progeny). Ticks harboring rickettsiae are substantially less fecund than uninfected ticks; thus, horizontal transmission (acquisition of rickettsiae by taking a blood meal from transiently rickettsemic hosts such as small mammals or dogs) contributes to maintenance of rickettsial infections in ticks. Uninfected ticks that simultaneously feed (cofeed) with infected transmitting ticks easily become infected, even if feeding on an immune host and are also likely to be major contributors to natural transmission and maintenance. Ticks transmit the infectious agent to mammalian hosts (including humans) via infected saliva during feeding. The pathogen R. rickettsii in ticks becomes virulent after exposure to blood or increased temperature; thus, the longer the tick is attached, the greater the risk of transmission. The principal tick hosts of R. rickettsii are Dermacentor variabilis (the American dog tick) in the eastern United States and Canada, Dermacentor andersoni (the wood tick) in the western United States and Canada, Rhipicephalus sanguineus (the common brown dog tick) in the southwestern United States and in Mexico, and Amblyomma cajennense and Amblyomma aureolatum in Central and South America (Fig. 228-1).

Dogs can serve as reservoir hosts for R. rickettsii, can develop RMSF themselves, and can bring infected ticks into contact with humans. Serologic studies suggest that many patients with RMSF likely acquired the illness from ticks carried by the family dog.

Humans can also become infected when trying to remove an attached tick, because R. rickettsii—containing tick fluids or feces can be rubbed into the open wound at the bite site or into the conjunctivae by contaminated fingers. Finally, inhalation of aerosolized rickettsiae has caused severe infections and deaths in laboratory workers.

PATHOLOGY AND PATHOGENESIS
Systemic infection is most obvious on the skin (rash), but nearly all organs and tissues are affected. Following inoculation of tick saliva into the dermis, rickettsial outer surface proteins bind to the vascular endothelial cell surface proteins, which signals focal cytoskeletal changes that lead to endocytosis. Thereafter, rickettsia phospholipase-mediated dissolution of the endosomal membranes allows escape into the cytosol. Members of the spotted fever group actively nucleate actin polymerization on one pole to achieve directional movement, allowing some rickettsiae to propel into neighboring cells despite minimal initial damage to its host cell. The rickettsiae proliferate and damage the host cells by oxidative membrane alterations, protease activation, or continued phospholipase activity. It is likely that some aspects of intracellular infection are mediated by rickettsial protein effectors delivered into the host cell by a type 4 secretion system.

The histologic correlate of the initial macular or maculopapular rash is perivascular infiltration of lymphoid and histiocytic cells with edema but without significant endothelial damage. Proliferation of rickettsiae within the cytoplasm of infected endothelial cells leads to endothelial injury and lymphohistiocytic or leukocytoclastic vasculitis of small venules and capillaries, which allows extravasation of intravascular erythrocytes into the dermis and manifests as a petechial rash. This process is systemic and ultimately results in widespread microvascular
The presence of the infectious agent initiates an inflammatory cascade, including release of cytokines and chemokines such as tumor necrosis factor-α, interleukin-1β, and interferon-γ, and RANTES (regulated upon activation, normal T-cell expressed and secreted). Infection of endothelial cells by R. rickettsii induces surface E-selectin expression and procoagulant activity followed by chemokine recruitment of lymphocytes, macrophages, and, occasionally, neutrophils. Local inflammatory and immune responses are suspected to contribute to the vascular injury; however, the benefits of effective inflammation and immunity are greater. Blockade of tumor necrosis factor-α and interferon-γ action in animal models diminishes survival and increases morbidity; reactive oxygen intermediates, nitric oxide expression, and sequestration of tryptophan from rickettsiae are mechanisms by which rickettsiae are killed within cells. Direct contact of infected endothelial cells with perforin-producing CD8 T lymphocytes and interferon-γ action in animal models diminishes survival and increases morbidity; reactive oxygen intermediates, nitric oxide expression, and sequestration of tryptophan from rickettsiae are mechanisms by which rickettsiae are killed within cells. Direct contact of infected endothelial cells with perforin-producing CD8 T lymphocytes and interferon-γ–producing natural killer cells, accompanied by rickettsia antibody, helps control the infection. The timing and balance between rickettsia-mediated increases in vascular permeability and the benefits of induction of innate and adaptive immunity are likely the major determinants of severity and outcome.

**CLINICAL MANIFESTATIONS**

The incubation period of RMSF in children varies from 2-14 days (median: 7 days). In 49% of cases, patients or their parents report a history of removing an attached tick, although the site of the tick bite is usually inapparent. Epidemiologic clues include living in or visiting an endemic area, playing or hiking in the woods, typical season, similar illness in family members, and close contact with a dog. In patients presenting for care, the illness is initially nonspecific, and most patients are not diagnosed during their first visit with a healthcare practitioner. Manifestations often (>50%) include fever, rash, nausea and vomiting, and headache, and less often (<50%) myalgias, abdominal pain, diarrhea, conjunctival injection, altered mental status, lymphadenopathy, and peripheral edema. Pain and tenderness of calf muscles are particularly common in children.

The typical clinical triad of fever, headache, and rash is observed in 58% of pediatric patients overall, but is present in only 3% of all patients at presentation. Fever and headache persist if the illness is untreated. Fever can exceed 40°C (104°F) and may be persistently elevated or can fluctuate dramatically. Headache is severe, unremitting, and unresponsive to analgesics.

Rash usually appears after only 1-2 days of illness, and an estimated 3-5% of children never develop a rash that is recognized. Initially, discrete, pale, rose-red blanching macules or maculopapules appear; characteristically this initial rash is observed on the extremities, including the wrists, ankles, or lower legs (Fig. 228-2). In 65% of patients, the initial rash spreads rapidly to involve the entire body, including the soles and palms. The rash can become petechial or even hemorrhagic, sometimes with palpable purpura. In severe disease, the petechiae can enlarge into ecchymoses, which can become necrotic. Severe vascular obstruction secondary to the rickettsial vasculitis and thrombosis is uncommon but can result in gangrene of the digits, earlobes, scrotum, nose, or an entire limb.

**Central nervous system** infection usually manifests as changes in mental status (33%) or as photophobia (18%), seizure (17%), or meningismus (16%). Patients can also manifest ataxia, coma, or auditory deficits. Cerebrospinal fluid parameters are usually normal, but one-third have pleocytosis (<10-300 cells/μL), either mononuclear or less often neutrophil-dominated. Some (20%) have elevated protein (<200 mg/dL) in the cerebrospinal fluid; hypoglycorrhachia is rare. Neuroimaging studies generally reveal only subtle abnormalities that do not alter treatment. Cerebral edema, meningeal enhancement, and prominent perivascular spaces have been observed in patients with severe disease.

**Other**

Pulmonary disease occurs more often in adults than in children. However, 33% of children examined have a chest radiograph interpreted as an infiltrate or pneumonia. The clinical presentation in these cases can manifest as rales, infiltrates, and noncardiogenic pulmonary edema. Other findings can include conjunctival suffusion, periorbital edema, dorsal hand and foot edema, and hepatosplenomegaly. Severe disease can include myocarditis, acute renal failure, and vascular collapse.

Persons with glucose-6-phosphate dehydrogenase deficiency are at increased risk for fulminant RMSF, defined as death from R. rickettsii infection within 5 days. The clinical course of fulminant RMSF is characterized by profound coagulopathy and extensive thrombosis leading to kidney, liver, and respiratory failure. Features associated with increased risk of death include altered mental status, admission to an intensive care unit, need for inotropic support, coma, and need for rapidly administered intravenous fluid.

Occasionally, clinical signs and symptoms suggest a localized process such as appendicitis or cholecystitis. Thorough evaluation usually reveals evidence of a systemic process and unnecessary surgical interventions are avoided.

**LABORATORY FINDINGS**

Laboratory abnormalities are common but nonspecific. Thrombocytopenia occurs in 60%, and the total white blood cell count is most often normal, with leukocytosis in 24% and leukopenia in 9%. Other characteristic abnormalities include a left-shifted leukocyte differential, anemia (33%), hyponatremia (<135 mEq/mL in 52%), and elevated serum aminotransferase levels (50%).

**DIAGNOSIS**

Delays in diagnosis and treatment are associated with severe disease and death. Because no reliable diagnostic test is available to confirm RMSF during acute illness, the decision to treat must be based on compatible epidemiologic, clinical, and laboratory features. RMSF should be considered in patients presenting spring through fall with an acute febrile illness accompanied by headache and myalgia (particularly if they report exposure to ticks or contact with a dog or have been in forested or tick-infested rural areas). A history of tick exposure, a rash (especially if on the palms or soles), a normal or low leukocyte count with a marked left shift, a relatively low or decreasing platelet count, and a low serum sodium concentration are all clues that can support a diagnosis of RMSF. In patients without a rash or in dark-skinned patients in whom a rash can be difficult to appreciate, the diagnosis can be exceptionally elusive and delayed. One half of pediatric deaths occur within 9 days of onset of symptoms. Thus, treatment
should not be withheld pending definitive laboratory results for a patient with clinically suspected illness. Further, prompt response to early treatment is diagnostically helpful.

If a rash is present, a vasculotropic rickettsial infection can be diagnosed as early as day 1 or 2 of illness with biopsy of a petechial lesion and immunohistochemical or immunofluorescent demonstration of specific rickettsial antigen in the endothelium. Although very specific, the sensitivity of this method is probably 70% at most. Furthermore, it can be adversely influenced by prior antimicrobial therapy, suboptimal selection of skin lesions for biopsy, and examination of insufficient tissue because of the focal nature of the infection. Tissue or blood can also be evaluated for *R. rickettsii* nucleic acids by polymerase chain reaction (PCR) at the CDC and selected public health or reference laboratories; PCR on blood is less sensitive than PCR on tissue and of similar sensitivity to tissue immunohistology, probably because the level of rickettsialemia is generally very low (<5 rickettsiae/mL).

Definitive diagnosis is most often accomplished by serology, which is retrospective, because a rise in titer is not seen until after the 1st wk of illness. The gold standard for the diagnosis of RMSF is a 4-fold increase in immunoglobulin G antibody titer by indirect fluorescent antibody assay between acute and convalescent (at 2-4 wk) sera or demonstration of seroconversion. A single titer is neither sensitive (patients can die before seroconversion) nor specific (an elevated titer can represent prior infection); despite the historic role of immunoglobulin M testing, its role in early diagnosis has recently become controversial and cannot be advocated. With current serologic methods, RMSF cannot be reliably distinguished from other spotted fever group rickettsiae infections. Cross-reactions with typhus group rickettsiae also occur, but titers may be lower for the typhus group. Cross-reactions are not seen with *Ehrlichia or Anaplasma* infections. Weil-Felix antibody testing should not be performed, because it lacks both sensitivity and specificity. RMSF and other spotted fever group rickettsioses are reportable diseases in the United States.

**DIFFERENTIAL DIAGNOSIS**

Other rickettsial infections are easily confused with RMSF, especially all forms of human ehrlichiosis and murine typhus and novel spotted fever group rickettsioses that result from *R. parkeri* or *R. rickettsii* infections. RMSF can also mimic a variety of other diseases, such as meningococcemia and enteroviral infections. Negative blood cultures can exclude meningococcemia. PCR can differentiate enterovirus from *R. rickettsii* in patients with aseptic meningitis and a lymphocytic cerebrospinal fluid pleocytosis. Other diseases in the differential diagnosis are typhoid fever, secondary syphilis, Lyme disease, leptospirosis, rat-bite fever, scarlet fever, toxic shock syndrome, rheumatic fever, rubella, parvovirus infection, Kawasaki disease, idiopathic thrombocytopenic purpura, thrombotic thrombocytopenic purpura, Henoch-Schönlein purpura, hemolytic uremic syndrome, aseptic meningitis, acute gastrointestinal illness, acute abdomen, hepatitis, infectious mononucleosis, hemorrhagic syndromes, dengue fever, and drug reactions.

**TREATMENT**

The time-proven effective therapies for RMSF are tetracyclines and chloramphenicol. The treatment of choice for suspected RMSF in patients of all ages, including for young children, is doxycycline (4 mg/kg/day divided every 12 hr PO or IV; maximum: 200 mg/day). Tetracycline (25-50 mg/kg/day divided every 6 hr PO; maximum: 2 g/day) is an alternative. Chloramphenicol (50-100 mg/kg/day divided every 6 hr IV; maximum: 4 g/day) should be reserved for patients with doxycycline allergy and for pregnant women, because chloramphenicol is an independent risk factor for increased mortality vs tetracyclines. If used, chloramphenicol should be monitored to maintain serum concentrations of 10-30 µg/mL. Chloramphenicol is preferred for pregnant women because of potential adverse effects of doxycycline on fetal teeth and bone and maternal liver function. Although tetracycline and doxycycline can be associated with tooth discoloration in children younger than 8 yr of age, RMSF is a life-threatening illness for which prompt therapy is imperative. Furthermore, tooth discoloration with tetracyclines is dose dependent and is unlikely to occur in children prescribed short-course therapy. Chloramphenicol is rarely associated with aplastic anemia and is no longer available as an oral preparation in the United States. An additional benefit of doxycycline over chloramphenicol is its effectiveness against potential concomitant ehrlichia infection. Sulphonamides should not be used, because they are associated with greater morbidity and mortality with all rickettsial infections. Other antibiotics, including penicillins, cephalosporins, and aminoglycosides, are not effective. The use of alternative antimicrobial agents, such as fluoroquinolones and the macrolides (azithromycin and clarithromycin), has not been evaluated.

Therapy should be continued for a minimum of 5-7 days and until the patient has been afebrile for at least 3 days to avoid relapse, especially in patients treated early. Treated patients usually defervesce within 48 hr, so the duration of therapy is usually <10 days.

**SUPPORTIVE CARE**

Most infections resolve rapidly with appropriate antimicrobial therapy and do not require hospitalization or other supportive care. Infection requires intensive care in 36% of cases. Particular attention to hemodynamic status is mandatory in severely ill children, because iatrogenic pulmonary or cerebral edema could be easily precipitated owing to diffuse microvascular injury of the lungs, meninges, and brain. Judgment use of corticosteroids for meningoencephalitis has been advocated by some, but no controlled trials have been conducted.

**COMPLICATIONS**

Complications of RMSF include noncardiogenic pulmonary edema from pulmonary microvascular leakage, cerebral edema from meningoencephalitis, and multiorgan damage (hepatitis, pancreatitis, cholestasis, epidermal necrosis, and gangrene) mediated by rickettsial vasculitis and/or the accumulated effects of hypoperfusion and ischemia (acute renal failure). Long-term neurologic sequelae can occur in any child with RMSF but are more likely to occur in those hospitalized for ≥2 wk. Examples of neurologic sequelae include speech or swallowing disorders; global encephalopathy; cerebellar, vestibular, and motor dysfunction; hearing loss; and cortical blindness. Learning disabilities and behavioral problems are the most common neurologic sequelae among children who have survived severe disease.

**PROGNOSIS**

Delays in diagnosis and therapy are significant factors associated with death or severe illness. Before the advent of effective antimicrobial therapy for RMSF, the case fatality rate was 10% for children and 30% for adults. Although overall case fatality rate decreased to an historic low (0.3%) during 2003-2007, the case fatality rate of children 5-9 yr of age was 2.4%, and rates as high as 8.5% and 11.8% were documented in Texas (1986 through 1996) and in Arizona (1999-2007), respectively. Diagnosis based on serology alone underestimates the true mortality of RMSF because death often occurs within 14 days (before developing a serologic response). Deaths occur despite the availability of effective therapeutic agents, indicating the need for clinical vigilance and a low threshold for early empiric therapy. Even with administration of appropriate antimicrobials, delayed therapy can lead to irreversible vascular or end-organ damage and long-term sequelae or death. Early therapy in uncomplicated cases usually leads to rapid defervescence within 1-3 days and recovery within 7-10 days. A slower response may be seen if therapy is delayed. In those who survive despite no treatment, fever subsides in 2-3 wks.

**PREVENTION**

No vaccines are available. Prevention of RMSF is best accomplished by preventing or treating tick infestation in dogs, avoiding areas where ticks reside, using insect repellents containing N,N-diethyl-3-methylbenzamide (DEET), wearing protective clothing, and carefully inspecting children after play in areas where they are potentially exposed to ticks. Recovery from infection yields lifelong immunity.

Prompt and complete removal of attached ticks helps reduce the risk for transmission because rickettsiae in the ticks need to be reactivated.
to become virulent, and this requires at least several hours to days of exposure to body heat or blood. Contrary to popular belief, the application of petroleum jelly, 70% isopropyl alcohol, fingernail polish, or a hot match are not effective in removing ticks. A tick can be safely removed by grasping the mouth parts with a pair of forceps at the site of attachment to the skin and applying gentle and steady pressure to achieve retraction without twisting, thereby removing the entire tick and its mouth parts. The site of attachment should then be disinfected. Ticks should not be squeezed or crushed, because their fluids may be infectious. The removed tick should be soaked in alcohol or flushed down the toilet, and hands should be washed to avoid accidental inoculation into conjunctivae, mucous membranes, or breaks in skin. Typically, prophylactic antimicrobial therapy is not recommended because tetracyclines and chloramphenicol are only rickettsiostatic; however, the evidence to support this position is meager.

### 228.2 Mediterranean Spotted Fever or Boutonneuse Fever (Rickettsia conorii)

Megan E. Relier and J. Stephen Dumler

Boutonneuse fever is caused by *R. conorii* and its related subspecies; it is also called MSF, Kenya tick typhus, Indian tick typhus, Israeli spotted fever, and Astrakhan fever. It is a moderately severe vasculotropic rickettsiosis in adults, and comparatively mild in children, that is often initially associated with an eschar at the site of the tick bite. Minor differences in clinical presentation could be associated with genetic diversity of the rickettsial subspecies.

### ETIOLOGY

MSF is caused by systemic endothelial cell infection by the obligate intracellular bacterium *R. conorii*. Similar species are distributed globally, such as *R. sibirica* and *Rickettsia mongolotimonae* in Russia, China, Mongolia, and Pakistan; *R. australis* and *R. honei* in Australia; *R. japonica* in Japan; and *R. africae* in South Africa (see Table 220-1). Analysis of antigens and related DNA sequences show that all are closely related within a genetic clade that includes spotted fever group *Rickettsia* species such as *R. rickettsii*, the cause of RMSF.

### EPIDEMIOLOGY

*R. conorii* is distributed over a large geographic region, including India, Pakistan, Russia, Ukraine, Georgia, Israel, Morocco, southern Europe, Ethiopia, Kenya, and South Africa. Reported cases of MSF in southern Europe have steadily increased since 1980, and the seroprevalence is 11-26% in some areas. The peak in reported cases occurs during July and August in the Mediterranean basin; in other regions it occurs during warm months when ticks are active.

### TRANSMISSION

Transmission occurs after the bite of the brown dog tick, *R. sanguineus*, or other tick species such as *Dermacentor*, *Haemaphysalis*, *Amblyomma*, *Hyalomma*, and *Ixodes*. Clustering of human cases of boutonneuse fever, infected ticks, and infected dogs implicate the household dog as a potential vehicle for transmission.

### PATHOLOGY AND PATHOGENESIS

The underlying pathology seen with MSF is nearly identical to that of RMSF, except that eschars are often present at the site of tick bite where inoculation of rickettsiae occurs. The histopathology of the resultant lesion includes necrosis of dermal and epidermal tissues with a superficial crust; a dermis densely infiltrated by lymphocytes, histiocytes, and scattered neutrophils; and damaged capillaries and venules in the dermis. Immunohistochemical stains and nucleic acid amplification tests confirm that the lesions contain rickettsia-infected endothelial cells, but the vascular structure might not be apparent owing to extensive inflammation and necrosis. The necrosis results from both direct rickettsia-mediated vasculitis and resultant extensive local inflammation. Rickettsiae thus have ready access to lymphatics and venous blood and disseminate to cause systemic disease.

### CLINICAL MANIFESTATIONS AND LABORATORY FINDINGS

Typical findings in children include fever (93-100%), a maculopapular rash that appears 3-5 days after onset of fever (94-100%), hepatosplenomegaly (20-66%), myalgias and arthralgias (10-42%), headache (29-63%), and nausea, vomiting, or diarrhea (5-28%). In 60-90% of patients, a painless eschar or *tache noire* appears at the site of the tick bite, often on the scalp, with accompanying regional lymphadenopathy (50-60%). Although previously considered self-limited, this infection can be severe, mimicking RMSF. Findings can include seizures, purpuric skin lesions, neurologic deficits, respiratory and/or acute renal failure, and severe thrombocytopenia. Even though the case fatality rate can be as high as 10% in adults and severe infections occur in approximately 9% of children, pediatric deaths are rare. As with RMSF, a particularly severe form occurs in patients with glucose-6-phosphate dehydrogenase deficiency and in patients with underlying conditions such as alcoholic liver disease or diabetes mellitus.

### DIAGNOSIS

Laboratory diagnosis of MSF and related spotted fever group rickettsioses is the same as that for RMSF. Cases can be confirmed by immunohistologic or immunofluorescent demonstration of or amplification of nucleic acids from rickettsiae in skin biopsies, in vitro cultivation via centrifugation-assisted shell vial tissue culture, or demonstration of seroconversion or accompanied by a 4-fold rise in serum antibody titer to spotted fever group rickettsiae between acute and convalescent sera. Antibodies to spotted fever group antigens crossreact, so RMSF or other spotted fever group rickettsiosis in the United States or MSF in Europe, Africa, and Asia cannot be distinguished by these methods.

### DIFFERENTIAL DIAGNOSIS

The differential diagnosis includes conditions also associated with single eschars, such as anthrax, bacterial echyma, brown recluse spider bite, rat-bite fever (caused by *Spirillum minus*), and other rickettsioses (such as rickettsialpox, African tick-bite fever, and scrub typhus). The spotted fever group rickettsia *R. africae* causes African tick-bite fever, a milder illness than MSF that is often associated with multiple eschars and occasionally a vesicular rash. African tick bite fever can be contracted in North Africa, where MSF also occurs and is a common infection of travelers to sub-Saharan Africa who encounter bush or high grasslands on safari.

### TREATMENT AND SUPPORTIVE CARE

In adults, MSF is effectively treated with tetracycline, doxycycline, chloramphenicol, ciprofloxacin, ofloxacin, levofloxacin, azithromycin, or clarithromycin. For children, the treatment of choice is doxycycline (4 mg/kg/day divided every 12 hr PO or IV; maximum: 200 mg/day). Tetracycline and chloramphenicol are alternatives, as for RMSF. Azithromycin (10 mg/kg/day once daily PO for 3 days) and clarithromycin (15 mg/kg/day divided twice daily PO for 7 days) are also used. Specific fluoroquinolone regimens effective for children have not been established, although recent reports suggest the use of fluoroquinolones is associated with increased disease severity as compared with doxycycline. Intensive care may be required.

### COMPLICATIONS

The complications of MSF are similar to those of RMSF. The case fatality rate is approximately 2%. Particularly severe infections have been noted in patients with underlying medical conditions, including glucose-6-phosphate dehydrogenase deficiency and diabetes mellitus.

### PREVENTION

MSF is transmitted by tick bites, and prevention is the same as recommended for RMSF. No vaccine is currently available.
Rickettsialpox is caused by *R. akari*, a transitional group *Rickettsia* species that is transmitted by the mouse mite, *Allodermanyssus sanguineus*. The mouse host for this mite is widely distributed in cities in the United States, Europe, and Asia. Seroepidemiologic studies suggest a high prevalence of this infection in urban settings. The disease is uncommon and is usually mild. Unlike the situation with most forms of rickettsiosis, the macrophage is an important target cell for *R. akari*.

Rickettsialpox is best known because of its association with a varicelliform rash. In fact, this rash is a modified form of an antecedent typical macular or maculopapular rash like those seen in other vasculotropic rickettsioses, and is occasionally seen with other rickettsioses such as African tick bite fever. Clinical descriptions in children are infrequent. At presentation, most patients have fever, headache, and chills. In up to 90% of cases, there is a painless papular or ulcerative lesion or eschar at the initial site of inoculation, which may be associated with regional lymphadenopathy that is often tender. In some patients, the maculopapular rash becomes vesicular, involving the trunk, head, and extremities. The infection generally resolves spontaneously and does not require therapy. However, a short course of doxycycline hastens resolution and is sometimes used in patients older than 8 yr of age and in young children with relatively severe illness. Complications and fatalities are rare; however, clear examples of severe disease in children like that observed with RMSF are described.

*Bibliography is available at Expert Consult.*
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Scrub typhus is an important cause of acute febrile illness in South and East Asia and the Pacific. The causative agent is distinct from, but related to, *Rickettsia* species. The infection is transmitted via chigger (larval mite) bites and involves many antigenically diverse strains of *Orientia tsutsugamushi*, hampering vaccine development.

**ETIOLOGY**

The causative agent of scrub typhus, or tsutsugamushi fever, is *O. tsutsugamushi*, which is distinct from other spotted fever and typhus group rickettsiae (see Table 228-1 in Chapter 228). *O. tsutsugamushi* lacks both lipopolysaccharide and peptidoglycan in its cell wall. Like other vasculotropic rickettsiae, *O. tsutsugamushi* infects endothelial cells and causes vasculitis, the predominant clinicopathologic feature of the disease. However, the organism also infects macrophages and cardiac myocytes. A new Candidatus species, *Orientia chuto*, was isolated from a patient in the Middle East, suggesting a wider range for scrub typhus and related infections.

**EPIDEMIOLOGY**

Approximately 1 million infections occur each year, and it is estimated that more than 1 billion people are at risk. Scrub typhus occurs mostly in Asia, including areas delimited by Korea, Pakistan, and northern Australia. Outside these tropical and subtropical regions, the disease occurs in Japan, the Primorye of far eastern Russia, Tajikistan, Nepal, and nontropical China, including Tibet. Cases imported to the United States and other parts of the world are reported. Most infections in children are acquired in rural areas. In Thailand and Sri Lanka, scrub typhus is the cause of 1-8% of acute fevers of unknown origin. Infections are most common during rainy months, usually June through November. Reported cases in boys are higher than in girls.

**TRANSMISSION**

*O. tsutsugamushi* is transmitted via the bite of the larval stage (chigger) of a trombiculid mite (*Leptotrombidium*), which serves as both vector and reservoir. Transovarial transmission (passage of the organism from infected mites to their progeny) is the major mechanism for maintenance in nature. Because only the larval stage takes blood meals, a role for horizontal transmission from infected rodent hosts to uninfected mites has not been proved, but transmission among cofeeding larval mites is a possibility. Multiple serotypes of *O. tsutsugamushi* are recognized, and some share antigenic cross reactivity; however, they do not stimulate protective cross-immunity.

**PATHOLOGY AND PATHOGENESIS**

The pathogenesis of scrub typhus is uncertain. Recent studies suggest that the process is stimulated by widespread infection of vascular endothelial cells, which corresponds to the distribution of disseminated vasculitic and perivascular inflammatory lesions observed in histopathologic examinations. In autopsy series, the major result of the vascular injury appears to be hemorrhage. However, data support the concept that vascular injury initiated by the infection is sustained by immune-mediated inflammation that together cause significant vascular leakage. The net result is significant vascular compromise and ensuing end-organ injury, most often manifested in the brain and lungs, as with other vasculotropic rickettsioses.

**CLINICAL MANIFESTATIONS AND LABORATORY FINDINGS**

Scrub typhus can be mild or severe in children. Most patients present with fever for 9-11 days (range: 1-30 days) before seeking medical care. Regional or generalized lymphadenopathy is reported in 23-93% of patients, hepatomegaly in about two-thirds, and splenomegaly in about one-third of children with scrub typhus. Gastrointestinal symptoms, including abdominal pain, vomiting, and diarrhea, occur in up to 40% of children at presentation. A single painless eschar with an erythematous rim at the site of the chigger bite is seen in 7-68% of cases, and a maculopapular rash is present in <30%; both can be absent. Hemophagocytic lymphohistiocytosis has been described. Leukocyte and platelet counts are most commonly within normal ranges, although thrombocytopenia occurs in one-quarter to one-third of children, and leukocytosis is observed in approximately 40%.

**DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS**

Owing to the potential for severe complications, diagnosis and decision to initiate treatment should be based on clinical suspicion and confirmed by *O. tsutsugamushi* serologic tests such as indirect fluorescent antibody or immunoperoxidase assays. The indirect fluorescent antibody assay is approximately 90% sensitive with 11 days or more of fever. Although the rickettsiae can be cultivated using tissue culture methods, polymerase chain reaction tests are not highly sensitive, and these diagnostic methods are not widely available. The differential diagnosis includes fever of unknown origin, enteric fever, typhoid fever, dengue hemorrhagic fever, other rickettsioses, tularemia, anthrax, dengue, leptospirosis, malaria, and infectious mononucleosis.

**TREATMENT AND SUPPORTIVE CARE**

The recommended treatment regimen for scrub typhus is doxycycline (4 mg/kg/day PO or IV divided every 12 hr; maximum: 200 mg/day). Alternative regimens include tetracycline (25-50 mg/kg/day PO divided every 6 hr; maximum: 2 g/day) or chloramphenicol (50-100 mg/kg/day divided every 6 hr IV; maximum: 4 g/24 hr). If used, chloramphenicol should be monitored to maintain serum concentrations of 10-30 µg/mL. Therapy should be continued for a minimum of 5 days and until the patient has been afebrile for at least 3 days to avoid
relapse. However, a single dose of oral doxycycline was reported effective for all 38 children treated with this regimen in a large series of children with scrub typhus from Thailand. Most children respond rapidly to doxycycline or chloramphenicol within 1-2 days (range: 1-5 days). Strains of O. tsutsugamushi with modestly higher doxycycline minimal inhibitory concentrations are reported in some regions of Thailand. Clinical trials showed that azithromycin could be as effective and that rifampicin is superior to doxycycline in such cases and may have a role as an alternative therapy, especially for pregnant women. The use of ciprofloxacin in pregnant women resulted in an adverse outcome in 5 of 5 pregnancies among Indian women. Intensive care may be required for hemodynamic management of severely affected patients.

**COMPLICATIONS**

Serious complications include pneumonitis in 20-35% and meningoencephalitis in approximately 10% of children. Acute renal failure, myocarditis, and a septic shock-like syndrome occur much less often. Cerebrospinal fluid examination shows a mild mononuclear pleocytosis with normal glucose levels. Chest radiographs reveal transient perihilar or peribronchial interstitial infiltrates in most children who are examined. The case fatality rate in untreated patients may be as high as 30%, although deaths in children are uncommon.

**PREVENTION**

Prevention is based on avoidance of the chiggers that transmit O. tsutsugamushi. Protective clothing is the next most useful mode of prevention. Infection provides immunity to reinfection by homologous but not heterologous strains; however, because natural strains are highly heterogeneous, infection does not always provide complete protection against reinfection. No vaccines are currently available.

*Bibliography is available at Expert Consult.*
Bibliography


Rattus rickettsia transmitted from γ 1505 -

Ctenocephalides felis

Transovarial transmission (passage of the organism from infected fleas infected fleas to rats, other rodents, or opossums and back to fleas. This organism is found in cat fleas obtained from areas endemic for murine typhus in the United States and increasingly worldwide.

ETIOLOGY

Murine typhus is caused by R. typhi, a rickettsia transmitted from infected fleas to rats, other rodents, or opossums and back to fleas. Transovarial transmission (passage of the organism from infected fleas to their progeny) in fleas is inefficient. Transmission depends on infection from the flea to uninfected mammals that then sustain transient rickettsiaemia and serve as sources of the bacterium for uninfected fleas that bite during the period of rickettsiaemia.

R. felis is a species identified as a cause of a murine typhus-like illness worldwide. This rickettsia is genetically a member of a transitional Rickettsia group and is capable of highly efficient transovarial transmission in cat fleas. This organism is found in cat fleas obtained from areas endemic for murine typhus in the United States and increasingly worldwide.

EPIDEMIOLOGY

Murine typhus has a worldwide distribution and occurs especially in warm coastal ports, where it is maintained in a cycle involving rat fleas (Xenopsylla cheopis) and rats (Rattus species). Peak incidence occurs when rat populations are highest during spring, summer, and fall. Sentinel surveillance studies suggest that travel-acquired murine typhus occurs most often in those visiting Southeast Asia and Africa. In the United States, the disease is recognized most often in south Texas and southern California. However, seroprevalence studies among children indicate that murine typhus is acquired across the southeast and central United States, thus expanding the endemic areas in which pediatricians must be alert for this infection. In the coastal areas of south Texas and in Southern California, the disease is seen predominantly from March through June and is associated with a “sylvatic” cycle involving opossums and cat fleas (Ctenocephalides felis).

TRANSMISSION

R. typhi normally cycles between rodents or midsize animals such as opossums and their fleas. Human acquisition of murine typhus occurs when rickettsiae-infected flea feces contaminate flea bite wounds. Direct inoculation via flea bite is possible, but inefficient.

PATHOLOGY AND PATHOGENESIS

R. typhi is a vasculotropic rickettsia that causes disease in a manner similar to Rickettsia rickettsii (see Chapter 228.1). R. typhi organisms in flea feces deposited on the skin as part of the flea feeding reflex are inoculated into the pruritic flea bite wound. After an interval for local proliferation, the rickettsiae spread systemically via lymphatics to infect the endothelium in many tissues. As with spotted fever group rickettsiae, typhus group rickettsiae infect endothelial cells, but unlike the spotted fever group rickettsiae, they polymerize intracellular actin poorly, have limited intracellular mobility, and probably cause cellular injury by either enzymatic membrane or mechanical lysis after accumulating in large numbers within the endothelial cell cytoplasm. Intracellular infection leads to endothelial cell damage, recruitment of inflammatory cells, and vasculitis. The inflammatory cell infiltrates bring in a number of effector cells, including macrophages that produce proinflammatory cytokines, and CD4, CD8, and natural killer lymphocytes, which can produce immune cytokines such as interferon-γ and participate in cell-mediated cytotoxic responses. Intracellular rickettsial proliferation of typhus group rickettsiae is inhibited by cytokine-mediated mechanisms and nitric oxide–dependent and –independent mechanisms.

Pathologic findings include systemic vasculitis in response to rickettsiae within endothelial cells. This manifests as interstitial pneumonitis, meningoencephalitis, interstitial nephritis, myocarditis, and mild hepatitis with perportal lymphohistiocytic infiltrates. As vasculitis and inflammatory damage accumulate, multiorgan damage can ensue.

CLINICAL MANIFESTATIONS

Murine typhus is a moderately severe infection that is similar to other vasculotropic rickettsioses. The incubation period varies from 1-2 wk. The initial presentation is often nonspecific and mimics typhoid fever; fever of undetermined origin is the most common presentation. Pediatric patients with murine typhus exhibit symptoms classically attributed to other vasculotropic rickettsioses, such as rash (48-80%), myalgias (29-57%), vomiting (29-45%), cough (15-40%), headache (19-77%), and diarrhea or abdominal pain (10-40%). A petechial rash...
is observed in <15% of children, and the usual appearance is that of macules or maculopapules distributed on the trunk and extremities. The rash can involve both the soles and palms. Lymphadenopathy and hepatosplenomegaly are reported often among children with murine typhus in Europe. Murine-typhus associated hemophagocytic syndrome was recently described. Although neurologic involvement is a common finding in adults with murine typhus, photophobia, confusion, stupor, coma, seizures, meningsismus, and ataxia are seen in <20% of hospitalized children and <6% of infected children treated as outpatients.

LABORATORY FINDINGS
Although nonspecific, laboratory findings that could be helpful include mild leukopenia (36-40%) with a moderate left shift, mild to marked thrombocytopenia (43-60%), hyponatremia (20-66%), hypoaalbuminemia (46-87%), and elevated aspartate aminotransferase (82%) and alanine aminotransferase (38%). Elevations in serum urea nitrogen are usually a result of prerenal mechanisms.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS
As for other vasculotropic rickettsioses, delays in diagnosis and therapy are associated with increased morbidity and mortality; thus, diagnosis must be based on clinical suspicion. Occasionally, patients present with findings suggesting pharyngitis, bronchitis, hepatitis, gastroenteritis, or sepsis; thus, the differential diagnosis may be extensive.

Confirmation of the diagnosis is usually accomplished by comparing acute and convalescent-phase antibody titers obtained with the indirect fluorescent antibody assay to demonstrate a 4-fold rise in titer. Research tools now being evaluated include polymerase chain reaction amplification of rickettsial nucleic acids in acute-phase blood, rickettsial culture by the centrifugation-assisted shell vial assay, and immunohistochemistry on skin biopsy.

TREATMENT
Therapy for murine typhus includes tetracyclines or chloramphenicol, similar to treatment for Rocky Mountain spotted fever. No controlled trials of other antimicrobial agents have been performed. Clinical studies show that ciprofloxacin is as effective as doxycycline and chloramphenicol to treat murine typhus; however, treatment failures have been reported. In vitro experiments suggest that minimal inhibitory concentrations of azithromycin and clarithromycin for \textit{R. typhi} should be easily achieved.

The time-honored recommended treatment for murine typhus is doxycycline (4 mg/kg/day divided every 12 hr PO or IV; maximum: 200 mg/day). Alternative regimens include tetracycline (25-50 mg/kg/day divided every 6 hr PO; maximum: 2 g/day) or chloramphenicol (50-100 mg/kg/day divided every 6 hr IV; maximum: 4 g/day). Therapy should be continued for a minimum of 5 days and until the patient has been afebrile for at least 3 days to avoid relapse, especially in patients treated early.

SUPPORTIVE CARE
Although disease is usually mild, 7% of children with murine typhus require intensive care to manage complications such as meningoencephalitis or a disseminated intravascular coagulation–like condition. As for other rickettsial infections with significant systemic vascular injury, careful hemodynamic management is mandatory to avoid pulmonary or cerebral edema.

COMPLICATIONS
Complications of murine typhus in pediatric patients are uncommon; however, relapse, stupor, facial edema, dehydration, splenic rupture, and meningoencephalitis are reported. Predominance of abdominal pain has led to surgical exploration to exclude a perforated viscus.

PREVENTION
Control of murine typhus was dependent on elimination of the flea reservoir and control of flea hosts, and this remains important. However, with the recognition of cat fleas as potentially significant reservoirs and vectors, the presence of these flea vectors and their mammalian hosts in suburban areas where close human exposures occur poses increasingly difficult control problems. It is not known with certainty if infection confers protective immunity; reinfection appears to be rare.

230.2 Epidemic (Louse-Borne) Typhus \textit{(Rickettsia prowazekii)}
Megan E. Reller and J. Stephen Dumler

ETIOLOGY
Humans are considered the principal reservoir of \textit{R. prowazekii}, the causative agent of epidemic or louse-borne typhus and its recrudescent form, Brill-Zinsser disease. Another reservoir exists in flying squirrels, their ectoparasites, and potentially ticks, in a sylvatic cycle with small rodents. \textit{R. prowazekii} is the most pathogenic member of the genus \textit{Rickettsia} and multiplies to very large intracellular quantities before rupture of infected endothelial cells.

EPIDEMIOLOGY
The infection is characteristically seen in winter or spring and especially during times of poor hygienic practices associated with crowding, war, famine, extreme poverty, and civil strife. A cause of some sporadic cases of a mild, typhus-like illness in the United States is \textit{R. prowazekii}; such cases are associated with exposure to flying squirrels harboring infected lice or fleas. \textit{R. prowazekii} organisms isolated from these squirrels appear to be genetically similar to isolates obtained during typical outbreaks.

Most cases of louse-borne typhus in the developed world are sporadic, but outbreaks have been identified in Africa (Ethiopia, Nigeria, and Burundi), Mexico, Central America, South America, Eastern Europe, Afghanistan, Russia, northern India, and China within the past 25 yr. Following the Burundi Civil War in 1993, 35,000-100,000 cases of epidemic typhus were diagnosed in displaced refugees, resulting in an estimated 6,000 deaths.

TRANSMISSION
Human body lice (\textit{Pediculus humanus corporis}) become infected by feeding on persons who have rickettsiae circulating in their blood owing to endothelial infection. The ingested rickettsiae infect the midgut epithelial cells of the lice and are passed into the feces, which, in turn, are introduced into a susceptible human host through abrasions or perforations in the skin, through the conjunctivae, or rarely through inhalation as fomites in clothing, bedding, or furniture.

CLINICAL MANIFESTATIONS
Louse-borne typhus can be mild or severe in children. The incubation period is usually <14 days. The typical clinical manifestations include fever, severe headache, abdominal tenderness, and rash in most patients, as well as chills (82%), myalgias (70%), arthralgias (70%), anorexia (48%), nonproductive cough (38%), dizziness (35%), photophobia (33%), nausea (32%), abdominal pain (30%), tinnitus (23%), constipation (23%) meningsismus (17%), visual disturbances (15%), vomiting (10%), and diarrhea (7%). However, investigation of recent African outbreaks has shown a lower incidence of rash (25%) and a high incidence of delirium (81%) and cough associated with pneumonitis (70%). The rash is initially pink or erythematous and blanches. In one-third of patients, red, nonblanching macules and petechiae appear predominantly on the trunk. Infections identified during the preantibiotic era typically produced a variety of central nervous system findings, including delirium (48%), coma (6%), and seizures (1%). Estimates of case fatality rates range between 3.8% and 20% in outbreaks.

\textit{Brill-Zinsser disease} is a form of typhus that becomes recrudescent months to years after the primary infection, thus rarely affecting children. When bacteremic with rickettsiae, these infected patients can transmit the agent to lice, potentially providing the initial event that triggers an outbreak if hygienic conditions permit.
TREATMENT
Recommended treatment regimens for louse-borne or sylvatic typhus are identical to those used for murine typhus. The treatment of choice is doxycycline (4 mg/kg/day divided every 12 hr PO or IV; maximum: 200 mg/day). Alternative treatments include tetracycline (25-50 mg/kg/day divided every 6 hr PO; maximum: 2 g/day) or chloramphenicol (50-100 mg/kg/day divided every 6 hr IV; maximum: 4 g/day). Therapy should be continued for a minimum of 5 days and until the patient is afebrile for at least 3 days to avoid relapse, especially in patients treated early. Good evidence exists that doxycycline as a single 200 mg oral dose (4.4 mg/kg if <45 kg) is also efficacious.

PREVENTION
Immediate destruction of vectors with an insecticide is important in the control of an epidemic. Lice live in clothing rather than on the skin; thus, searches for ectoparasites should include examination of clothes. For epidemic typhus, antibiotic therapy and delousing measures interrupt transmission, reduce the prevalence of infection in the human reservoir, and diminish the impact of an outbreak. Dust containing excreta from infected lice is stable and capable of transmitting typhus, and care must be taken to prevent its inhalation. Infection confers solid protective immunity. However, recrudescence can occur years later with Brill-Zinsser disease, implying that immunity is not complete.

Bibliography is available at Expert Consult.
Bibliography


Although these infections are caused by bacteria assigned to various genera, the name ehrlichiosis has been applied to all and the etiologic agents are all classified within the Anaplasmataceae family. **Human monocytic ehrlichiosis (HME)** is used to describe disease characterized by infection of predominantly monocytes caused by *E. chaffeensis*, **human granulocytic anaplasmosis (HGA)** to describe disease of where circulating neutrophils are infected by *Anaplasma phagocytophilum*, and **ewingii ehrlichiosis** caused by *E. ewingii* (see Table 228-1 in Chapter 228).

All of these organisms are tick-transmitted, small, obligate intracellular bacteria with Gram-negative–type cell walls. *Neorickettsia sennetsu* is another related bacterium that rarely causes human disease and is not transmitted by ticks. *E. chaffeensis* alters host signaling and transcription once inside the cell. It survives in an endosome that enters a receptor recycling pathway to avoid phagosome-lysosome fusion and growth into a “morula,” an intravacuolar aggregate of bacteria. *A. phagocytophilum* survives in a unique vacuole that becomes decorated by microbial proteins which prevent endosomal maturation and lysosome fusion. Little is known about the vacuoles in which *E. ewingii* and *E. muris*–like agent grow. These bacteria are pathogens of phagocytic cells in mammals, and characteristically each species has a specific host cell affinity: *E. chaffeensis* infects mononuclear phagocytes, and *A. phagocytophilum* and *E. ewingii* infect neutrophils. Infection leads to direct modifications in function, in part the result of changes in intracellular signal transduction or epigenetic modulation of transcription of the host cell that diminish host defenses toward the bacterium; yet, host immune and inflammatory reactions are still activated and in part account for many of the clinical manifestations in ehrlichiosis.

**EPIDEMIOLOGY**

Infections with *E. chaffeensis* occur across the southeastern, south central, and mid-Atlantic states of the United States in a distribution that parallels that of RMSF; cases have also been reported in northern California. Suspected cases with appropriate serologic and occasionally molecular evidence have been reported in Europe, Africa, South America, and the Far East, including China and Korea. Human infections with *E. ewingii* have only been identified in the United States in areas where *E. chaffeensis* also exists, perhaps owing to the shared tick vector. Canine infections are documented in both sub-Saharan Africa and in South America.

Although the median age of patients with HME and HGA is generally older (>51 yr), many infected children have been identified, and for HME the case fatality rate is higher in those 5-9 yr of age. Little is known about the epidemiology of *E. ewingii* infections, although many patients have also been children. All infections are strongly associated with tick exposure and tick bites and are identified predominantly during May through September. Although both nymphal and adult ticks can transmit infection, nymphs are more likely to transmit disease, because they are most active during the summer.

**TRANSMISSION**

The predominant tick species that harbors *E. chaffeensis* and *E. ewingii* is *A. americanum*, the Lone Star tick (see Fig. 228-1D in Chapter 228). The tick vectors of *A. phagocytophilum* are *Ixodes* spp., including *I. scapularis* (black-legged or deer tick) in the eastern United States (see Fig. 228-1 in Chapter 228), *Ixodes pacificus* (western black-legged tick) in the western United States, *Ixodes ricinus* (sheep tick) in Europe, and *Ixodes persulcatus* in Eurasia. These ticks also transmit *Borrelia burgdorferi*, *Babesia microti*, and tickborne encephalitis–associated flaviviruses in Europe, Powassan viruses in North America. Coinfections with these agents and *A. phagocytophilum* have been documented in children and adults.

*Ehrlichia* and *Anaplasma* species are maintained in nature predominantly by horizontal transmission (tick to mammal to tick), because the organisms are not transmitted to the progeny of infected adult female ticks (transovarial transmission). The major reservoir for *E. chaffeensis* is the white-tailed deer (*Odocoileus virginianus*), which is found abundantly in many parts of the United States. A reservoir for
A. phagocytophilum in the eastern United States appears to be the white-footed mouse, Peromyscus leucopus. Deer or domestic ruminants may also have persistent asymptomatic infections, but the genetic variants in these reservoirs might not be infectious for humans. Efficient transmission requires persistent infections of mammals. Although E. chaffeensis and A. phagocytophilum can cause persistent infections in animals, documentation of chronic infections in humans is exceedingly rare. Transmission of Ehrlichia can occur within hours of tick attachment, in contrast to the 1-2 days of attachment required for transmission of B. burgdorferi to occur. Transmission of A. phagocytophilum is via the bite of the small nymphal stage of ixodes spp., including I. scapularis (see Fig. 228-1A in Chapter 228), which is very active during late spring and early summer in the eastern United States.

PATHOLOGY AND PATHOGENESIS
Although HME and anaplasmosis often clinically mimic RMSF or typhus, vasculitis is rare. Pathologic findings include mild, diffuse peri-vascular lymphohistiocytic infiltrates; Kupffer cell hyperplasia and mild lobular hepatitis with infrequent apoptotic hepatocytes and less frequently centrilobular necrosis, cholestasis and steatosis; infiltrates of mononuclear phagocytes in the spleen, lymph nodes, and bone marrow with occasional erythropagocytosis; granulomas of the liver and bone marrow in patients with E. chaffeensis infections; and hyperplasia of one or more bone marrow hematopoietic lineages.

The exact pathogenetic mechanisms are poorly understood, but histopathologic examinations suggest diffuse macrophage activation and poorly regulated host immune and inflammatory reactions. This activation results in moderate to profound leukopenia and thrombocytopenia despite persistently elevated prothrombin time, suggesting a coagulopathy. The major microvascular pathology in the skin is extravasation of red blood cells, and fibrinoid necrosis may be triggered by the bacterium but more closely related to induction of innate and adaptive immune effectors. Meningoencephalitis with a mononuclear cell pleocytosis in the cerebrospinal fluid (CSF) occurs with HME, but is rare with HGA.

CLINICAL MANIFESTATIONS
The clinical manifestations of HME, HGA, and ewingii ehrlichiosis are similar. Many well-characterized infections of HME and HGA of variable severity have been reported in children, including deaths. Children with ehrlichiosis are often ill for 4-12 days, shorter than in adults. In series of children with HME, most required hospitalization and many (25%) required intensive care; these statistics might represent preferential reporting of severe cases. However, review of case reports and electronic surveillance of HGA to the Centers for Disease Control and Prevention identified that 42% of patients 5-9 yr of age required hospitalization.

Leukopenia (57-80%) and thrombocytopenia (38-93%); cytopenias reach a nadir several days into the illness. Lymphopenia is common in both HME and HGA, and neutropenia is reported in adults with HGA. Leukocytosis can also occur, but usually after the 1st wk of illness or with effective antimicrobial treatment. Adults with pancytopenia often have a cellular or reactive bone marrow examination, and in nearly 75% of bone marrow specimens from adults with HME, granulomas and granulomatous inflammation are present; this finding is not a feature of adults with HGA. Mild to severe elevated serum hepatic transaminase levels are frequent in both HME (85-92%) and HGA (40-50%). Hyponatremia (<135 mEq/L) is present in most cases. A clinical picture similar to disseminated intravascular coagulopathy has also been reported.

LABORATORY FINDINGS
Characteristically, most children with HME and HGA present with leukopenia (57-80%) and thrombocytopenia (38-93%); cytopenias reach a nadir several days into the illness. Lymphopenia is common in both HME and HGA, and neutropenia is reported in adults with HGA. Leukocytosis can also occur, but usually after the 1st wk of illness or with effective antimicrobial treatment. Adults with pancytopenia often have a cellular or reactive bone marrow examination, and in nearly 75% of bone marrow specimens from adults with HME, granulomas and granulomatous inflammation are present; this finding is not a feature of adults with HGA. Mild to severely elevated serum hepatic transaminase levels are frequent in both HME (85-92%) and HGA (40-50%). Hyponatremia (<135 mEq/L) is present in most cases. A clinical picture similar to disseminated intravascular coagulopathy has also been reported.

DIAGNOSIS
Any delays in diagnosis or treatment are major contributors to increased morbidity or mortality in adults, where those not started on doxycycline at hospital admission are much more likely to require intensive care and a significantly longer course of illness and hospitalization. Thus, treatment must begin as early as possible based on clinical suspicion. Because both HME and anaplasmosis can be fatal, therapy should not be withheld while waiting for the results of confirmatory testing. In fact, prompt response to therapy supports the diagnosis.

While several reports document pediatric patients with E. chaffeensis infection diagnosed based on typical *Ehrlichia* morulae in peripheral blood leukocytes (Fig. 231-1A), this finding is too infrequent to be considered a useful diagnostic approach. In contrast, HGA in adults presents with a small but significant percentage (1-40%) of circulating neutrophils (Fig. 231-1B) containing typical morulae in 20-60% of patients. E. chaffeensis and A. phagocytophilum infections can be confirmed by demonstrating a 4-fold change in immunoglobulin G titer by indirect immunofluorescence assay between paired sera or detection of specific DNA by polymerase chain reaction or demonstration of specific antigen in a tissue sample by immunohistochemistry or isolation of the organism in cell culture. A single specific titer of >264 or identification of morulae in monocytes or macrophages for *E. chaffeensis* or in neutrophils or eosinophils for *A. phagocytophilum* by microscopy is suggestive. *E. ewingii* infection can only be confirmed by polymerase chain reaction, because it has not been cultured and serologic antigens are not available. *E. ewingii* antibodies cross react with *E. chaffeensis* in routine serologic tests. Up to 15% of patients with HGA have serologic cross-reactions with *E. chaffeensis*; thus, serodiagnosis depends on testing with both *E. chaffeensis* and *A. phagocytophilum* antigens and demonstrating a 4-fold or higher difference between titers. During the acute phase of illness when antibodies are often not detected, polymerase chain reaction amplification of *E. chaffeensis* or *A. phagocytophilum* DNA is sensitive in >86% of cases. Although *E. chaffeensis* and *A. phagocytophilum* can be cultivated in tissue culture, this method is not timely or widely available.

DIFFERENTIAL DIAGNOSIS
Because of the nonspecific presentation, ehrlichiosis mimics other arthropod-borne infections such as RMSF, tularemia, babesiosis, Lyme
disease, murine typhus, relapsing fever, and Colorado tick fever. Other potential diagnoses often considered include otitis media, streptococcal pharyngitis, infectious mononucleosis, Kawasaki disease, endocarditis, respiratory or gastrointestinal viral syndromes, hepatitis, leptospirosis, Q fever, collagen–vascular diseases, hemophagocytic syndromes, and leukemia. If rash and disseminated intravascular coagulopathy predominate, meningococcemia, bacterial sepsis, and toxic shock syndrome are also suspected. Meningoencephalitis might suggest aseptic meningitis caused by enterovirus or herpes simplex virus, bacterial meningitis, or RMSF. Severe respiratory disease may be confused with bacterial, viral, and fungal causes of pneumonia.

**TREATMENT**

Both HME and HGA are effectively treated with tetracyclines, especially doxycycline, and the majority of patients improve within 48 hr. In vitro tests document that both *E. chaffeensis* and *A. phagocytophilum* have minimal inhibitory concentrations to chloramphenicol above blood levels that can be safely achieved. Therefore, a short course of doxycycline is the recommended regimen. Doxycycline is used safely in children younger than 8 yr of age because tooth discoloration is dose dependent and the need for multiple courses is unlikely. Few data exist to recommend alternative therapies; however, both *E. chaffeensis* and *A. phagocytophilum* are susceptible in vitro to rifampin, which has been used successfully to treat HGA in pregnant women and children.

The recommended regimen for patients of all ages with severe or complicated HME and HGA is doxycycline (for those who weigh <45 kg, 4 mg/kg/day PO or IV divided every 12 hr; maximum: dose 100 mg/dose). An alternative regimen is tetracycline (25-50 mg/kg/day divided every 6 hr PO; maximum: 2 g/day). For children who weigh more than 45 kg, the adult dose, 100 mg twice daily by oral or intravenous route can be used. Therapy should be continued for ≥5 days and until the patient has been afebrile for ≥2-4 days.

Other broad-spectrum antibiotics, including penicillins, cephalosporins, aminoglycosides, and macrolides, are not effective. In vitro studies suggest that fluoroquinolones are active against *A. phagocytophilum*, although at least 1 patient relapsed when levofloxacin was discontinued. *E. chaffeensis* is naturally resistant to fluoroquinolones owing to a single nucleotide change in *gyrA*, which suggests that *A. phagocytophilum* could also become resistant to fluoroquinolones rapidly.

**COMPLICATIONS AND PROGNOSIS**

Fatal HME is reported in at least 1 pediatric patient, where the findings were initially dominated by pulmonary involvement with respiratory failure complicated by nosocomial bacterial pneumonia. The pattern of severe pulmonary involvement culminating in diffuse alveolar damage and acute respiratory distress syndrome and secondary nosocomial or opportunistic infections is now well-documented with HME and HGA in adults. One child with HGA died after 3 wk of fever, thrombocytopenia, and lymphadenopathy suspected to be a hematologic malignancy. Other severe complications include a toxic shock-like illness, meningoencephalitis with long-term neurologic sequelae, brachial plexopathy, demyelinating polyneuropathy, myocarditis, rhabdomyolysis, and renal failure. Hemophagocytic lymphohistiocytosis is increasingly reported in children with both HME and HGA. Patients who are immunocompromised (e.g., HIV infection, high-dose corticosteroid therapy, cancer chemotherapy, immunosuppression for organ transplantation) are at high risk for fulminant *E. chaffeensis* infection, and severe HGA has been reported after stem cell transplantation in pediatric oncology.

**PREVENTION**

HME, HGA, and ewingii ehrlichiosis are tickborne diseases, and any activity that increases exposure to ticks increases risk. Avoiding tick-infested areas, wearing appropriate light-colored clothing, spraying tick repellents on clothing, carefully inspecting for ticks after exposure, and promptly removing any attached ticks diminish the risk. The interval between tick attachment and transmission of the agents may be as short as 4 hr; thus, attached ticks should be removed promptly. A role of prophylactic therapy for ehrlichiosis and anaplasmosis after tick bites has not been investigated. It is not known if infection confers protective immunity; however, reinfection appears to be exceedingly rare.

_Bibliography is available at Expert Consult._

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**Figure 231-1** Morulae in peripheral blood leukocytes in patients with human monocytic ehrlichiosis and human granulocytic anaplasmosis. **A**, A morula (arrow) containing *Ehrlichia chaffeensis* in a monocyte. **B**, A morula (arrowhead) containing *Anaplasma phagocytophilum* in a neutrophil. Wright stains, original magnifications ×1,200. *E. chaffeensis* and *A. phagocytophilum* have similar morphologies but are serologically and genetically distinct.
Bibliography


Q fever (for query fever, the name given following an outbreak of febrile illness in an abattoir in Queensland, Australia) is rarely reported in children but is probably underdiagnosed. Symptomatic patients can have acute or chronic disease.

ETIOLOGY
Although previously classified within the order Rickettsiales, *Coxiella burnetii* (the causative agent of Q fever) is genetically distinct from the
genera *Rickettsia*, *Orientia*, *Ehrlichia*, and *Anaplasma*. Hence, based on small genome analysis, it best aligns within the order Legionellales, family Coxiellaceae. *C. burnetii* is highly infectious for both humans and animals; even a single organism can cause infection. The agent has been nationally notifiable since 1999 and is listed as a Category B agent of bioterrorism by the Centers for Disease Control and Prevention (CDC). Unlike *Rickettsia*, the organism can enter a sporogenenic differentiation cycle, which renders it highly resistant to chemical and physical treatments.

*C. burnetii* resides intracellularly within macrophages. In vitro, the organism undergoes lipopolysaccharide phase variation similar to that described for smooth and rough strains of Enterobacteriaceae. Unlike *Ehrlichia*, *Anaplasma*, and *Chlamydia*, *C. burnetii* survives and proliferates within acidified phagosomes to form aggregates of >100 bacteria.

**EPIDEMIOLOGY**

The disease is reported worldwide, except in New Zealand. Although seroepidemiologic studies suggest that infection occurs just as often in children as in adults, children less often present with clinical disease than do adults. During the large outbreak of Q fever in the Netherlands in 2007–2009, only 3.5% of those diagnosed with Q fever were age 19 yr or younger. Although infections are recognized more often in men than in women, reported cases in boys and girls are equal. Approximately 60% of infections are asymptomatic, and only 5% of symptomatic patients require hospitalization. Seroprevalence surveys show that 6–70% of children in endemic European and African communities have evidence of past infection. In France, the overall incidence of Q fever is estimated to be 50 cases per 100,000 persons. A similar estimate is not available for Africa, where cases are likely misdiagnosed as malaria. The seroprevalence of Q fever in the United States is estimated to be 3.1%. Reported cases of Q fever in the United States, which have been received from every state, increased by greater than 9-fold from 17 cases in 2000 to 167 cases in 2008, which might reflect an increase in incidence, increased reporting after September 11, 2001, improved diagnostic tools, or a combination of factors. Reported cases in Asia and Australia have also increased. Most infections in children are identified during the lamb birthing season in Europe (January through June), following farm visits, or after exposure to placentas of dogs, cats, and rabbits. The largest (~4,000 human cases) community outbreak ever described occurred in the Netherlands in 2007–2010 and was associated with intensive farming of dairy goats and dairy sheep. In 2011, the first multistate outbreak of Q fever in humans was linked to interstate sale of infected goats; an outbreak of unknown source was also reported. From 2000–2010, 60% of cases reported to CDC occurred in those without reported exposure to livestock. More than 20% of cases of clinically recognized acute or chronic Q fever occurred in immunosuppressed hosts or in persons with prosthetic valves or damaged native valves or vessels. These findings highlight the need for considering Q fever in those with clinically compatible illness, especially but not exclusively in those with likely exposures and in vulnerable hosts.

**TRANSMISSION**

In contrast to other rickettsial infections, humans usually acquire *C. burnetii* by inhaling infectious aerosols (e.g., contaminated barnyard dust) or ingesting (and likely aspirating) contaminated foods. Ticks are rarely implicated. Cattle, sheep, and goats are the primary reservoirs, but infection in other livestock and domestic pets is also described. Organisms are excreted in milk, urine, and feces of infected animals, but especially in amniotic fluids and the placenta. An increase in incidence is associated with the seasonal mistral winds in France that coincide with lamb birthing season and with consumption of cheese among children in Greece. In Nova Scotia and Maine, exposure to newborn animals, especially kittens, has been associated with small outbreaks of Q fever in families. Exposure to domestic ruminants is the major risk in Europe and Australia, although many urban dwellers in France also acquire Q fever without such an exposure. Person-to-person transmission is possible but rare. Clinical Q fever during pregnancy can result from primary infection or reactivation of latent infection and is associated with miscarriage, intrauterine growth retardation, and premature births. Obstetricians and other related healthcare workers are at risk for acquiring infection because of the quantity of *C. burnetii* sequestered in the placenta. Sexual transmission and cases attributable to blood transfusion or bone marrow transplantation are also reported.

**PATHOLOGY AND PATHOGENESIS**

The pathology of Q fever depends on the mode of transmission, route of dissemination, specific tissues involved, and course of the infection. When acquired via inhalation, a mild interstitial lymphocytic pneumonia and macrophage- and organism-rich intraalveolar exudates are often seen. When the liver is involved, a mild to moderate lymphocytic lobular hepatitis can be seen. Inflammatory pseudotumors can develop in the pulmonary parenchyma or other tissues. Classic fibrinoid (“doughnut”) granulomas, generally associated with acute, self-limited infections, are occasionally identified in liver, bone marrow, meninges, and other organs. Typically, infected tissues are also infiltrated by lymphocytes and histiocytes.

Recovery from symptomatic or asymptomatic acute infection can result in persistent subclinical infection and possibly maintained by dysregulated cytokine responses. The persistence of *C. burnetii* in tissue macrophages at sites of preexisting tissue damage elicits low-grade chronic inflammation and, depending on the site of involvement, can result in irreversible cardiac valve damage, persistent vascular injury, or osteomyelitis. Endocarditis of native or prosthetic valves is characterized by infiltrates of macrophages and lymphocytes in necrotic fibrinous valvular vegetations and an absence of granulomas.

**CLINICAL MANIFESTATIONS AND COMPLICATIONS**

Only approximately 40–50% of people infected with *C. burnetii* develop symptoms. Two forms of symptomatic disease occur. **Acute Q fever** is more common and usually manifests as self-limited undifferentiated fever or an influenza-like illness with interstitial pneumonitis. **Chronic Q fever** in adults usually involves native heart valves, prosthetic valves, or other endovascular prostheses. Q fever osteomyelitis is less common but proportionally more common in children.

**Acute Q Fever**

Acute Q fever develops approximately 3 wk (range: 14–39 days) after exposure to the causative agent. The severity of illness in children ranges from subclinical infection to a systemic illness of sudden onset characterized by high fever, severe frontal headache, nonproductive cough, chest pain, vomiting, diarrhea, abdominal pain, arthralgias, and myalgias. Approximately 40% of children with acute Q fever present with fever, 25% with pneumonia or an influenza-like illness, >10% with meningoencephalitis, and >10% with myocarditis. Other manifestations include pericarditis, hepatitis, hemophagocytosis, rhabdomyolysis, and a hemolytic uremic–like syndrome. Rash, ranging from maculopapular to purpuric lesions, is an unusual finding in adults with Q fever but is observed in approximately 50% of pediatric patients. Rigors and night sweats are common in adults with Q fever and occur less often in children. Prominent clinical findings that can create diagnostic confusion include fatigue, vomiting, abdominal pain, and meningismus. Hepatomegaly and splenomegaly may be detected in some patients.

Routine laboratory investigations in pediatric acute Q fever are usually normal but can reveal mild leukocytosis and thrombocytopenia. Up to 85% of children have modestly elevated serum hepatic transaminase levels that usually normalize within 10 days. Hyperbilirubinemia is uncommon in the absence of complications. C-reactive protein is uniformly elevated in pediatric Q fever. Chest radiographs are abnormal in 27% of all patients; in children, the most common findings include single or multiple bilateral infiltrates with reticular markings in the lower lobes.
Acute Q fever in children is usually a self-limited illness, with fever persisting for only 7-10 days compared with 2-3 wk in adults. However, severe manifestations of acute illness, such as myocarditis requiring cardiac transplantation, meningoencephalitis, pericarditis, and hemophagocytosis, as well as a relapsing febrile illness lasting for several months have been reported.

Chronic Q Fever

The risk for developing chronic Q fever is strongly correlated with advancing age and underlying conditions such as cardiac valve damage or immunosuppression; chronic Q fever is rarely diagnosed in children. A review identified only 5 cases of chronic Q fever endocarditis and 6 cases of osteomyelitis among children, none of whom had known predisposing immune deficiencies. Four of the 5 cases of endocarditis occurred in children with underlying congenital heart abnormalities and involved the aortic, pulmonary, and tricuspid valves. Four of the 6 children with Q fever osteomyelitis had a prior diagnosis or clinical course consistent with idiopathic chronic recurrent multifocal osteomyelitis. A long interval before diagnosis and lack of high fever are common in pediatric cases of chronic Q fever.

Although Q fever endocarditis often results in death (23-65% of cases) in adults, mortality has not been reported for children. Endocarditis associated with chronic Q fever can occur months to years after acute infection and can occur in the absence of recognized acute Q fever. Chronic hepatitis has also been reported.

LABORATORY FINDINGS

Laboratory features in children with chronic Q fever are poorly documented; adult patients often have an erythrocyte sedimentation rate of >20 mm/hr (80% of cases), hypergammaglobulinemia (54%), and hyperfibrinogenemia (67%). In children, the presence of rheumatoid factor in >50% of cases and circulating immune complexes in nearly 90% suggest an autoimmune process, as do antiphase I antibody titers, anti-smooth muscle antibodies, antimitochondrial antibodies, circulating anticoagulants, and positive direct Coombs tests.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

Although uncommonly diagnosed, Q fever should be considered in children who have fever of unknown origin, atypical pneumonia, myocarditis, meningoencephalitis, culture-negative endocarditis, or recurrent osteomyelitis and who live in rural areas or who are in close contact with domestic livestock, cats, or animal products.

The diagnosis of Q fever is most easily and commonly confirmed by testing acute and convalescent sera (2-4 wk apart), which show a 4-fold increase in indirect fluorescent immunoglobulin G antibody titers to phase II C. burnetii antigens. The phase II antibody response to C. burnetii appears first and is higher than the phase I antibody response. Phase II immunoglobulin G antibodies can remain elevated for months to years regardless of initial symptoms or lack thereof. In contrast, chronic Q fever is characterized by the rise of phase I immunoglobulin G antibodies and an antibody titer greater than 800 raises the suspicion of Q fever endocarditis in patients with valvular heart disease or other sites of chronic, active Q fever infection. Cross-reactions with antibodies to Legionella and Bartonella can occur.

Although culture has been considered the gold standard, sensitivity (compared with a composite standard including serology and polymerase chain reaction) is low. C. burnetii has been cultivated in tissue culture cells, which can become positive within 48 hr, but isolation and antimicrobial susceptibility testing of C. burnetii should be attempted only in specialized biohazard facilities. Testing by polymerase chain reaction can be performed on blood, serum, and tissue samples and is available only in some public health, reference, or research laboratories. Although polymerase chain reaction has been helpful in patients with equivocal titers, sensitivity has been improved by real-time methods and use of repeated sequences as targets. Immunohistochemical staining has also been used, but is not readily available.

The differential diagnosis depends on the clinical presentation. In patients with respiratory disease, Mycoplasma pneumoniae, Chlamydia pneumoniae, legionellosis, psittacosis, and Epstein-Barr virus infection should be considered. In patients with granulomatous hepatitis, tuberculous and nontuberculous mycobacterial infections, salmonellosis, visceral leishmaniasis, toxoplasmosis, Hodgkin disease, monocytic ehrlichiosis, granulocytic anaplasmosis, brucellosis, cat scratch disease (Bartonella henselae), or autoimmune disorders such as sarcoidosis should be considered. Culture-negative endocarditis suggests infection with Brucella, Bartonella, or HACEK organisms (Haemophilus, Aggregatibacter, Cardiobacterium hominis, Eikenella corrodens, Kingella), partially treated bacterial endocarditis, or nonbacterial endocarditis.

TREATMENT

Selection of an appropriate antimicrobial regimen for children is difficult owing to the lack of rigorous studies, the limited therapeutic window for drugs that are known to be efficacious, and the potential length of therapy required to preclude relapse.

Most pediatric patients with Q fever have a self-limited illness that is identified only on retrospective serologic evaluation. However, to prevent potential complications, treatment should be considered for patients who present with acute Q fever within 3 days of onset of symptoms, because therapy started more than 3 days after onset of illness has little effect on the course of acute Q fever. Because confirmatory testing in early acute infection is not possible and because tetracycline and doxycycline can be associated with tooth discoloration in children younger than 9 yr of age, empirical therapy is warranted in those with clinically suspected Q fever who are 8 yr of age or older or at high risk for severe illness. Doxycycline (4 mg/kg/day PO or IV divided every 12 hr; maximum: 200 mg/day) is the drug of choice; the usual course is 2 wk. Children at high risk include those hospitalized or with severe illness; those diagnosed after prolonged (>2 wk) unremitting symptoms; and those with preexisting valvular heart disease or who are immunocompromised. Because tooth discoloration is both dose and duration dependent and few children require multiple courses, younger children with mild Q fever could be treated with 5 days of doxycycline followed by 14 days of trimethoprim-sulfamethoxazole if symptoms persist. During pregnancy, Q fever is best treated with trimethoprim-sulfamethoxazole. The fluoroquinolones are also effective, and success with a combination of a fluoroquinolone and rifampin is also achieved with prolonged therapy (16-21 days). Macrolides, including erythromycin and clarithromycin, are less-effective alternatives.

For chronic Q fever, especially endocarditis and mostly in adults, therapy for 18-36 mo is mandatory. The current recommended regimen for chronic Q fever endocarditis is a combination of doxycycline and hydroxychloroquine for 18 mo or longer. For patients with heart failure, valve replacement could be necessary. Interferon-γ therapy has been used as adjunct therapy for intractable Q fever.

PREVENTION

Recognition of the disease in livestock or other domestic animals should alert communities to the risk for human infection. Milk from infected herds must be pasteurized at temperatures sufficient to destroy C. burnetii. C. burnetii is resistant to significant environmental conditions but can be inactivated with a solution of 1% Lysol, 1% formaldehyde, or 5% hydrogen peroxide. Special isolation measures are not required because person-to-person transmission is rare, except when others are exposed to the placenta of an infected patient. A vaccine is available and provides protection against Q fever for at least 5 yr in abattoir workers. Because the vaccine is strongly reactogenic and no trials in children have been conducted, it should only be used when extreme risk is judged to exist. Clusters of cases resulting from intense natural exposures, such as in slaughterhouses or on farms, are well documented. Clusters of cases that occur in the absence of such an exposure should be investigated as potential sentinel events for bioterrorism.

Bibliography is available at Expert Consult.
Bibliography


Section 12
Fungal Infections

Chapter 233
Principles of Antifungal Therapy

As a result of advances in aggressive antineoplastic agents and organ transplantation, invasive fungal infections are a major cause of morbidity and mortality in children. Fortunately, the therapeutic armamentarium for invasive fungal infections has markedly increased since the 1990s (Table 233-1).

**POLYENES**

Amphotericin B

The prototype of the oldest antifungal class, the polyene macrolides, is amphotericin B deoxycholate. Amphotericin B was once the preferred treatment for invasive fungal infections as well as the standard of comparison for all newer antifungal agents. Amphotericin B is so named because it is amphoteric, forming soluble salts in both acidic and basic environments. However, because of its insolubility in water, amphotericin B for clinical use is actually amphotericin B mixed with the detergent deoxycholate. Amphotericin B binds to ergosterol, the major sterol found in fungal cytoplasmic membranes, and acts by creating transmembrane channels. The fungicidal activity is the result of a damaged barrier and subsequent cell death through leakage of essential nutrients from the fungal cell.

Amphotericin B is released from its carrier and distributes very efficiently with lipoproteins, taken up preferentially by organs of the reticuloendothelial system. Following an initial 24-48 hr distributional half-life there is very slow release and a subsequent terminal elimination half-life of up to 15 days. In addition to conventional amphotericin B deoxycholate, 3 fundamentally different lipid-associated formulations have been developed that offer the advantage of an increased daily dosage of the parent drug, better delivery to the primary reticuloendothelial organs (lungs, liver, spleen), and reduced toxicity. Amphotericin B lipid complex is a tightly packed ribbon-like structure of a bilayered membrane, amphotericin B colloidal dispersion is composed of disk-like structures of cholesteryl sulfate complexed with amphotericin B, and liposomal amphotericin B (L-amphotericin B) consists of small uniformly sized vesicles of a lipid bilayer of amphotericin B. Lipid formulations of amphotericin B generally have a slower onset of action, presumably owing to the required disassociation of free amphotericin B from the lipid vehicle. The ability to safely administer higher daily doses of the parent drugs improves their efficacy, comparing favorably with amphotericin B deoxycholate but with less toxicity. Lipid formulations have the added benefit of increased tissue concentrations compared to conventional amphotericin B, specifically in the liver, lungs, and spleen. However, it is not entirely clear if these higher concentrations in tissue are truly available to the microfoci of infection.

Tolerance to amphotericin B deoxycholate is limited by its acute and chronic toxicities. In addition to interacting with fungal ergosterol, the drug also interacts with cholesterol in human cell membranes, likely accounting for its toxicity. Up to 80% of patients receiving amphotericin B develop either infusion-related toxicity or nephrotoxicity, especially with concomitant therapy with nephrotoxic drugs such as aminoglycosides, vancomycin, cyclosporine, or tacrolimus. Renal function usually returns to normal after cessation of amphotericin B, although permanent renal impairment is common after larger doses. Amphotericin B nephrotoxicity is generally less severe in infants and children than in adults, likely because of the more rapid clearance of the drug in children. Lipid formulations appear to stabilize amphotericin B in a self-associated state so that it is not available to interact with the cholesterol of human cellular membranes.

Unlike older guidelines, there is no total dosage of amphotericin B recommended, and the key to success is to give high dosages in the initial phase of therapy and to reduce the dosage if toxicity develops. There are no data or consensus opinions among authorities indicating improved efficacy of any new amphotericin B lipid formulation over conventional amphotericin B deoxycholate. One exception is that

<table>
<thead>
<tr>
<th>DRUG FORMULATIONS</th>
<th>SUGGESTED PEDIATRIC DOSAGE</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amphotericin B deoxycholate</td>
<td>IV 1 mg/kg/day</td>
<td>Generally less toxicity in children than adults; do not start with smaller test doses</td>
</tr>
<tr>
<td>Lipid amphotericin B formulations</td>
<td>IV 5 mg/kg/day</td>
<td>Generally all lipid formulations are dosed the same; there is no clear indication of one formulation over another for clinical efficacy</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>IV, PO 12 mg/kg/day</td>
<td>Loading dose (25 mg/kg) is suggested based on pharmacokinetic simulations, but insufficiently studied</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>IV, PO 2.5 mg/kg/dose bid</td>
<td>Divide dosage twice daily in children; follow trough levels</td>
</tr>
<tr>
<td>Voriconazole</td>
<td>IV, PO 8 mg/kg/dose bid IV maintenance, 9 mg/kg/dose bid oral maintenance</td>
<td>Linear pharmacokinetics in children requires higher dosing than in adults; 9 mg/kg/dose bid IV loading, followed by maintenance dosing; follow trough levels</td>
</tr>
<tr>
<td>Posaconazole</td>
<td>PO 12-24 mg/kg/day divided tid</td>
<td>Dosage unclear in children at present In adults, max dosage is 800 mg/day, and optimally divide this into 2 or 3 doses; follow trough levels</td>
</tr>
<tr>
<td>Micafungin</td>
<td>IV 2-10 mg/kg/day</td>
<td>Highest dosages in neonates (10 mg/kg/day), and lower dosages in children; older than 8 yr of age, use adult dosage</td>
</tr>
<tr>
<td>Anidulafungin</td>
<td>IV 1.5 mg/kg/day</td>
<td>Loading dose of 3 mg/kg/day</td>
</tr>
<tr>
<td>Caspofungin</td>
<td>IV 50 mg/m²/day</td>
<td>Load with 70 mg/m²/day, then 50/mg/m²/day as maintenance dosage</td>
</tr>
</tbody>
</table>
1-ampathericin B shows fewer infusion-related adverse events than the other lipid formulations or conventional amphotericin B.

PYRIMIDINE ANALOGS
5-Fluorocytosine
5-Fluorocytosine is a fluorinated analog of cytosine, and its antifungal activity results from the rapid conversion into 5-fluorouracil (5-FU) within susceptible fungal cells. Clinical and microbiologic antifungal resistance appears to develop quickly to 5-fluorocytosine (5-FC) monotherapy, so clinicians have reserved it for combination approaches to augment other, more potent antifungals. Fungistic 5-FC is thought to enhance the antifungal activity of amphotericin B, especially in anatomic sites where amphotericin B penetration is often suboptimal, such as cerebrospinal fluid (CSF), heart valves, and the vitreal body. 5-FC penetrates well into most body sites because it is small, highly water soluble, and not bound by serum proteins to any great extent. The bioavailability of approximately 90% relative to intravenous administration is an advantage, as oral administration has been well tolerated by nearly all patients. While 5-FC is essentially insoluble, it is water soluble, and not bound by serum proteins. The increased volume of distribution is thought to be from the larger amount of body water found in the total body volume of neonates. A pharmacokinetic study in premature infants suggests that maintenance fluconazole doses of 12 mg/kg/day are necessary to achieve exposures similar to those in older children and adults. In addition, a loading dose of 25 mg/kg would achieve steady-state concentrations sooner than the traditional dosing scheme. Side effects of fluconazole are uncommon but generally include gastrointestinal upset (vomiting, diarrhea, nausea) and skin rash.

Fluconazole plays an important role in the treatment of invasive candidiasis. The latest guidelines suggest use of the fungistatic fluconazole in patients who have invasive candidiasis but who are not critically ill or neutropenic. Although most isolates of *Candida albicans* remain susceptible to fluconazole, for certain *Candida* species fluconazole is not an ideal agent: *Candida krusei* is generally resistant and *Candida glabrata* is often resistant. In treating infection caused by these *Candida* species, it is critical to treat with an echinocandin or amphotericin B rather than fluconazole. There is no confirmed role for combination antifungal therapy with fluconazole and another antifungal against invasive candidiasis.

Prophylaxis with fluconazole to prevent neonatal candidiasis in premature infants remains a controversial topic. In a prospective, randomized double-blind trial over a 30 mo period of 100 infants with birth weights <1,000 g, infants who received fluconazole for 6 wk had a decrease in fungal colonization (22% vs 60%) and a decrease in the development of invasive fungal infection (0% vs 20%) compared to placebo. Other studies have yielded similarly encouraging results and have demonstrated that use of fluconazole prophylaxis for 4-6 wk in high-risk infants does not increase the incidence of fungal colonization and infections caused by natively fluconazole-resistant *Candida* species. The universal implementation of such a strategy across nurseries is discouraged, because the rate of *Candida* infections varies greatly among centers and there are insufficient neurodevelopmental follow-up data in these infants to justify prophylaxis.

Itraconazole
Compared to fluconazole, itraconazole has the benefit of antifungal activity against *Aspergillus* species but comes with several practical constraints, such as erratic oral absorption in high-risk patients and significant drug interactions. These pharmacokinetic concerns have been addressed with both an intravenous formulation and a better-absorbed oral solution to replace the capsules used earlier. Itraconazole has a high volume of distribution and accumulates in tissues, and tissue-bound levels are probably more clinically relevant to infection treatment than serum levels. Dissolution and absorption of itraconazole are affected by gastric pH. Patients with achlorhydra or taking H$_2$-receptor antagonists might demonstrate impaired absorption, and conoadministration of the capsule with acidic beverages such as colas or cranberry juice can enhance absorption. Administration with food significantly increases the absorption of the capsule formulation, but the oral suspension with a cyclodextrin base is better absorbed on an empty stomach.

Side effects are relatively few and include nausea and vomiting (10%), elevated transaminases (5%), and peripheral edema. There are reports in adults of development of cardiomyopathy. Itraconazole also is associated with important drug interactions, and prior or concurrent use of rifampin, phenytoin, carbamazepine, and phenobarbital should be avoided.

Itraconazole has a role in treating less-serious infections with endemic mycoses (histoplasmosis, coccidioidomycosis, and blastomycosis), as well as use in prophylaxis against invasive fungal infections
in high-risk patients. The plethora of drug interactions make itraconazole a concern in complex patients receiving other medications, and itraconazole serum levels (to achieve ≥0.5 µg/mL) are recommended to confirm appropriate dosing. Itraconazole is no longer recommended for primary therapy of invasive aspergillosis.

**Voriconazole**

Voriconazole is a second-generation triazole and a synthetic derivative of fluconazole. Voriconazole generally has the spectrum of activity of itraconazole but the better bioavailability than fluconazole. Importantly, it is fungicidal against *Aspergillus* and fungistatic against *Candida*. It is extensively metabolized by the liver and has approximately 90% oral bioavailability. The cytochrome P450 2C19 (CYP2C19) enzyme appears to play a major role in the metabolism of voriconazole, and polymorphisms in CYP2C19 are associated with slow voriconazole metabolism. As many as 20% of non-Indian Asians have low CYP2C19 activity and develop voriconazole levels as much as 4-fold higher than those in homozous subjects, leading to potentially increased toxicity.

Voriconazole is available as an oral tablet, an oral suspension, and an intravenous solution. In adults, voriconazole exhibits nonlinear pharmacokinetics, has a variable half-life of approximately 6 hr with large interpatient variation in blood levels, and achieves good CSF penetration. In contrast to the situation in adults, elimination of voriconazole is linear in children. A multicenter safety, population pharmacokinetic study of intravenous voriconazole dosages in immunocompromised pediatric patients showed that body weight was more influential than age in accounting for the observed variability in voriconazole pharmacokinetics, and voriconazole needs to be dosed higher in pediatric patients than adult patients. Adult patients load with 6 mg/kg/dose and then transition to a maintenance dosage of 4 mg/kg/dose, but children should begin and continue with 9 mg/kg/dose intravenously (see Table 233-1) and continue maintenance dosing at 8 mg/kg/dose. This need for an increased dosage in treating children is crucial to understand and is mandated by the fundamentally different pharmacokinetics of this drug in pediatric patients. Obtaining voriconazole serum levels (to achieve ≥1-2 µg/mL) is critical for therapeutic success. Oral voriconazole is best absorbed on an empty stomach. Generally a trough level greater than the minimum inhibitory concentration of the infecting organism is preferred, and very high voriconazole levels have been associated with toxicity (generally >7 µg/mL). The main side effects of voriconazole include reversible dosage-dependent visual disturbances (increased brightness, blurred vision) in as many as one-third of treated patients, elevated hepatic transaminases with increasing dosages, and occasional skin reactions likely caused by photosensitization.

The largest prospective clinical trial of voriconazole as primary therapy for invasive aspergillosis compared initial randomized therapy with voriconazole vs amphotericin B and demonstrated improved response and survival with voriconazole over amphotericin B. Voriconazole is guideline-recommended as the preferred primary therapy against invasive aspergillosis. Voriconazole also has a role in treating candidiasis, but its fungistatic nature makes it often less than ideal for treating critically ill or neutropenic patients where the fungicidal echinocandin antifungals are preferred.

**Posaconazole**

Posaconazole is a second-generation triazole that is a derivative of itraconazole and is currently available as an intravenous formulation, an extended-release oral tablet, and an oral suspension. The antimicrobial spectrum of posaconazole is similar to that of voriconazole; however, the former is active against *Zygomycetes* such as mucormycosis, and voriconazole is not active against these particular mold infections. When administered with a nonfat or high-fat diet, posaconazole exposure and maximum concentration are 3-4 times higher than when administered in the fasting state, emphasizing the importance of diet to increase serum levels of posaconazole (the opposite of voriconazole). Posaconazole exposure is maximized with acidic beverages, administration in divided doses, and the absence of proton pump inhibitors. Posaconazole causes transient hepatic reactions, including mild to moderate elevations in liver transaminases, alkaline phosphatase, and total bilirubin.

The correct pediatric dosage of posaconazole is not known, because initial studies are still ongoing. In adult patients, dosages >800 mg/day do not result in increased serum levels, and division of daily dosing into 3 or 4 doses/day results in greater serum levels than a once- or twice-daily dosing scheme. Similar to itraconazole and voriconazole, posaconazole should be monitored with trough levels (to achieve ≥0.7 µg/mL).

In an international randomized, single-blinded study of posaconazole vs fluconazole or itraconazole in neutropenic patients undergoing chemotherapy for acute myelogenous leukemia or myelodysplastic syndromes, posaconazole was superior in preventing invasive fungal infections. Fewer patients in the posaconazole group had invasive aspergillosis, and survival was significantly longer among recipients of posaconazole than among recipients of fluconazole or itraconazole. Another multisite international randomized, double-blinded study in patients with allogeneic hematopoietic stem-cell transplantation and graft-versus-host disease showed that posaconazole was not inferior to fluconazole in the prevention of invasive fungal infections. Posaconazole is approved for prophylaxis against invasive fungal infections but has shown great efficacy in clinical experience with recalcitrant mold infections.

In patients with chronic granulomatous disease and proven invasive fungal infection refractory to standard therapy, posaconazole proved to be well tolerated and quite effective. This agent might prove to be very useful in this patient population where long-term therapy with an oral agent is required.

**Echinocandins**

The echinocandins are a class of antifungals and interfere with cell wall biosynthesis by noncompetitive inhibition of 1,3-β-D-glucan synthase, an enzyme present in fungi but absent in mammalian cells. 1,3-β-D-Glucan is an essential cell wall polysaccharide and provides structural integrity for the fungal cell wall. Echinocandins are generally fungicidal in vitro against *Candida* species, although not as rapidly as amphotericin B, and are fungistatic against *Aspergillus*. As a class these agents are not metabolized through the CYP enzyme system, lessening some of the drug interactions and side effects seen with the azole class. The echinocandins appear to have a prolonged and dosage-dependent fungicidal antifungal effect on *C. albicans*, compared to the fungistatic fluconazole. Three compounds in this class (caspofungin, micafungin, and anidulafungin) are FDA approved for use. Owing to the large size of the molecules, the current echinocandins are only available in an intravenous formulation. Because 1,3-β-D-glucan is a selective target present only in fungal cell walls and not in mammalian cells, this eliminates much of the drug mechanism–based toxicity for the echinocandins, and there appears to be no apparent myelotoxicity or nephrotoxicity with the agents.

**Caspofungin**

At present there is no known maximum tolerated dosage and no toxicity-determined maximum length of therapy for caspofungin. The usual course is to begin with a loading dose followed by a lesser daily maintenance dosage, which is 70 mg followed by 50 mg daily in adult patients. Much of the dosage accumulation is achieved in the 1st wk of dosing, and renal insufficiency has little effect on the pharmacokinetics of caspofungin. Caspofungin has been evaluated at double the recommended dosage (100 mg/day in adults) with no adverse effects, and it is unclear if higher dosage of this relatively safe agent results in greater clinical efficacy.

Pharmacokinetics are slightly different in children, with caspofungin levels lower in smaller children and with a reduced half-life. A study evaluated the pharmacokinetics of caspofungin in children with neutropenia and showed that in patients receiving 50 mg/m²/day (maximum: 70 mg/day), the levels were similar to those in adults receiving 50 mg/day and were consistent across age ranges. In this study, weight-based dosing (1 mg/kg/day) was suboptimal when
 compared to body surface area regimens, so caspofungin should be appropriately dosed in children as a loading dose of 70 mg/m\(^2\)/day, followed by daily maintenance dosing of 50 mg/m\(^2\)/day.

Caspofungin was approved for refractory aspergillosis or intolerance to other therapies and for candidemia and various other sites of invasive *Candida* infections. In the pivotal clinical study, patients with acute invasive aspergillosis underwent “salvage” therapy after failing primary therapy, and recipients had a 41% favorable response with caspofungin. In a multicenter trial of patients with invasive candidiasis, 73% of patients who received caspofungin had a favorable response at the end of therapy, compared to 62% in the amphotericin B group. Importantly, caspofungin treatment performed equally well to amphotericin B treatment for all the major *Candida* species, but other studies show that some infections with *Candida parapsilosis* do not clear as effectively with an echinocandin. Current guideline recommendations state that infection with *C. parapsilosis* should be treated initially with fluconazole or amphotericin B for this reason. Caspofungin was also evaluated against L-amphotericin B in the empirical treatment of patients with persistent fever and neutropenia and was not inferior to liposomal amphotericin B in more than 1,000 patients.

Caspofungin in children is reported to be safe. Caspofungin pharmacokinetics were evaluated in older infants and toddlers at 50 mg/m\(^2\)/day and found to be similar to adults receiving the standard 30 mg daily dose. Caspofungin in newborns has been used as single or adjuvant therapy for refractory cases of disseminated candidiasis. Neonates with invasive candidiasis are at high risk for central nervous system involvement; it is not known if the dosages of caspofungin studied provide sufficient exposure to penetrate the central nervous system at levels necessary to cure infection. Therefore, caspofungin is not recommended as monotherapy in neonatal candidiasis.

**Micafungin**

The pharmacokinetics of micafungin have been evaluated in children and young infants. An inverse relation between age and clearance was observed, where mean systemic clearance was significantly greater and mean half-life was significantly shorter in patients 2-8 yr of age compared to patients 9-17 yr of age. Therefore, dosing of micafungin in children is age-related and needs to be higher in children younger than 8 yr old. To achieve micafungin exposures equivalent to exposures in adults receiving 100, 150, and 200 mg daily, as evidenced by simulation profiles, children require dosages >3 mg/kg.

Several pharmacokinetic studies of micafungin in term and preterm infants show that micafungin in infants has a shorter half-life and a more rapid rate of clearance compared with published data in older children and adults. These results suggest that young infants should receive 10 mg/kg daily of micafungin if used to treat invasive candidiasis.

The safety profile of micafungin is optimal when compared to other antifungal agents. Clinical trials including those of micafungin used for treatment of localized and invasive candidiasis as well as prophylaxis studies in patients following stem cell transplantation have demonstrated fewer adverse events compared to liposomal amphotericin B and fluconazole. The most common adverse events experienced by these patients are related to the gastrointestinal tract (nausea, diarrhea). Hypersensitivity reactions associated with micafungin have been reported, and liver enzymes are elevated in 5% of patients receiving this agent. Hyperbilirubinemia, renal impairment, and hemolytic anemia related to micafungin use have also been identified in postmarketing surveillance of the drug.

An open-label, noncomparative, multinational study in adult and pediatric patients with a variety of diagnoses evaluated the use of micafungin monotherapy and combination therapy in 225 patients with invasive aspergillosis. Of those only treated with micafungin, favorable responses were seen in 50% of the primary and 41% of the salvage therapy group.

Micafungin at dosages of 100 and 150 mg daily was also noninferior to caspofungin in an international, randomized, double-blinded study of adults with candidemia or invasive candidiasis and was found to be superior to fluconazole in the prevention of invasive fungal infections in a randomized study of adults undergoing hematopoietic stem cell transplantation.

Of the 3 drugs within the echinocandin class, micafungin has been the one most extensively studied in children, including several pharmacokinetic studies in neonates. A pediatric substudy as part of a double-blind, randomized, multinational trial comparing micafungin (2 mg/kg/day) with liposomal amphotericin B (3 mg/kg/day) as first-line treatment for invasive candidiasis showed similar success for micafungin and liposomal amphotericin B. In general, micafungin was better tolerated than liposomal amphotericin B as evidenced by fewer adverse events leading to discontinuation of therapy. Micafungin doses up to 15 mg/kg/day have been evaluated in small cohorts of premature infants and found to be well tolerated; doses of 8-10 mg/kg/day achieve exposures comparable to adults in this population.

**Anidulafungin**

Anidulafungin has the longest half-life of all the echinocandins (approximately 18 hr). In a study of 25 neutropenic children receiving anidulafungin as empirical therapy, 4 patients in the group receiving 0.75 mg/kg/day experienced adverse events such as facial erythema and rash, elevation in serum blood urea nitrogen, and fever and hypotension. In a pharmacokinetic study in neonates and young infants, anidulafungin exposures comparable to adults were achieved with doses of 1.5 mg/kg/day (3 mg/kg loading dose). One infant in this cohort supported by extracorporeal membrane oxygenation achieved the lowest exposure, which suggests that dose adjustments are required in this population.

A randomized, double-blind study in adult patients without neutropenia with invasive candidiasis showed that anidulafungin was not inferior to fluconazole in the treatment of invasive candidiasis. In this study, the incidence and types of adverse events were similar in the 2 groups, and all-cause mortality was 31% in the fluconazole group and 23% in the anidulafungin group. No clinical studies of anidulafungin in pediatric patients are currently available.

*Bibliography is available at Expert Consult.*
Bibliography
Candidiasis encompasses many clinical syndromes that may be caused by several species of Candida. Invasive candidiasis (Candida infections of the blood and other sterile body fluids) is a leading cause of infection-related mortality in hospitalized immunocompromised patients. 

Candida exists in 3 morphologic forms: oval to round blastospores or yeast cells (3-6 mm in diameter); double-walled chlamydomspores (7-17 mm in diameter), which are usually at the terminal end of a pseudohypha; and pseudomycelium, which is a mass of pseudohyphae and represents the tissue phase of Candida. Pseudohyphae are filamentous processes that elongate from the yeast cell without the cytoplasmic connection of a true hypha. Candida grows aerobically on routine laboratory media but can require several days of incubation for visible growth.

Candida albicans accounts for most human infections, but Candida parapsilosis, Candida tropicalis, Candida krusei, Candida lusitaniae, Candida glabrata, and several other species are commonly isolated from hospitalized children. C. albicans forms a germ tube when suspended in rabbit or human serum and incubated for 1-2 hr; consequently, a rapid germ tube test should be performed before further
identification tests are conducted. The other clinically important Candida species can be identified within 48 hr on the basis of biochemical test results. Differentiation and susceptibility testing are important owing to increasing frequency of fluconazole resistance.

Treatment of invasive Candida infections is complicated by the emergence of non-albicans strains. Amphotericin B deoxycholate is inactive against approximately 20% of strains of C. lusitaniae. Fluconazole is useful for many Candida infections but is inactive against all strains of C. krusei and 5-25% of strains of C. glabrata. Susceptibility testing of these clinical isolates is recommended.

234.1 Neonatal Infections
Jessica Ericson, P. Brian Smith, and Daniel K. Benjamin Jr.

Candida is a common cause of oral mucous membrane infections (thrush) and perineal skin infections (Candida diaper dermatitis) in young infants. Rare presentations include congenital cutaneous candidiasis, caused by an ascending infection into the uterus during gestation, and invasive fungal dermatitis, a postnatal skin infection resulting in positive blood cultures. Invasive candidiasis is a common infectious complication in the neonatal intensive care unit (NICU) because of improved survival of extremely preterm infants.

EPIDEMIOLOGY
Candida species are the third most common cause of bloodstream infection in premature infants. The cumulative incidence is <0.3% among infants >2,500 g birthweight admitted to the NICU. The cumulative incidence increases to 8% for infants <750 g birthweight. In addition, the incidence varies greatly by individual NICU. Among centers in the National Institutes of Health-sponsored Neonatal Research Network, the cumulative incidence of candidiasis among infants <1,000 g birthweight ranges from 2-28%. Colonization is associated with a significantly increased risk of future invasive Candida infection. Up to 10% of full-term infants are colonized as the result of vertical transmission from the mother at birth, with slightly higher rates of colonization in premature infants. Colonization rates increase to >50% among infants admitted to the NICU by 1 mo of age. Histamine-2 blockers and broad-spectrum antibiotics facilitate Candida colonization and overgrowth.

Significant risk factors for neonatal invasive candidiasis include prematurity, low birthweight, exposure to broad-spectrum antibiotics, abdominal surgery, and presence of a central venous catheter.

PATHOGENESIS
Immunologic immaturity along with an underdeveloped layer of skin, need for invasive measures (endotracheal tubes, central venous catheters), and exposure to broad-spectrum antibiotics places preterm infants at great risk for invasive candidiasis. Premature infants are also at high risk for spontaneous intestinal perforations and necrotizing enterocolitis. Both conditions require abdominal surgery, prolonged exposure to broad-spectrum antibiotics, and total parenteral nutrition administration requiring placement of central venous catheters. Each of these factors increases the risk of invasive candidiasis by decreasing the physiologic barriers that protect against invasive infection.

CLINICAL MANIFESTATIONS
The manifestations of neonatal candidiasis vary in severity from oral thrush and Candida diaper dermatitis (see Chapter 234.2) to invasive candidiasis that can manifest with overwhelming sepsis (see Chapter 234.3). Signs of invasive candidiasis among premature infants are often nonspecific and include temperature instability, lethargy, apnea, hypotension, respiratory distress, abdominal distension, and thrombocytopenia.

Central nervous system involvement is common and is most accurately described as meningocerephalitis. Candida infections involving the central nervous system often result in abscesses leading to unremarkable cerebrospinal fluid parameters (white blood cell count, glucose, protein) even though central nervous system infection is present. Endophthalmitis is an uncommon complication affecting <5% of infants with invasive candidiasis. In addition, candidemia is associated with an increased risk of severe retinopathy of prematurity. Renal involvement commonly complicates neonatal invasive candidiasis. Renal involvement may be limited to candiduria or can manifest with diffuse infiltration of Candida throughout the renal parenchyma or the presence of Candida and debris within the collecting system. Other affected organs include the heart, bones, joints, liver, and spleen.

DIAGNOSIS
Mucocutaneous infections are most often diagnosed by direct clinical exam. Scrapings of skin lesions may be examined with a microscope after Gram staining or suspension in KOH. Definitive diagnosis of invasive disease requires histologic demonstration of the fungus in tissue specimens or recovery of the fungus from normally sterile body fluids. Hematologic parameters are sensitive but not specific. Thrombocytopenia occurs in more than 80% of premature infants with invasive candidiasis, but also occurs in 75% of premature infants with Gram-negative bacterial sepsis and nearly 50% of infants with Gram-positive bacterial sepsis. Blood cultures have very low sensitivity for invasive candidiasis. In a study of autopsy-proven candidiasis in adult patients, the sensitivity of multiple blood cultures for detecting single-organ disease was 28%. Blood culture volumes in infants are often only 0.5-1 mL, making the sensitivity in this population almost certainly lower. Blood culture volume should be maximized as much as possible to increase sensitivity. Fungal-specific media can improve sensitivity when Candida is present as a coinfection with bacteria and can also decrease the time to positivity leading to more rapid diagnosis.

Further assessment of infants in the presence of documented candidemia should include ultrasound or computerized tomography of the head to evaluate for abscesses; ultrasound of the liver, kidney, and spleen; cardiac echocardiography; ophthalmologic exam; lumbar puncture; and urine culture. These tests are necessary to determine if more than 1 body system is infected, which is commonly the case.

PROPHYLAXIS
NICUs with a high incidence of invasive candidiasis should consider prophylaxis with fluconazole in infants <1,000 g birthweight. Twice-weekly fluconazole at 3 and 6 mg/kg/dose decreases rates of both colonization with Candida species and invasive fungal infections. Use of this dosing strategy has not been shown to increase the frequency of infections caused by fluconazole-resistant strains, but use of an alternative antifungal class for cases of breakthrough infection is suggested.

TREATMENT
In the absence of systemic manifestations, topical antifungal therapy is the treatment of choice for congenital cutaneous candidiasis in full-term infants. Congenital cutaneous candidiasis in preterm infants can progress to systemic disease, and therefore systemic therapy is warranted.

Every attempt should be made to remove or replace central venous catheters once the diagnosis of candidemia is confirmed. Delayed removal has been consistently associated with increased mortality and morbidity including poor neurodevelopmental outcomes.

Although no well-powered randomized, controlled trials exist to guide length and type of therapy, 21 days of systemic antifungal therapy from the last positive Candida culture is recommended in infants. Antifungal therapy should be targeted based on susceptibility testing. Amphotericin B deoxycholate has been the mainstay of therapy for systemic candidiasis and is active against both yeast and mycelial forms. Nephrotoxicity, hypokalemia, and hypomagnesemia are common, but amphotericin B deoxycholate is better tolerated in infants than in adult patients. C. lusitaniae, an uncommon pathogen in infants, is often resistant to amphotericin B deoxycholate. Liposomal amphotericin B is associated with worse outcomes in infants and should be used only when urinary tract involvement can reliably be excluded. Fluconazole is often used instead of amphotericin B deoxycholate for treatment of invasive neonatal Candida infections because of its effectiveness and low incidence of side effects. It is particularly useful for urinary
For recalcitrant or recurrent infections, a single dose of fluconazole may be useful. In breastfed infants, simultaneous treatment of infant and mother with topical nystatin or oral fluconazole may be indicated.

### DIAPER DERMATITIS

Diaper dermatitis is the most common infection caused by *Candida* (see Chapter 666) and is characterized by a confluent erythematous rash with satellite pustules. *Candida* diaper dermatitis often complicates other noninfectious diaper dermatitides and often occurs following a course of oral antibiotics. A common practice is to presumptively treat any diaper rash that has been present for longer than 3 days with topical antifungal therapy such as nystatin, clotrimazole, or miconazole. If significant inflammation is present, the addition of hydrocortisone 1% may be useful for the 1st 1-2 days, but topical corticosteroids should be used cautiously in infants because the relatively potent topical corticosteroid can lead to adverse effects. Frequent diaper changes and short periods without diapers are important adjunctive treatments.

### UNGUAL AND PERIUNGUAL INFECTIONS

Paronychia and onychomycosis may be caused by *Candida*, although *Trichophyton* and *Epidermophyton* are more common causes (see Chapter 663). *Candida* onychomycosis differs from tinea infections by its propensity to involve the fingernails and not the toenails, and by the associated paronychia. *Candida* paronychia often responds to treatment consisting of keeping the hands dry and using a topical antifungal agent. Psoriasis and immune dysfunction, including HIV and primary immunodeficiencies, predispose to *Candida* ungual infections. Ungual infections often require systemic antifungal therapy. Once-weekly fluconazole for 4-12 mo is an effective treatment strategy with fairly low toxicity.

### VULVOVAGINITIS

Vulvovaginitis is a common *Candida* infection of pubertal and postpubertal female patients (see Chapter 549). Predisposing factors include pregnancy, use of oral contraceptives, and use of oral antibiotics. Prepubertal girls with *Candida* vulvovaginitis usually have a predisposing factor such as diabetes mellitus or prolonged antibiotic treatment. Clinical manifestations can include pain or itching, dysuria, vulvar or vaginal erythema, and an opaque white or cheesy exudate. More than 80% of cases are caused by *C. albicans*. *Candida* vulvovaginitis can be effectively treated with either vaginal creams or troches of nystatin, clotrimazole, or miconazole. Oral therapy with a single dose of fluconazole is also effective.

### Bibliography

Bibliography is available at Expert Consult.

#### 234.2 Infections in Immunocompetent Children and Adolescents

Jessica Ericson, P. Brian Smith, and Daniel K. Benjamin Jr.

#### 234.3 Infections in Immunocompromised Children and Adolescents

Jessica Ericson, P. Brian Smith, and Daniel K. Benjamin Jr.

#### ETIOLOGY

*C. albicans* is the most common cause of invasive candidiasis among immunocompromised pediatric patients and is associated with higher rates of mortality and end-organ involvement than are non-*albicans* species.

#### CLINICAL MANIFESTATIONS

**HIV-Infected Children**

Oral thrush and diaper dermatitis are the most common *Candida* infections in HIV-infected children. Besides oral thrush, 3 other types of oral *Candida* infections can occur in HIV-infected children: atrophic candidiasis, which manifests as a fiery erythema of the mucosa or loss of papillae of the tongue; chronic hyperplastic candidiasis, which presents with oral symmetric white plaques and angular cheilitis, in which there is erythema and fissuring of the angles of the mouth. Topical antifungal therapy may be effective, but systemic treatment
Bibliography
Bibliography
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dosing regimen for onychomycosis treatment, *J Dermatolog Treat* 24(1):75–80,
2013.
with fluconazole or itraconazole is usually necessary. Symptoms of dysphagia or poor oral intake can indicate progression to *Candida* esophagitis, requiring systemic antifungal therapy. In HIV patients, esophagitis can also be caused by cytomegalovirus, herpes simplex virus, reflux, or lymphoma; *Candida* is the most common cause, and *Candida* esophagitis can occur in the absence of thrush.

*Candida* dermatitis and onychomycosis are more common in HIV-infected children. These infections are generally more severe than they are in immunocompetent children and can require systemic antifungal therapy.

**Cancer and Transplant Patients**

Fungal infections, especially *Candida* and *Aspergillus* infections, are a significant problem in oncology patients with chemotherapy-associated neutropenia (see Chapter 178). Greater than 5 days of fever during a neutropenic episode is associated with presence of an invasive fungal infection. Accordingly, empirical antifungal therapy should be started if fever and neutropenia persist for 5 or more days. Fluconazole can be used if the patient is not critically ill and the drug is not already being used for prophylaxis. An echinocandin or liposomal amphotericin B should be used when these conditions are not met. High-risk oncology patients warrant prophylaxis against invasive *Candida* infection. Both fluconazole and echinocandins are used for this indication; lower doses are typically used for this purpose than those used for treatment.

Bone marrow transplant recipients have a much higher risk of fungal infections because of the dramatically prolonged duration of neutropenia. Voriconazole prophylaxis decreases the incidence of candidemia in bone marrow transplant recipients with the additional benefit over fluconazole of mold prophylaxis. The use of myeloablative colony-stimulating factor reduces the duration of neutropenia after chemotherapy and is associated with decreased risk for candidemia. When *Candida* infection occurs in this population, the lung, spleen, kidney, and liver are involved in more than 50% of cases.

Solid-organ transplant recipients are also at increased risk for superficial and invasive *Candida* infections. Studies in liver transplant recipients demonstrate the utility of antifungal prophylaxis with amphotericin B deoxycholate, fluconazole, voriconazole, or caspofungin in high-risk patients (those with prolonged surgical time, comorbidities, recent antibiotic exposure, or bile leak).

**Catheter-Associated Infections**

Central venous catheter infections occur most often in oncology patients but can affect any patient with a central catheter (see Chapter 179). Neutropenia, use of broad-spectrum antibiotics, and parenteral alimentation are associated with increased risk for *Candida* central catheter infection. Treatment typically requires removing or replacing the catheter followed by a 2-3 wk course of systemic antifungal therapy. Removal of the central catheter in place at time of positive blood culture and use of a peripheral IV or enteral support for at least 48 hr prior to obtaining central access is advocated. Removal of the original catheter followed by immediate replacement with a new central catheter in a different anatomic location is acceptable if an interval without central access is not feasible.

**DIAGNOSIS**

The diagnosis is often presumptive in neutropenic patients with prolonged fever because positive blood cultures for *Candida* occur only in a minority of patients who are later found to have disseminated infection. If isolated, *Candida* grows readily on routine blood culture media, with ≥90% of positive cultures identified within 72 hr. CT may demonstrate findings consistent with invasive fungal infection but also is limited by nonspecific findings and false negatives. The role of screening by CT scan has not been well defined.

**TREATMENT**

Echinocandins are favored as empirical therapy for moderately or severely ill children; fluconazole is acceptable for those who are infected with a susceptible organism and are less critically ill; amphotericin B products are also acceptable. Definitive antifungal selection should be made based on susceptibility testing results. Fluconazole is not effective against *C. krusei* and some isolates of *C. glabrata*. *C. parapsilosis* has occasional resistance to the echinocandins, but the overall rate is still low. Amphotericin B deoxycholate is inactive against approximately 20% of the strains of *C. lusitaniae*, and therefore susceptibility testing should be performed for all strains (Table 234-2).

**PRIMARY IMMUNE DEFECTS**

Chronic mucocutaneous candidiasis involves *Candida* infections of the oral cavity, esophagus, and/or genital mucosa, as well as involvement of skin and nails, that is recurrent or persistent and difficult to treat. There is a broad spectrum of genetic immune defects associated with chronic mucocutaneous candidiasis mostly related to severe T-cell defects or disorders of interleukin-17 production (see Chapter 125). Genes or disorders associated with chronic mucocutaneous candidiasis include severe combined immunodeficiency syndrome, NEMO or IKBG deficiency, DOCK8 deficiency, STAT3 deficiency (autosomal dominant hyperimmunoglobulin E syndrome), autoimmune polyendocrinopathy type 1, CARD9 deficiency, STAT1 gain of function mutations, and IL17RA mutations.

Primary immunodeficiencies associated with an increased risk of invasive *Candida* infections include severe congenital neutropenia, CARD 9 deficiency, chronic granulomatous disease, and leukocyte adhesion deficiency type 1.

*Bibliography is available at Expert Consult.*

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**Table 234-2**  
**Dosing of Antifungal Agents in Children Older Than 1 Year of Age for Treatment of Invasive Disease**

<table>
<thead>
<tr>
<th>DRUG</th>
<th>SUGGESTED DOSAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amphotericin B deoxycholate</td>
<td>1 mg/kg/day</td>
</tr>
<tr>
<td>Amphotericin B lipid complex</td>
<td>5 mg/kg/day</td>
</tr>
<tr>
<td>Liposomal amphotericin B</td>
<td>5 mg/kg/day</td>
</tr>
<tr>
<td>Amphotericin B colloidal dispersion</td>
<td>5 mg/kg/day</td>
</tr>
<tr>
<td>Fluconazole†</td>
<td>12 mg/kg/day</td>
</tr>
<tr>
<td>Voriconazole</td>
<td>8 mg/kg every 12 hr</td>
</tr>
<tr>
<td>Micafungin*†</td>
<td>2-4 mg/kg/day</td>
</tr>
<tr>
<td>Caspofungin</td>
<td>50 mg/m²/day</td>
</tr>
<tr>
<td>Anidulafungin</td>
<td>1.5 mg/kg/day</td>
</tr>
</tbody>
</table>

*Use adult dosages in children older than 8 yr of age.
†Loading doses should be used for fluconazole (25 mg/kg), voriconazole (9 mg/kg q 12 × 24 hr), caspofungin (70 mg/m²), and anidulafungin (3 mg/kg).
Chapter 234  Candida  1518.e1

Bibliography


Cryptococcus neoformans

ETIOLOGY
Cryptococcosis is an invasive fungal disease caused by a monomorphic, encapsulated yeast. Cryptococcus neoformans var. neoformans is the most common etiologic agent worldwide and is the predominant pathogenic fungal infection among persons infected with HIV.
EPIDEMIOLOGY

C. neoformans var. neoformans (serotypes A, D, and AD) is distributed in temperate climates predominantly in soil contaminated with droppings from certain avian species, including pigeons, canaries, and cockatoos. It may also be found on fruits and vegetables and may be carried by cockroaches. C. neoformans var. gattii (serotypes B and C) is found in the tropics and subtropics and is associated with several species of eucalyptus trees. This species causes endemic disease primarily in immunologically competent hosts living in the tropics and is associated with the formation of large granulomas known as cryptococcomas. The distribution and ecology of C. gattii seem to be changing, and this organism can now be found in association with a wide range of trees, including firs and oaks. C. gattii has caused disease in approximately 24 patients residing in Oregon and Washington, most occurring since 2006. Pulmonary disease with or without meningoencephalitis was the most common manifestation. C. gattii is believed to be more virulent clinically than C. neoformans. It is critical to distinguish between the 2 cryptococcal species because C. gattii is less susceptible to fluconazole. Cryptococcus laurentii is occasionally reported as a cause of invasive fungal disease, usually in immunocompromised patients and most recently in the premature neonatal population. C. neoformans exposure is much more common than previously thought. Seroprevalence studies in temperate urban environments have shown that most children older than 2 yr of age and nearly all adults have been exposed to this organism. Despite this high prevalence, clinical disease is unusual in immunocompetent persons and is rare in children. Pigeon breeders and laboratory personnel who work with Cryptococcus are at greatest risk. Cryptococcosis is also rare (<1%) among HIV-infected children but occurs in 5-10% of HIV-infected adults, with higher rates of infection reported from developing countries. Pediatric cases of cryptococcosis are evenly divided among immunocompetent and immunocompromised persons. Cryptococcosis is the third most common invasive fungal infection after candidiasis and aspergillosis in solid organ transplant patients. Other risk factors for cryptococcal infection include diabetes mellitus, renal failure, cirrhosis, and use of corticosteroids, chemotherapy agents, and monoclonal antibodies such as etanercept, infliximab, and alemtuzumab. Children with primary immunodeficiency diseases are at increased risk for infection; these include those with autoantibodies to granulocyte-macrophage colony-stimulating factor or interferon-γ, CD40 ligand deficiency, and monomAC syndrome (monocytopenia, B and natural killer cell lymphopenia). Interestingly organ transplant recipients who are receiving calcineurin-inhibitor–based immunosuppression are less likely to have cryptococcal central nervous system (CNS) infection and more likely to have disease limited to the lung, because these agents have antifungal activity in vivo.

PATHOGENESIS

In most cases C. neoformans is acquired by inhalation of fungal spores (<5-10 μm), which are engulfed by alveolar macrophages. Local inoculation leads to cutaneous or ophthalmic infection rarely. An additional portal of entry can be seen with organ transplantation of infected tissue. Direct entry through the gastrointestinal tract can also occur. After entry into the body, either latent infection or acute disease is produced. Cell-mediated immunity is the most important host defense for producing granulomatous inflammation and thus containing cryptococcal infection. Patients with compromised cell-mediated immunity have the highest risk for developing cryptococcal disease. In most immunocompetent persons, infection is limited to the lung. When the immune system fails to contain the infection, dissemination follows, with potential involvement of the brain, meninges, skin, eyes, prostate, and skeletal system.

In immunocompetent patients, C. neoformans can produce both a suppurative and granulomatous tissue reaction or a granulomatous reaction alone with varying degrees of necrosis. Healing is characterized by fibrosis usually without calcification. In immunocompromised patients tissue reactions may be minimal or absent, leading to the proliferation of yeast and the development of mucoid cystic lesions. Pulmonary cryptococcosis produces granulomas that are often subpleural in location and contain yeast forms. Cystic cryptococcomas occur in the CNS of 20% of non–HIV-infected patients with disseminated disease and may be found in the absence of overt meningitis. Granulomas and microabscesses containing yeast occur in patients with skin and bone infection.

CLINICAL MANIFESTATIONS

The manifestations of cryptococcal infection reflect the route of inoculation and the immunocompetence of the host. Sites of infection include lung, CNS, blood, skin, bone, and mucous membranes.

Pneumonia

Pneumonia is the most common form of cryptococcosis. Asymptomatic pulmonary infections occur often, especially among pigeon breeders, bird fanciers, and laboratory workers. Asymptomatic carriage can occur in persons with underlying chronic lung disease. Progressive pulmonary disease is symptomatic with fever, cough, pleuritic chest pain, and constitutional symptoms. In a 2006 review of 24 patients with pulmonary cryptococcosis, cough was the most common symptom. Pulmonary disease often precedes disseminated infection in immunocompromised persons. Chest radiographs can demonstrate a poorly localized bronchopneumonia, nodular changes, or lobar consolidations; cavities and pleural effusions are rare. Immunocompromised patients can have alveolar and interstitial infiltrates that can mimic Pneumocystis pneumonia. In adults with HIV infection, cryptococcal pneumonia is usually asymptomatic, although >90% of patients have concomitant CNS infection.

Disseminated Infection

Disseminated infection usually follows primary pulmonary disease, especially among immunocompromised persons. Advanced HIV infection is the most common predisposing factor for disseminated cryptococcosis. Other major predisposing conditions include lymphoproliferative disorders, corticosteroid therapy, primary immunodeficiencies affecting both T- and B-cell lineages, and immunosuppressive therapy for rheumatic disorders, celiac disease, and organ transplantation.

Meningitis

Subacute or chronic meningitis is the most common clinical manifestation of disseminated cryptococcal infection. The clinical presentation is variable and prognostic. Good outcomes are associated with headache as the initial symptom, normal mental status, absence of a predisposing condition, normal cerebrospinal fluid (CSF) opening pressure, normal CSF glucose, negative India ink stain, absence of extraneural infection by culture, and cryptococcal antigen titers in CSF and serum of <1:32. Overt symptoms of meningitis and HIV infection predict a poor outcome. HIV-infected patients typically present with unexplained fevers, headache, and malaise; cryptococcal antigen titers in these patients are often >1:1,024. Computed tomography of the brain identifies cryptococcomas in as many as 30% of patients with disseminated infection, even with no clinical signs of CNS involvement. The mortality rate for cryptococcal meningitis is 15-30%, and most deaths occur within several weeks of diagnosis. The fatality rates are higher among HIV-infected patients, who had relapse rates of >50% before the use of lifelong maintenance highly active antiretroviral therapy (HAART). In adults, relapse rates have decreased to <5% with daily fluconazole therapy. Relapse is unusual in adequately treated immunocompetent persons. Postinfectious sequelae are common and include hydrocephalus, decreased visual acuity, deafness, cranial nerve palsies, seizures, and ataxia.

Sepsis Syndrome

Sepsis syndrome is a rare manifestation of cryptococcosis and occurs almost exclusively among HIV-infected patients. Fever is followed by respiratory distress and multiorgan system disease that is often fatal.
**Cutaneous Infection**

Cutaneous disease most commonly follows disseminated cryptococcosis and rarely local inoculation. Early lesions are erythematous, may be single or multiple, and are variably indurated and tender. Lesions often become ulcerated with central necrosis and raised borders. Cutaneous cryptococcosis in immunocompromised patients can resemble molluscum contagiosum.

**Skeletal Infection**

Skeletal infection occurs in approximately 5% of patients with disseminated infection but rarely in HIV-infected patients. The onset of symptoms is insidious and chronic. Bone involvement is typified by soft tissue swelling and tenderness, and arthritis is characterized by effusion, erythema, and pain on motion. Skeletal disease is unifocal in approximately 75% of cases. The vertebrae are the most common sites of infection, followed by the tibia, ileum, rib, femur, and humerus. Concomitant bone and joint disease results from contiguous spread.

**Ocular Infection**

Chorioretinitis is rare, occurs primarily in adults, and is usually a manifestation of disseminated disease, although direct inoculation of the eye has been described. Eye infection is characterized by the acute loss of visual acuity, eye pain, visual floaters, and photophobia. Examination usually reveals choroiditis with or without retinitis. Retinal and vitreal masses and anterior uveitis are seen less commonly. Eye disease is often a manifestation of disseminated infection and is associated with a mortality rate of >20%. Only 15% of survivors recover full vision.

**Lymph Nodes**

Lymphonodular disease has been reported in 2 children, 1 of whom had an underlying immunodeficiency. Lymphonodular cryptococcosis is characterized by disseminated lymphadenopathy including thoracic and abdominal nodes, subcutaneous lesions, liver granulomas, and concomitant pulmonary disease.

**DIAGNOSIS**

Recovery of the fungus by culture or demonstration of the fungus in histologic sections of infected tissue is definitive. A latex agglutination test, which detects cryptococcal antigen in serum and CSF, is the most useful diagnostic test. Titers of >1:4 in bodily fluid strongly suggest infection, and titers of >1:1024 reflect high burden of yeast, poor host immune response, and greater likelihood of therapeutic failure. India ink preparations of CSF are useful prognostically but are less sensitive than culture and antigen detection. Skin test antigens are poorly characterized, and the sensitivity and specificity of this test are unknown. Serum cryptococcal antibody tests have poor sensitivity and specificity and are generally not helpful in diagnosing cryptococcosis. Cryptococci can grow easily on standard fungal and bacterial culture media. Colonies can be seen within 48-72 hr when grown aerobically at standard temperatures. Polymerase chain reaction tests are in development.

**TREATMENT**

The choice of treatment depends on the sites of involvement and the host immune status. The immunocompetent patient with asymptomatic or mild disease limited to the lungs may be closely observed without therapy or, alternatively, treated with oral fluconazole (pediatric dose 6-12 mg/kg/day and adult dose 200-400 mg/day) or itraconazole (pediatric dose 5-10 mg/kg/day divided every 12 hr and adult dose 200-400 mg/day) for 3-12 mo, with the duration dependent on clinical response.

Patients with cryptococcemia or severe symptoms and non–HIV-immunocompromised hosts with lung disease with cryptococcal antigen titers of >1:8 or with CNS, urinary tract, or cutaneous disease should be treated in a staged approach, because these factors suggest disseminated disease. In general, these patients receive induction therapy with amphotericin B (0.7-1 mg/kg/day) plus flucytosine (100-150 mg/kg/day divided every 6 hr assuming normal kidney function) for a minimum of 2 wk, keeping serum flucytosine concentrations between 40 and 60 µg/mL. Depending on the clinical response, induction therapy may be continued as long as 6-10 wk.

Induction is followed by a consolidation phase with oral fluconazole or itraconazole for 6-12 mo. Itraconazole does not penetrate well into CSF, so consolidation therapy for CNS disease should be accomplished with fluconazole. Lifelong maintenance therapy may be required for children who remain immunocompromised. Lipid-complex amphotericin B (3-6 mg/kg/day) is recommended for patients intolerant of the deoxycholate amphotericin, although experience with this agent in children with cryptococcosis is limited. The current echinocandins do not have clinical activity against cryptococcal infections. Effectiveness of anticytotoxic therapy is monitored by serial cryptococcal antigen testing. Serum or CSF values of ≥1:8 predict relapse. Ventriculoperitoneal shunts may be required for patients with hydrocephalus, and aggressive medical management of increased intracranial pressure might also be required.

Because of the high rate of relapse, pulmonary, CNS, or disseminated cryptococcal infections in HIV-infected patients require induction, consolidation, and maintenance therapy. Patients with pulmonary disease most often require lifelong therapy with fluconazole or itraconazole. For those with CNS disease, the most commonly used regimen is amphotericin B (0.7 mg/kg/day) and flucytosine (100 mg/kg/day) for a minimum of 2 wk and as long as 6-10 wk (induction), followed by fluconazole for a minimum of 8-10 wk (consolidation). Fluconazole should be continued for life (maintenance therapy) after the completion of consolidation therapy. Itraconazole should be used only in cases where the patient is intolerant or has failed fluconazole therapy due to the higher relapse rates with itraconazole. Cessation of maintenance therapy in children whose HIV infection is well controlled with HAART has not been well studied to date.

Cutaneous infections are usually treated medically, although surgical biopsy may be required for diagnosis. Skeletal infections generally require surgical debridement in addition to systemic antifungal therapy. Chorioretinitis also requires systemic antifungal therapy with amphotericin B and either fluconazole or flucytosine, both of which achieve high drug concentrations in the vitreous.

**PREVENTION**

Persons at high risk should avoid exposures such as bird droppings. Effective HAART for persons with HIV infection reduces the risk of cryptococcal disease. Fluconazole prophylaxis is effective for preventing cryptococcosis in patients with AIDS and CD4 lymphocyte counts <100/µL. A cryptococcal glucuronoxylomannan–tetanus toxoid conjugate vaccine has been developed that elicits protective antibodies in mice but awaits clinical trials in children. Passive immunization with protective monoclonal antibodies has yet to be studied in children.

*Bibliography is available at Expert Consult.*
Bibliography


Members of the genus *Malassezia* include the causative agents of *tinea versicolor* (also pityriasis versicolor) (Fig. 236-1) and are associated with other dermatologic conditions and with fungemia in patients with indwelling catheters. *Malassezia* species are commensal lipophilic yeasts with a predilection for the sebum-rich areas of the skin. They are considered a part of the normal skin flora, with presence established by 3-6 mo of age.

The history of *Malassezia* nomenclature is complex and can be confusing. Because the yeast forms may be oval or round, these organisms were formally designated *Pityrosporum ovale* and *Pityrosporum*...
causes of fungal sepsis, it is unusual for catheter-related *Malassezia* fungemia to be associated with secondary focal infection. *Malassezia* species do not grow readily on standard fungal media, and successful culture requires overlaying the agar with olive oil. Recovery of *Malassezia* from blood culture is optimized by supplementing the medium with olive oil or palmitic acid.

Fungemia caused by *M. furfur* or other species can be successfully treated in most cases by immediately discontinuing the lipid infusion and removing the involved catheter. For persistent or invasive infections, amphotericin B (deoxycholate or lipid-complex formulations), fluconazole, and itraconazole are effective. Flucytosine has no activity against *Malassezia*.

Bibliography is available at Expert Consult.

orbiculare*. Newer technologies have allowed an improved classification system, with 13 recognized species. Only *Malassezia pachydermatis*, a zoophilic yeast that causes dermatitis in dogs, is not lipophilic.

Transformation of the yeast form to a hyphal form facilitates invasive disease. The clusters of thick-walled blastospores together with the hyphae produce the characteristic *spaghetti-and-meatballs* appearance of *Malassezia* species.

*Malassezia globosa*, *Malassezia sympodialis*, *Malassezia restricta*, and *Malassezia furfur* are the major causes of tinea versicolor (see Chapter 666). *Malassezia* organisms are also increasingly associated with other dermatologic conditions. *M. sympodialis* and *M. globosa* are implicated in neonatal acne, and *M. globosa* and *M. restricta* are most closely associated with seborrheic dermatitis and dandruff. *Malassezia* are also causally associated with scalp psoriasis, *Pityrosporum* folliculitis, and head and neck atopic dermatitis. *Malassezia* may be isolated from sebum-rich areas of asymptomatic persons, emphasizing that demonstration of the fungus does not equate with infection.

The traditional primary therapy for *tinea versicolor* is topical selenium sulfide 2.5% applied daily for at least 10 min for a week, followed by weekly to monthly applications for several months to prevent relapse. Additional topical agents that have efficacy include terbinafine, clotrimazole, and topical azoles. *Malassezia*-associated skin diseases limited to the head and neck can be managed with either 1% ciclopirox, ketoconazole, or zinc pyrithione shampoos.

Oral therapy for *tinea versicolor* with fluconazole, itraconazole, or ketoconazole is easier to administer but is more expensive, has higher side effect risks, and may be less effective than topical therapy. Various dosing regimens have been used with success, including ketoconazole 200 mg daily for 10 days, fluconazole 300 mg weekly for 2-4 wk, and itraconazole 200 mg daily for 3-7 days or 100 mg daily for 2 wk. Single-dose therapy with 400 mg of ketoconazole has also been used but with lower success rates. Regardless of the regimen chosen, patients should be encouraged to exercise while taking these medications so as to increase the skin concentration of the drug through sweating.

Despite successful treatment, repigmentation might not occur for several months. Relapses are common and can require repeat or alternative therapies.

*M. furfur* is the species most commonly causing *fungemia*, and *M. pachydermatis* has been implicated in several outbreaks in neonatal intensive care units. The use of lipid emulsions containing medium-chain triglycerides inhibits the growth of *Malassezia* and can prevent infection. Infection is most common in premature infants, although immunocompromised patients, especially those with malignancies, can also be infected. Symptoms of catheter-associated fungemia are indistinguishable from other causes of catheter-associated infections (see Chapter 179) but should be suspected in patients, especially neonates, receiving intravenous lipid infusions. Compared with other
Bibliography
The aspergilli are ubiquitous fungi whose normal ecologic niche is that of a soil saprophyte that recycles carbon and nitrogen. The genus *Aspergillus* contains approximately 185 species, but most human disease is caused by *Aspergillus fumigatus*, *A. flavus*, *A. niger*, *A. terreus*, and *A. nidulans*. Invasive disease is most commonly caused by *A. fumigatus*. *Aspergillus* reproduces asexually via production of spores (conidia). Most cases of *Aspergillus* disease (*aspergillosis*) are a result of inhalation of airborne conidia that subsequently germinate into fungal hyphae and invade host tissue. People are likely exposed to conidia on a daily basis. When inhaled by an immunocompetent person, conidia are rarely deleterious, presumably because they are efficiently cleared by phagocytic cells. Macrophage- and neutrophil-mediated host defenses are required for resistance to invasive disease.

*Aspergillus* is a relatively unusual pathogen in that it can create very different disease states depending on the host characteristics, including allergic (hypersensitivity), saprophytic (noninvasive), chronic, or invasive disease. Immunodeficient hosts are at risk for invasive disease, whereas immunocompetent hosts tend to develop allergic disease. Disease manifestations include primary allergic reactions; colonization of the lungs or sinuses; localized infection of the lung or skin; chronic infection; invasive pulmonary disease; or widely disseminated disease of the lungs, brain, skin, eye, bone, heart, and other organs. Clinically, these syndromes often manifest with mild, nonspecific, and late-onset symptoms, particularly in the immunosuppressed host, complicating accurate diagnosis and timely treatment. Immunocompromised patients, at risk for invasive disease, include those treated for malignancies with myelosuppressing chemotherapy but may also include those with primary immunodeficiency syndromes. Genetic disorders of immune regulation in the latter group of patients include those with chronic granulomatous disease, STAT3 deficiency (autosomal dominant hyperimmunoglobulin E syndrome), severe congenital neutropenia, monoMAC syndrome (monocytopenia, B and natural killer cell lymphopenia), and leukocyte adhesion deficiency type 1.

### 237.1 Allergic Disease (Hypersensitivity Syndromes)

**ASTHMA**

Attacks of atopic asthma can be triggered by inhalation of *Aspergillus* conidia, producing allergic responses and subsequent bronchospasm.
Exposure to fungi, especially *Aspergillus*, needs to be considered as a trigger in a patient with an asthma flare, especially in those patients with severe asthma.

**EXTRINSIC ALVEOLAR ALVEOLITIS**

Extrinsic alveolar alveolitis is a hypersensitivity pneumonitis that occurs from repetitive inhalational exposure to inciting materials, including *Aspergillus* conidia. Symptoms typically occur shortly after exposure and include fever, cough, and dyspnea. Neither blood nor sputum eosinophilia is present. Chronic exposure to the triggering material can lead to pulmonary fibrosis.

**ALLERGIC BRONCHOPULMONARY ASPERGILLOSIS**

Allergic bronchopulmonary aspergillosis (ABPA) is a hypersensitivity disease resulting from immunologic sensitization to *Aspergillus* antigens. It is primarily seen in patients with asthma or cystic fibrosis. Inhalation of conidia produces noninvasive colonization of the bronchial airways, resulting in persistent inflammation and development of hypersensitivity inflammatory responses. Disease manifestations are a result of abnormal immunologic responses to *A. fumigatus* antigens and include wheezing, pulmonary infiltrates, bronchiectasis, and even fibrosis.

There are 7 primary diagnostic criteria for ABPA: episodic bronchial obstruction, peripheral eosinophils, immediate cutaneous reactivity to *Aspergillus* antigen, precipitating antibodies to *Aspergillus* antigen, elevated immunoglobulin (Ig) E, pulmonary infiltrates, and central bronchiectasis. Secondary diagnostic criteria include repeated detection of *Aspergillus* from sputum by identification of morphologically consistent fungal elements or direct culture, coughing brown plugs or specks, elevated *Aspergillus* antigen-specific IgE antibodies, and late skin reaction to *Aspergillus* antigen. Radiologically, bronchial wall thickening, pulmonary infiltrates, and central bronchiectasis can be seen.

Treatment depends on relieving inflammation via an extended course of systemic corticosteroids. Addition of oral antifungal agents, such as itraconazole or voriconazole, is used to decrease the fungal burden and diminish the inciting stimulus for inflammation. Because disease activity is correlated with serum IgE levels, these levels are used as 1 marker to define duration of therapy. An area of research interest is the utility of anti-IgE antibody therapy in the management of ABPA.

**ALLERGIC ASPERGILLUS SINUSITIS**

Allergic *Aspergillus* sinusitis is thought to be similar in etiology to ABPA. It has been primarily described in young adult patients with asthma and may or may not be seen in combination with ABPA. Patients often present with symptoms of chronic sinusitis or recurrent acute sinusitis, such as congestion, headaches, and rhinitis, and are found to have nasal polyps and opacification of multiple sinuses on imaging. Laboratory findings can include elevated IgE levels, precipitating antibodies to *Aspergillus* antigen, and immediate cutaneous reactivity to *Aspergillus* antigen. Sinus tissue specimens might contain eosinophils, Charcot-Leyden crystals, and fungal elements consistent with *Aspergillus* species. Surgical drainage is an important aspect of treatment, often accompanied by courses of either systemic or inhaled steroids. Use of an antifungal agent may also be considered.

Bibliography is available at Expert Consult.

**237.2 Saprophytic (Noninvasive) Syndromes**

*William J. Steinbach*

**PULMONARY ASPERGILLOMA**

Aspergillomas are masses of fungal hyphae, cellular debris, and inflammatory cells that proliferate without vascular invasion, generally in the setting of preexisting cavitary lesions or ectatic bronchi. These cavitary lesions can occur as a result of infections such as tuberculosis, histoplasmosis, or resolved abscesses, or secondary to congenital or acquired defects such as pulmonary cysts or bullous emphysema. Patients may be asymptomatic, with diagnosis made through imaging for other reasons, or they might present with hemoptysis, cough, or fever. On imaging, there may be thickening of the walls of a cavity initially, or later, a solid round mass separated from the cavity wall, as the fungal ball develops. Detection of *Aspergillus* antibody in the serum suggests this diagnosis. Treatment is indicated for control of complications, such as hemoptysis. Surgical resection is the definitive treatment but has been associated with significant risks. Systemic antifungal treatment with azole-class agents may be indicated in certain patients.

**CHRONIC PULMONARY ASPERGILLOSIS**

Chronic aspergillosis is a condition in patients with normal immune systems or mild degrees of immunosuppression, including intermittent corticosteroids. Three categories have been proposed to describe different manifestations of chronic aspergillosis. The first is chronic cavitary pulmonary aspergillosis, which is similar to aspergilloma, except that multiple cavities form and expand with occupying fungal balls. The second is chronic fibrosing pulmonary aspergillosis, where the multiple individual lesions progress to significant pulmonary fibrosis. The third is chronic necrotizing pulmonary aspergillosis, also known as *subacute invasive* or *semiinvasive pulmonary aspergillosis*, a slowly progressive subset found in patients with mild to moderate immune impairment.

Management of chronic cavitary pulmonary aspergillosis can sometimes be via surgical resection, although long-term antifungal therapy is indicated. Management of chronic necrotizing pulmonary aspergillosis is similar to that of invasive pulmonary aspergillosis; however, the disease is more indolent, and thus there is a greater emphasis on oral therapy. Direct instillation of antifungals into the lesion cavity has been employed with some success.

**SINUSITIS**

Sinus aspergillosis typically manifests with chronic sinus symptoms that are refractory to antibacterial treatment. Imaging can demonstrate mucosal thickening in the case of *Aspergillus* sinusitis or a single mass within the maxillary or ethmoid sinus in the case of sinus aspergilloma. If untreated, sinusitis can progress and extend into the ethmoid sinuses and orbits. Therapy of sinusitis depends on surgical debridement and drainage, including surgical removal of the fungal mass in cases of sinus aspergilloma.

**OTOMYCOSIS**

*Aspergillus* can colonize the external auditory canal, with possible extension to the middle ear and mastoid air spaces if the tympanic membrane is disrupted by concurrent bacterial infection. Symptoms include pain, itching, decreased unilateral hearing, or otorrhea. Oto mycosis is more often seen in patients with impaired mucosal immunity, such as patients with hypogammaglobulinemia, diabetes mellitus, chronic eczema, or HIV and those using chronic steroids. Treatments have not been well studied, but topical treatment with acetic or boric acid instillations or azole creams as well as oral azoles, such as voriconazole, itraconazole, and posaconazole, have been described.

Bibliography is available at Expert Consult.

**237.3 Invasive Disease**

*William J. Steinbach*

Invasive aspergillosis (IA) occurs after conidia enter the body, escape immunologic control mechanisms, and germinate into fungal hyphae that subsequently invade tissue parenchyma and vasculature. The invasion of the vasculature can result in thrombosis and localized necrosis and facilitates hematogenous dissemination. The incidence of IA increased over the last 2 decades, likely as a result of more use of
Bibliography
Bibliography

severely immunosuppressive therapies for a widening array of underlying diseases and better management of other infections found in the at-risk populations. The most common site of primary infection is the lung, but primary infection is also seen in the sinuses and skin, and rarely elsewhere. Secondary infection can be seen after hematogenous spread, often to the skin, central nervous system (CNS), eye, bone, and heart.

IA is primarily a disease of immunocompromised hosts, and common risk factors include cancer or chemotherapy-induced neutropenia, particularly if severe and/or prolonged; hematopoietic stem cell transplantation, especially during the initial preengraftment phase or if complicated by graft-versus-host disease; neutrophil or macrophage dysfunction such as occurs in severe combined immunodeficiency or chronic granulomatous disease (CGD); prolonged high-dose steroid use; solid organ transplantation; and, rarely, HIV. Studies in the pediatric age group have identified similar risk factors for IA, but a well-defined incidence of IA among pediatric patients has not been determined to date.

**INVASIVE PULMONARY ASPERGILLOSIS**

Invasive pulmonary aspergillosis is the most common form of aspergillosis. It plays a significant role in morbidity and mortality in the patient populations mentioned at increased risk for IA. Presenting symptoms can include fever despite initiation of empirical broad-spectrum antibacterial therapy, cough, chest pain, hemoptysis, and pulmonary infiltrates. Patients on high-dose steroids are less likely to present with fever. Symptoms in these immunocompromised patients can be very vague, and thus maintaining a high index of suspicion when confronted with a high-risk patient is essential.

**Diagnosis**

Imaging can be helpful, although no finding is pathognomonic for invasive pulmonary aspergillosis. Characteristically, multiple, ill-defined nodules can be seen, though lobar or diffuse consolidation is not uncommon and normal chest radiographs do not rule out disease. Classic radiologic signs on CT during neutropenia include the halo sign, when angioinvasion produces a hemorrhagic nodule surrounded by ischemia. Early on there is a rim of ground-glass opacification surrounding a nodule. Over time, these lesions evolve into cavitary lesions or lesions with an air crescent when the lung necroses around the fungal mass, often seen during recovery from neutropenia. Unfortunately, these findings are not specific to invasive pulmonary aspergillosis and can also be seen in other pulmonary fungal infections, as well as pulmonary hemorrhage and organizing pneumonia. In addition, several reviews of imaging results of pediatric aspergillosis cases suggest that cavitation and air crescent formation are less common among these patients than among adult patients. Computed tomographic pulmonary angiography demonstrates interruption or invasion of arterial vessels and may enhance the diagnosis of invasive pulmonary aspergillosis (Fig. 237-1). On MRI, the typical finding for

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**Figure 237-1** A and B, Representative high-resolution computed tomographic findings for patients with positive CT pulmonary angiographic (CTPA) findings and proven invasive mold disease. C, False-positive CTPA findings for a patient with Staphylococcus aureus pneumonia with septic emboli. D, Negative CTPA findings for a patient with bacterial pneumonia. Arrows indicate areas of vessel interruption (A-C) or lack of vessel interruption (D). (From Stanzani M, Battista G, Sassi C, et al: Computed tomographic pulmonary angiography for diagnosis of invasive mold diseases in patients with hematological malignancies. Clin Infect Dis 54:610–616, 2012, Fig. 1.)
pulmonary disease is the **target sign**, in which a nodule has a central signal that is lower than that of the rim-enhancing periphery.

Diagnosis of IA can be complicated for a number of reasons. Conclusive diagnosis requires culture of *Aspergillus* from a normally sterile site and histologic identification of tissue invasion by fungal hyphae consistent with *Aspergillus* morphology. However, obtaining tissue specimens is often impractical in critically ill, often thrombocytopenic, patients. In addition, depending on the specimen type, a positive result from culture can represent colonization rather than infection; however, this should be interpreted conservatively in high-risk patients. Isolation of *Aspergillus* from blood cultures is uncommon, likely because fungemia is low-level and intermittent.

Serology can be useful in the diagnosis of allergic *Aspergillus* syndromes as well as aspergillosis but is of low yield for invasive disease, likely because of deficient immune responses in the high-risk immunocompromised population. Bronchoalveolar lavage can be useful, but negative culture results cannot be used to rule out disease, owing to inadequate sensitivity. Addition of molecular biologic assays such as antigen detection and polymerase chain reaction can improve the diagnostic yield of bronchoalveolar lavage for aspergillosis. An enzyme-linked immunosorbent assay–based assay for galactomannan, one of the components of the *Aspergillus* cell wall, is useful for the diagnosis of IA in serum, bronchoalveolar lavage fluid, and cerebrospinal fluid. This molecular test is best used in serial monitoring for development of infection and is the most sensitive in detecting disease in cancer patients or hematopoietic stem cell transplant recipients, with less utility in solid organ transplant recipients. Earlier reports of increased false-positive reactions in children vs adults have been refuted, and the galactomannan assay is effective in diagnosing IA in children. This test does possess high rates of false negativity in patients with congenital immunodeficiency (e.g., CGD) and invasive *Aspergillus* infections. Another molecular assay, the β-glucan assay, is a fungal-nonspecific assay that detects the major component of the fungal cell wall and has been used to diagnose IA. Unlike the galactomannan assay, which is specific for *Aspergillus*, despite some cross reactivity with other fungi, the β-glucan assay will not discriminate which fungal infection is infecting the patient. Polymerase chain reaction–based assays are in development for the diagnosis of aspergillosis but are still being optimized and are not yet commercially available.

**Treatment**

Successful treatment of IA hinges on the ability to reconstitute normal immune function and use of effective antifungal agents until immune recovery can be achieved. Therefore, lowering overall immunosuppression, specifically via cessation of corticosteroid use, is vital to improve the ultimate outcome. In 2008, new treatment guidelines for *Aspergillus* infections were published by the Infectious Diseases Society of America, marking a major shift in management recommendations. In the past, first-line therapy was amphotericin B, notable for low response rates and significant infusion reactions and drug toxicity. Liposomal formulations of amphotericin B exist, which are associated with decreased toxicity and may still have a role as first-line therapy for invasive infection in certain patients.

Primary therapy is now the azole-class antifungal voriconazole, based on multiple studies showing both improved response rates and survival in patients receiving voriconazole when compared to amphotericin B. In addition, voriconazole is better tolerated than amphotericin B and can be given orally as well as intravenously. Azoles are metabolized through the cytochrome P450 system, and thus medication interactions can be a significant complication, specifically some contraindications with chemotherapeutic agents. Other triazole antifungals are also available, including posaconazole, which is approved for antifungal prophylaxis and may be an alternative agent for first-line treatment of IA. Although the dosing of itraconazole and voriconazole are established for pediatric patients, the pharmacokinetic studies for posaconazole are not yet complete. Importantly, the dose of voriconazole used in children is higher than that used in adults (see Chapter 233).

The echinocandin class of antifungals may also play a role in treatment of IA, but to date, these agents are generally employed as second-line medications, particularly for salvage therapy. Combination antifungal therapy has revealed disparate results in anecdotal studies, and currently there are no firm recommendations for combination antifungal therapy. However, it is possible that combination therapy may be beneficial to certain specific patient groups. Unfortunately, even with newer antifungals, complete or partial response rates for treatment of IA are only approximately 50%.

To augment antifungal therapies, patients have been treated with growth factors to increase neutrophil counts, granulocyte transfusions, interferon-γ, and surgery.

**Special Populations**

Patients with CGD represent a pediatric population at particular risk for pulmonary aspergillosis. Invasive pulmonary aspergillosis can be the first serious infection identified in these patients, and the lifetime risk of development is estimated to be 33%. Unlike classical IA in cancer patients, the onset of symptoms is often gradual, with slow development of fever, fatigue, pneumonia, and elevated sedimentation rate. The neutrophils of patients with CGD surround the collections of fungal elements but cannot kill them, thereby permitting local invasion with extension of disease to the pleura, ribs, and vertebrae, although angioinvasion is not seen. Imaging in these patients is much less likely to reveal the halo sign, infarcts, or cavitary lesions and instead generally shows areas of tissue destruction due to the ongoing inflammatory processes.

**CUTANEOUS ASPERGILLOSIS**

Cutaneous aspergillosis can occur as a primary disease or as a consequence of hematogenous dissemination or spread from underlying structures. Primary cutaneous disease classically occurs at sites of skin disruption, such as intravenous access device locations, adhesive dressings, or sites of injury or surgery. Premature infants are particularly at risk, given their immature skin and need for multiple access devices. Cutaneous disease in transplant recipients tends to reflect hematogenous distribution from a primary site of infection, often the lungs. Lesions are erythematous indurated papules that progress to painful, ulcerated, necrotic lesions. Treatment depends on the combination of surgical debridement and antifungal therapy, with systemic voriconazole recommended as primary therapy.

**INVASIVE SINONASAL DISEASE**

Invasive *Aspergillus* sinusitis represents a difficult diagnosis because the clinical presentation tends to be highly variable. Patients can present with congestion, rhinorrhea, epistaxis, headache, facial pain or swelling, orbital swelling, fever, or abnormal appearance of the nasal turbinates. Because noninvasive imaging can be normal, diagnosis rests on direct visualization via endoscopy and biopsy. Sinus mucosa may be pale, discolored, granulating, or necrotic depending on the stage and extent of disease. The infection can invade adjacent structures, including the eye and brain. This syndrome is difficult to distinguish clinically from other types of invasive fungal disease of the sinuses such as mucormycosis, rendering obtaining specimens for culture and histology extremely important. If the diagnosis is confirmed, treatment should be with voriconazole, similar to invasive pulmonary disease. Because voriconazole is not active against mucormycosis, amphotericin B formulations should be considered in invasive fungal sinusitis pending definitive identification.

**CENTRAL NERVOUS SYSTEM**

The primary site of *Aspergillus* infection tends to be the lungs, but as the hyphae invade the vasculature, fungal elements can dislodge and travel through the bloodstream, permitting establishment of secondary infection sites. One site commonly involved in disseminated disease is the CNS. Cerebral aspergillosis can also arise secondary to local extension of sinus disease. The presentation of cerebral aspergillosis is highly variable but can include changes in mental status, seizures, paralysis,
coma, and ophthalmoplegia. As the hyphae invade the CNS vasculature, hemorrhagic infarcts develop that convert to abscesses. Biopsy is required for definitive diagnosis, but patients are often too ill to tolerate surgery. Imaging can be helpful for diagnosis, and MRI is preferred. Lesions tend to be multiple, located in the basal ganglia, have intermediate intensity with no enhancement, and have no mass effect. CT shows hypodense, well-demarcated lesions, sometimes with ring enhancement and edema. Diagnosis often depends on characteristic imaging findings in a patient with known aspergillosis at other sites. Galactomannan assay testing of cerebrospinal fluid has been studied and may become a future methodology to confirm the diagnosis. In general, the prognosis for CNS aspergillosis is extremely poor, likely owing to the late onset at presentation. Reversal of immunosuppression is extremely important. Surgical resection of lesions may be useful. Voriconazole, usually at high doses, is the best therapy, and itraconazole, posaconazole, and liposomal formulations of amphotericin B are alternative options.

**EYE**

Fungal endophthalmitis and keratitis may be seen in patients with disseminated *Aspergillus* infection. Pain, photophobia, and decreased visual acuity may be present, though many patients are asymptomatic. Emergent ophthalmologic evaluation is important when these entities are suspected. Endophthalmitis is treated with intravitreal injection of either amphotericin B or voriconazole along with surgical intervention and systemic antifungal therapy with voriconazole. Keratitis requires topical and systemic antifungal therapy.

**BONE**

*Aspergillus* osteomyelitis can occur, most commonly in the vertebrae. Rib involvement occurs owing to extension of disease in patients with CGD and is most often caused by *A. nidulans*. Treatment depends on the combination of surgical débridement and systemic antifungals. Arthritis can develop owing to hematogenous dissemination or local extension, and treatment depends on joint drainage combined with antifungal therapy. Amphotericin B has been the most commonly employed agent in the past, although voriconazole is the preferred first-line therapy now.

**HEART**

Cardiac infection can occur as a result of surgical contamination, secondary to disseminated infection, or as a result of direct extension from a contiguous focus of infection and includes endocarditis, myocarditis, and pericarditis. Treatment requires surgical intervention in the case of endocarditis and pericarditis, along with systemic antifungals, sometimes lifelong because of the possibility of recurrent infection.

**EMPIRICAL ANTIFUNGAL THERAPY**

Because the diagnosis of invasive *Aspergillus* infections is often complicated and delayed, empirical initiation of antifungal therapy is often considered in high-risk patients. At present, antifungal coverage with amphotericin B (conventional or liposomal), voriconazole, itraconazole, or the echinocandin caspofungin or micafungin should be considered in patients at risk for prolonged neutropenia or with findings suggesting invasive fungal infections. At this time, our ability to diagnose and treat infections caused by *Aspergillus* remains suboptimal. Additional study of antigen detection assays based on galactomannan and other *Aspergillus* cell wall components, as well as standardization of polymerase chain reaction–based assays, will facilitate diagnosis. The optimal treatment remains another challenging question, because current therapeutic regimens tend to produce complete or partial response only approximately half of the time. Novel antifungals currently under development offer a future with hopefully improved survival, but immune reconstitution remains of paramount importance.

Bibliography is available at Expert Consult.
Bibliography


ETIOLOGY
Histoplasmosis is caused by *Histoplasma capsulatum*, a dimorphic fungus found in the environment as a saprophyte in the mycelial (mold) form and in tissues in the parasitic form as yeast.

EPIDEMIOLOGY
The saprophytic form is found in soil throughout the midwestern United States, primarily along the Ohio and Mississippi rivers. Sporadic cases of human and animal histoplasmosis have been reported from 31 of the 48 contiguous states. In parts of Kentucky and Tennessee, almost 90% of the population older than 20 yr of age have positive skin test results for histoplasmin. *Histoplasma* is endemic to parts of the Caribbean islands, Central and South America, certain areas of Southeast Asia, and the Mediterranean. *H. capsulatum* thrives in soil rich in nitrates such as areas that are heavily contaminated with bird or bat droppings or decayed wood. Fungal spores are often carried on the wings of birds. Focal outbreaks of histoplasmosis have been reported after aerosolization of microconidia resulting from construction in areas previously occupied by starling roosts or chicken coops or by chopping decayed wood or burning bamboo exposed to a blackbird roost. Unlike birds, bats are actively infected with *Histoplasma*. Focal outbreaks of histoplasmosis have also been reported after intense exposure to bat guano in caves and along bridges frequented by bats. Person-to-person transmission does not occur.

PATHOGENESIS
Inhalation of microconidia (fungal spores) is the initial stage of human infection. The conidia reach the alveoli, germinate, and proliferate as yeast. Alternatively, spores can remain as mold with the potential for activation. Most infections are asymptomatic or self-limited. When disseminated disease occurs, any organ system can be involved. The initial infection is a bronchopneumonia. As the initial pulmonary lesion ages, giant cells form, followed by formation of caseating or noncaseating granulomas and central necrosis. Granulomas contain viable yeast, and disease can relapse. At the time of spore germination, yeast cells are phagocytosed by alveolar macrophages, where they replicate and gain access to the reticuloendothelial system via the pulmonary lymphatic system and hilar lymph nodes. Dissemination with splenic involvement typically follows the primary pulmonary infection. In normal hosts, specific cell-mediated immunity follows in approximately 2 wk, enabling sensitized T cells to activate macrophages and kill the organism. The initial pulmonary lesion resolves within 2-4 mo but may undergo calcification resembling the Ghon complex of tuberculosis. Alternatively, “buckshot” calcifications involving the lung and spleen may be seen. Unlike tuberculosis, reinfection with *H. capsulatum* occurs and can lead to exaggerated host responses in some cases.

Children with certain primary congenital immune defects are at increased risk of histoplasmosis; these include interferon-γR1 deficiency, interleukin-12Rβ1 deficiency, STAT1 gain-of-function mutations, idiopathic CD4 lymphopenia, DOCK8 deficiency, X-linked CD40L deficiency, and monoMAC syndrome (monocytopenia, B-cell and natural killer cell lymphoma).
CLINICAL MANIFESTATIONS

There are 3 forms of human histoplasmosis: acute pulmonary infection, chronic pulmonary histoplasmosis, and progressive disseminated histoplasmosis.

Acute pulmonary histoplasmosis follows initial or recurrent respiratory exposure to microconidia. The majority of patients are asymptomatic. Symptomatic disease occurs more often in young children; in older patients, symptoms follow exposure to large inocula in closed spaces (e.g., chicken coops or caves) or prolonged exposure (e.g., camping on contaminated soil, chopping decayed wood). The median incubation time is 14 days. The prodrôme is not specific and usually consists of flu-like symptoms including headache, fever, chest pain, cough, and myalgias. Hepatosplenomegaly occurs more often in infants and young children. Symptomatic infections may be associated with significant respiratory distress and hypoxia and can require intubation, ventilation, and steroid therapy. Acute pulmonary disease can also manifest with a prolonged illness (10 days to 3 wk) consisting of weight loss, dyspnea, high fever, asthenia, and fatigue. In 10% of patients, infection is a sarcoid-like disease with arthritis or arthralgia, erythema nodosum, keratoconjunctivitis, iridocyclitis, and pericarditis. Pericarditis, with effusions both pericardial and pleural, is a self-limited benign condition that develops as a result of an inflammatory reaction to adjacent mediastinal disease. The effusions are exudative, and the organism is rarely culturable from fluid. Most children with acute pulmonary disease have normal chest radiographs. Patients with symptomatic disease typically have a patchy bronchopneumonia; hilar lymphadenopathy is variably present (Fig. 238-1). In young children, the pneumonia can coalesce. Focal or buckshot calcifications are convalent findings in patients with acute pulmonary infection.

Exaggerated host responses to fungal antigens within the lung parenchyma or hilar lymph nodes produce thoracic complications of acute pulmonary histoplasmosis. Histoplasmomas are of parenchymal origin and are usually asymptomatic. These fibroma-like lesions are often concentrically calcified and single. Rarely, these lesions produce broncholithiasis associated with “stone spitting,” wheezing, and hemoptysis. In endemic regions, these lesions can mimic parenchymal tumors and are occasionally diagnosed at lung biopsy. Mediastinal granulomas form when reactive hilar lymph nodes coalesce and mat together. Although these lesions are usually asymptomatic, huge granulomas can compress the mediastinal structures, producing symptoms of esophageal, bronchial, or vena caval obstruction. Local extension and necrosis can produce pericarditis or pleural effusions. Mediastinal fibrosis is a rare complication of mediastinal granulomas and represents an uncontrolled fibrotic reaction arising from the hilar nodes. Structures within the mediastinum become encased within a fibrotic mass, producing obstructive symptomatology. Superior vena cava syndrome, pulmonary venous obstruction with a mitral stenosis–like syndrome, and pulmonary artery obstruction with congestive heart failure have been described. Dysphagia accompanies esophageal entrapment, and a syndrome of cough, wheeze, hemoptysis, and dyspnea accompanies bronchial obstruction.

Chronic pulmonary histoplasmosis is an opportunistic infection in adult patients with centrilobular emphysema. This entity is rare in children.

Progressive disseminated histoplasmosis accounts for 10% of histoplasmosis cases and affects infants and immunocompromised patients. Disseminated disease of childhood occurs almost exclusively in children younger than 2 yr of age because of a relatively immature cellular immune system and follows primary pulmonary infection. The mortality of progressive disseminated histoplasmosis without therapy is 100%. Fever is the most common finding and can persist for weeks to months before the condition is diagnosed. The majority of patients have hepatosplenomegaly, lymphadenopathy, anemia, and thrombocytopenia. Pneumonia and pancytopenia are variably present. Some patients develop mucous membrane ulcerations and skin findings such as nodules, ulcers, or molluscum-like papules. Half of the infected infants have transient T-cell deficiencies, and many experience transient hypergammaglobulinemia. Elevated acute-phase reactants and hypercalcemia are typically seen but are not specific for disseminated histoplasmosis.

Although chest radiographs are normal in more than half of these children, the yeast can often be identified on bone marrow examination.

Children who are immunosuppressed (cancer patients, organ transplant recipients, patients with HIV infection) are at increased risk for disseminated histoplasmosis. In children who are not infected with HIV, disseminated disease manifests with unexplained fevers, weight loss, lymphadenopathy, and interstitial pulmonary disease. Extrapulmonary infection is a characteristic of disseminated disease and can include destructive bony lesions, oropharyngeal ulcers, Addison disease, menigitis, multifocal chorioretinitis, cutaneous infection, and endocarditis. Elevated liver function test results and high serum concentrations of angiotensin-converting enzyme may be observed.

Disseminated histoplasmosis in an HIV-infected patient is an AIDS-defining illness. Disseminated disease is often preceded or followed by another opportunistic infection in this patient population. HIV-infected patients at greatest risk for acquiring disseminated histoplasmosis are those with a history of exposure to avian excreta or bat guano, no prior history of antiretroviral therapy, or no history of previous antifungal prophylaxis. Fever and weight loss occur in most patients. In the majority of patients, pulmonary disease develops; hepatosplenomegaly, lymphadenopathy, skin rashes, and meningoencephalitis are variably present. A sepsis-like syndrome has been identified in a small number of HIV-infected patients with disseminated histoplasmosis and is characterized by the rapid onset of shock, multigorgan failure, and coagulopathy. Reactive hemophagocytic syndrome has been described in immunocompromised patients with severe disseminated histoplasmosis. Transplacental transmission of H. capsulatum has been reported in immunocompromised mothers.

DIAGNOSIS

Histoplasma typically grows within 6 wk on Sabouraud agar at 25°C (77°F). Identification of tuberculae macroconidia allows for only a presumptive diagnosis, because Sepedonium species form similar structures. A confirmatory test using a chemiluminescent DNA probe for H. capsulatum is necessary to establish a definitive identification. Recovery of H. capsulatum by culture differs with the form of infection. In normal hosts with symptomatic or asymptomatic acute pulmonary histoplasmosis, sputum cultures are rarely obtained and are variably positive; cultures of bronchoalveolar lavage fluid appear to have a slightly higher yield than sputum cultures. Sputum cultures are positive in 60% of adults with chronic pulmonary histoplasmosis. The yeast can be recovered from blood or bone marrow in >90% of patients with progressive disseminated histoplasmosis. Blood cultures are sterile in patients with acute pulmonary histoplasmosis, and cultures from any source are typically sterile in patients with the sarcoid form of the
and for a minimum of 12 wk is also recommended. The lipid preparations of itraconazole (5-10 mg/kg/day in 2 divided doses, not to exceed 400 mg daily) and amphotericin B (0.7-1.0 mg/kg/day) or amphotericin B lipid complex (3-5 mg/kg/day) until improved; continued therapy with oral itraconazole (0.7-1.0 mg/kg/day) or amphotericin B lipid complex (0.3-0.5 mg/kg/day) for 6-12 mo is also recommended. For severely immunocompromised HIV-infected children living in endemic regions, itraconazole (200 mg/day) is also required. For severely immunocompromised HIV-infected children living in endemic regions, itraconazole (200 mg/day) is also required. It is recommended to monitor urine antigen levels during therapy and for 12 mo after therapy has ended to ensure cure. In general, amphotericin B lipid complex may be substituted in severely ill children who are intolerant of the classic drug preparation. The newer azoles (voriconazole and posaconazole) have not been well studied in the treatment of histoplasmosis and are currently not recommended.

Relapses in HIV-infected patients with progressive disseminated histoplasmosis are common. Currently, induction therapy with amphotericin B or lipid complex amphotericin B is recommended. Lifelong suppressive therapy with daily itraconazole (5 mg/kg/day up to adult dose of 200 mg/day) is also required. For severely immunocompromised HIV-infected children living in endemic regions, itraconazole (2-5 mg/kg every 12-24 hr) may be used prophylactically. Care must be taken to avoid interactions between antifungal azoles and protease inhibitors.

**Bibliography is available at Expert Consult.**
Histoplasmosis

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Bibliography


ETIOLOGY
*Blastomyces dermatitidis* belongs to a group of fungi that exhibit thermal dimorphism. In the soil (22-25°C [71.6-77°F]), these fungi grow as mold and produce spores, which are the infectious particles. Following soil disruption, aerosolized mycelial fragments and spores inhaled into the lungs (37°C [98.6°F]) convert into pathogenic yeast and cause infection.

EPIDEMIOLOGY
*B. dermatitidis* causes disease in immunocompetent and immunocompromised children. Only 2-13% of blastomycosis cases occur in the pediatric population (average age: 9.1-11.5 yr; range: 19 days to 18 yr). Blastomycosis of newborns and infants is rare. In North America, the geographic distribution of blastomycosis cases is restricted to the Midwest, South-Central, and Southeastern United States and parts of
Canada bordering the Great Lakes and Saint Lawrence River Valley. In these geographic regions, several areas are hyperendemic for blastomycosis (e.g., Marathon and Vilas Counties, Wisconsin; Washington Parish, Louisiana; central and south-central Mississippi; Kenora, Ontario). Outside of North America, autochthonous infections have been reported from Africa (~100 cases) and India (<12 cases). B. dermatitidis is not endemic to the Middle East, Central America, South America, Europe, Asia, or Australia. In North America, B. dermatitidis grows in an ecologic niche characterized by forested, sandy soils with an acidic pH that have decaying vegetation and are near water. Most B. dermatitidis infections are sporadic; however, 15 outbreaks have been reported and most have involved pediatric patients. Outbreaks are associated with outdoor activities (camping, hiking, fishing); nonetheless some outbreaks have no identifiable risk factors other than geography. The severity of infection is influenced by the size of the inhaled inoculum and the integrity of the patient’s immune system. Those immunosuppressed by solid organ transplantation, AIDS, and tumor necrosis factor-α inhibitors are at risk for developing severe or disseminated infection.

PATHOGENESIS

The ability of mycelial fragments and spores to convert to yeast in the lung is a crucial event in the pathogenesis of infection with B. dermatitidis and other dimorphic fungi. This conversion, which is known as the phase transition, enables B. dermatitidis to evade the host immune system and establish infection. In the yeast form, B. dermatitidis produces BAD1 (Blastomyces adhesin-1; formerly WI-1), an essential virulence factor that is secreted into the extracellular milieu and binds back to a site on the fungal cell wall. BAD1 promotes binding of yeast to macrophages in lung alveoli, blocks the deposition of complement on the yeast surface, binds calcium, and suppresses the production of proinflammatory cytokines such as tumor necrosis factor-α in the host.

The phase transition from mold to yeast is a complex event that involves alteration in cell wall composition, metabolism, intracellular signaling, and gene expression. In B. dermatitidis, this transition is regulated, in part, by a histidine kinase known as DRK1 (dimorphism regulating kinase-1). This sensor kinase controls not only the conversion of mold to yeast but also spore production, cell wall composition, and BAD-1 expression; the loss of DRK1 expression through gene disruption renders B. dermatitidis avirulent in a murine model of blastomycosis.

The phase transition is reversible and following a drop in temperature from 37°C (98.6°F) to 22°C (71.6°F), B. dermatitidis yeast convert to sporulating mold. Growth as mold promotes survival in the soil, allows for sexual reproduction to enhance genetic diversity, and facilitates transmission to new hosts. The transition from yeast to mold is influenced by SREB (siderophore biosynthesis repressor in Blastomyces), which encodes a transcription factor. Deletion of SREB results in the failure of B. dermatitidis yeast to complete the conversion to mold.

Innate and adaptive immune systems are required to effectively control B. dermatitidis infection; humoral immunity is dispensable. Macrophages and neutrophils are capable of ingesting and killing B. dermatitidis conidia. In contrast, yeast are poorly killed by nonactivated macrophages, are resistant to reactive oxygen species, and suppress nitric oxide production. Adaptive immunity is mediated by T lymphocytes (Th1 and Th17), which activate macrophages and neutrophils to facilitate clearance of infection. Following infection, cell-mediated immunity against B. dermatitidis can last for at least 2 yr.

CLINICAL MANIFESTATIONS

The clinical manifestations of blastomycosis are diverse and include subclinical infection, symptomatic pneumonia, and disseminated disease. Clinical disease develops 3 wk to 3 mo following exposure to B. dermatitidis. Asymptomatic or subclinical infections are estimated to occur in 50% of patients. The most common clinical manifestation of blastomycosis is pneumonia, which can range from acute to chronic. Acute symptoms resemble community-acquired pneumonia and include fever, dyspnea, cough, chest pain, and malaise. Respiratory failure, including acute respiratory distress syndrome, can occur in patients with an overwhelming burden of infection. Chest imaging typically demonstrates air space consolidation, which can involve the upper or lower lobes. Other radiographic features include nodular, reticulonodular, and miliary patterns. Hilar adenopathy and pleural effusions are uncommon. Because the clinical and radiographic features can mimic bacterial pneumonia, patients can be mistakenly treated with antibiotics, resulting in disease progression. Patients with subacute or chronic pneumonia also present with fevers, chills, night sweats, cough, weight loss, hemoptysis, dyspnea, and chest pain. Air space consolidation, mass lesions, or cavitary disease can be present on chest roentgenography. These features can mimic tuberculosis or malignancy.

Extrapulmonary blastomycosis most often affects the skin or bone but can involve almost any organ. The incidence of extrapulmonary disease in children ranges from 38-50%, which is similar to rates in adult patients (25-40%). The skin is the most common site for extrapulmonary blastomycosis, which is usually the result of hematogenous dissemination. Direct inoculation of B. dermatitidis into the skin from trauma or a laboratory accident can result in primary cutaneous blastomycosis. Skin manifestations include plaques, papules, ulcers, nodules, and verrucous lesions. Erythema nodosum is rare in blastomycosis. Dissemination of B. dermatitidis to the bone results in lytic destruction, pain, soft tissue swelling, sinus tract formation, and ulceration. The ribs, skull, spine, and long bones are most commonly affected. Patients with osteomyelitis often have pulmonary or cutaneous involvement. Vertebral osteomyelitis can be complicated by paraspinal abscess, psoas abscess, and vertebral body collapse. Extension of long bone osteomyelitis can result in pathologic fracture or septic arthritis. Genitourinary blastomycosis occurs in 10-30% of adults but is rare in children.

Blastomycosis of the central nervous system occurs in <10% of immunocompetent patients and can result in brain abscess or meningitis. Some patients with central nervous system blastomycosis have widely disseminated disease. Symptoms include headache, altered mental status, memory loss, seizure, cranial nerve deficits, and focal neurologic deficits. Complications include hydrocephalus, cerebral herniation, infarction, panhypopituitarism, residual weakness, and poor functioning in school. Lumbar puncture demonstrates leukocytosis with a neutrophil or lymphocyte predominance, elevated protein, and low glucose. Growth of B. dermatitidis in culture from cerebral spinal fluid occurs in less than 50% of affected patients.

Blastomycosis can complicate pregnancy, and clinical information is limited to case reports. Disseminated infection involving the lungs, skin, and bone is common. Spread of infection to the placenta has been documented by histopathology; however, the frequency of placental blastomycosis remains unknown. Transmission of B. dermatitidis to the fetus may involve transplacental transmission or aspiration of infected vaginal secretions. Although clinical data are limited, blastomycosis during pregnancy does not appear to increase the risk for congenital malformations.

DIAGNOSIS

The diagnosis of blastomycosis requires a high index of suspicion, because the clinical and radiographic manifestations can mimic other diseases including community-acquired pneumonia, tuberculosis, and malignancy. Blastomycosis should be included in the differential diagnosis for patients with pneumonia who live in or visit areas in which this pathogen is endemic, fail to respond to antibiotics, or have chronic skin lesions or osteomyelitis. A detailed medical history regarding exposure risks (e.g., canoeing, hiking, fishing, playing in outdoor forts, beaver dam exploration, home remodeling, nearby road or commercial construction, use of a woodpile for a wood burning stove) should be obtained. In addition, the health of family pets such as dogs should also be ascertained, as canine disease may be a harbinger of human infection. The incidence of blastomycosis in dogs is 10-fold higher than in humans, and canine infection suggests a common source of exposure.

Growth of B. dermatitidis in culture from sputum, skin, bone, or other clinical specimens provides a definitive diagnosis. Sputum specimens should be stained with 10% potassium hydroxide or calcofluor white. Histopathology shows neutrophilic infiltration with noncaseating granulomas (pyogranulomas). B. dermatitidis yeast in tissue samples can be visualized using Gomori methenamine silver or peri-
odic acid–Schiff stains. Yeasts are 8-20 µm in size, have a double refractile cell wall, and display broad-based budding.

Nonculture diagnostic techniques should be used in conjunction with fungal smears and cultures to facilitate the diagnosis of blastomycosis. The development of a Blastomyces antigen test has supplanted insensitive serologic methods such as complement fixation and immunodiffusion. Urine, serum, cerebrospinal fluid, and bronchoalveolar fluid specimens can be collected for the Blastomyces antigen test. Sensitivity of the urine antigen test ranges from 85.1-92.9% and is influenced by the burden of infection. The antigen test can crossreact with other dimorphic fungi including Histoplasma capsulatum, Paracoccidioides brasiliensis, and Penicillium marneffei, which decreases the specificity to 76.9-79%. An antibody test against the BAD1 protein has been developed with a sensitivity of 87.8% and a specificity of 94-99%. Combination antigen and BAD1 antibody testing can increase diagnostic sensitivity to 97.6%.

TREATMENT
Antifungal therapy is influenced by the severity of the infection, involvement of the central nervous system, the integrity of the host’s immune system, and pregnancy. All persons diagnosed with blastomycosis should receive antifungal therapy. Newborns with blastomycosis should be treated with amphotericin B deoxycholate 1 mg/kg/day. Children with mild to moderately severe infection can be treated with itraconazole 10 mg/kg/day (maximum: 400 mg/day) for 6-12 mo. Children with severe disease or underlying immunodeficiency or immunosuppression should be treated with amphotericin B deoxycholate 0.7-1.0 mg/kg/day or lipid amphotericin B 3-5 mg/kg/day until there is clinical improvement, generally 7-14 days, and then itraconazole 10 mg/kg/day (maximum: 400 mg/day) for a total of 12 mo.

Central nervous system blastomycosis requires therapy with lipid amphotericin B 5 mg/kg/day for 4-6 wk followed by itraconazole, fluconazole, or voriconazole for ≥12 mo.

All pediatric patients of childbearing age should undergo pregnancy testing prior to initiation ofazole antifungals. Itraconazole can increase the risk for spontaneous abortion and fluconazole can cause craniofacial defects resembling Antley-Bixler syndrome. Voriconazole and posaconazole cause skeletal abnormalities in animal models. Treatment of blastomycosis in pregnant patients consists of lipid amphotericin B 3-5 mg/kg/day.

For patients receiving itraconazole, the oral antifungal of choice, serum drug levels need to be measured 14 days into therapy (goal ≥1 µg/mL) and liver function tests should be monitored periodically. The newest azole antifungal drugs, voriconazole and posaconazole, have activity against B. dermatitidis; however, clinical experience with these drugs remains limited. The echinocandins (caspofungin, micafungin, and anidulafungin) should not be used to treat blastomycosis. Serial measurement of urine antigen levels to assess response to therapy appears promising, but the clinical usefulness of this strategy remains to be determined.

Bibliography is available at Expert Consult.
**Bibliography**


Coccidioidomycosis (Coccidioides Species)

ETIOLOGY
Coccidioidomycosis (valley fever, San Joaquin fever, desert rheumatism, coccidioidal granuloma) is caused by Coccidioides spp., a soil-dwelling dimorphic fungi. Coccidioides spp. grow in the environment as spore-bearing (arthroconidia-bearing) mycelial forms. In their parasitic form, they appear as unique, endosporulating spherules in infected tissue. The 2 recognized species, C. immitis and C. posadasii, cause similar illnesses.

EPIDEMIOLOGY
Coccidioides spp. inhabit soil in arid regions. C. immitis is primarily found in California’s San Joaquin Valley. C. posadasii is endemic to southern regions of Arizona, Utah, Nevada, New Mexico, western Texas and regions of Mexico and Central and South America. Population migrations into endemic areas and increasing numbers of immunosuppressed persons have caused coccidioidomycosis to become an important health problem. Infection rates increased from 2000-2007. Approximately 150,000 newly reported infections occur annually in the United States. Coccidioidin skin test positivity in 5-7 yr old students in a highly endemic area demonstrated a decline from 10% to 2% in a 58 yr period ending in 2000. During 2002, 153 children required hospitalization for coccidioidomycosis, and infection was fatal in 9% of cases.

Infection results from inhalation of aerosolized spores. Incidence increases during windy, dry periods that follow rainy seasons. Seismic events, archaeologic excavations, and other activities that disturb contaminated sites have caused outbreaks. Person-to-person transmission does not occur. Rarely, infections result from spores that contaminate fomites or grow beneath casts or wound dressings of infected patients. Infection has also resulted from transplantation of organs from infected donors and from mother to fetus or newborn. Visitors to endemic areas can acquire infections, and diagnosis may be delayed when they are evaluated in nonendemic areas. Spores are highly virulent, and Coccidioides spp. are potential agents of bioterrorism (see Chapter 723).

PATHOGENESIS
Inhaled spores reach terminal bronchioles, where they transform into septated spherules that resist phagocytosis and within which many endospores develop. Released endospores transform into new spherules, and the process results in an acute focus of infection. Endospores can also disseminate lymphohematogenously. Eventually, a granulomatous reaction predominates. Both recovery and protection upon reexposure depend on effective cellular immunity.

Children with congenital primary immunodeficiency disorders may be at increased risk for infection; these disorders include interleukin-12Rβ1 deficiency, interferon-γR1 deficiency, and STAT1 gain-of-function mutations.

CLINICAL MANIFESTATIONS
The clinical spectrum (Fig. 240-1) encompasses pulmonary and extrapulmonary disease. Pulmonary infection occurs in 95% of cases and can be divided into primary, complicated, and residual infections. Approximately 60% of infections are asymptomatic. Symptoms in children are milder than those in adults. The incidence of extrapulmonary dissemination in children approaches that of adults.

Primary Coccidioidomycosis
The incubation period is 1-4 wk, with an average of 10-16 days. Early symptoms include malaise, chills, fever, and night sweats. Chest
Clinically apparent dissemination occurs in 0.5% of patients. Its incidence and sometimes require differentiation from malignancy. Persisting pulmonary nodules. Nodules are present in 5-7% of infections following intense exposure; this is associated with high mortality rates. Serious hemorrhage. Rarely, acute respiratory insufficiency occurs following the onset. Organism-specific skin lesions have a predilection for the nasolabial area and appear initially as papules, which evolve to form pustules, plaques, abscesses, and verrucous plaques. Biopsy of these lesions demonstrates spherules. Basilar meningitis is the most common manifestation and may be accompanied by ventriculitis, ependymitis, cerebral vasculitis, abscess, and syringomyelia. Headache, vomiting, meningismus, and cranial nerve dysfunction are often present. Untreated meningitis is almost invariably fatal. Bone infections account for 20-50% of extrapulmonary manifestations, are often multifocal, and can affect adjacent structures. Miliary dissemination and peritonitis can mimic tuberculosis.

**DIAGNOSIS**

Nonspecific tests have limited usefulness. The complete blood count might show an elevated eosinophil count, and marked eosinophilia can accompany dissemination.

**Culture, Histopathologic Findings, and Antigen Detection**

Although diagnostic, culture is positive in only 8.3% of respiratory tract specimens and in only 3.2% of all other sites. *Coccidioides* is isolated from clinical specimens as the spore-bearing mold form, and thus the laboratory should be informed and use special precautions when the diagnosis is suspected. The observation of endosporulating spherules in histopathologic specimens is also diagnostic.

A quantitative enzyme immunoassay (EIA) (MiraVista Diagnostics) that detects coccidoidal galactomannan in urine has excellent specificity and is positive in 70% of patients with severe infections. Although the EIA can cross-react with other endemic mycoses, interpretation is often straightforward because there is negligible geographic overlap with areas endemic for other mycoses.

Cerebrospinal fluid (CSF) analysis should be performed in patients with suspected dissemination. The findings in meningitis are similar to those seen with tuberculous meningitis (see Chapter 215). Eosinophil pleocytosis may be present. Fungal stains and culture are usually negative. Volumes of 10 mL in adults have improved the yield of culture.

**SEROLOGY**

Serologic tests provide valuable diagnostic information but may be falsely negative early in self-limited infections and in immunocompromised patients. Three major methods are used, including EIA, complement fixation (CF), and immunodiffusion. EIA and CF tests are best done in experienced reference laboratories.

**Table 240-1** Risk Factors for Poor Outcome in Patients with Active Coccidioidomycosis

<table>
<thead>
<tr>
<th>PRIMARY INFECTIONS</th>
<th>Risk Factors for Poor Outcome in Patients with Active Coccidioidomycosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe, prolonged (&gt;2 wk), or progressive infection</td>
<td></td>
</tr>
<tr>
<td>RISK FACTORS FOR EXTRAPULMONARY DISSEMINATION</td>
<td>Primary or acquired cellular immune dysfunction (including patients receiving tumor necrosis factor inhibitors)</td>
</tr>
<tr>
<td>Neonates, infants, the elderly</td>
<td></td>
</tr>
<tr>
<td>Male sex (adult)</td>
<td></td>
</tr>
<tr>
<td>Filipino, African, Native American, or Latin American ethnicity</td>
<td></td>
</tr>
<tr>
<td>Late-stage pregnancy and early postpartum period</td>
<td></td>
</tr>
<tr>
<td>Standardized complement fixation antibody titer &gt;1:16 or increasing titer with persisting symptoms</td>
<td></td>
</tr>
<tr>
<td>Blood group B</td>
<td></td>
</tr>
<tr>
<td>Human leukocyte antigen (HLA) class II allele-DRB1*1301</td>
<td></td>
</tr>
</tbody>
</table>

Discomfort occurs in 50-70% of patients and varies from mild tightness to severe pain. Headache and/or backache are sometimes reported. An evanescent, generalized, fine macular erythematous or urticarial eruption may be seen within the 1st few days of infection. Erythema nodosum can occur (more often in women) and is sometimes accompanied by an erythema multiforme rash, usually 3-21 days after the onset of symptoms. The clinical constellation of erythema nodosum, fever, chest pain, and arthralgias (especially knees and ankles) has been termed *desert rheumatism* and *valley fever*. The chest examination is often normal even if radiographic findings are present. Dullness to percussion, friction rub, or fine rales may be present. Pleural effusions can occur and can become large enough to compromise respiratory status. Hilar and mediastinal lymphadenopathy are common (Fig. 240-2).

**Complicated Pulmonary Infection**

Complicated infections include severe and persistent pneumonia, progressive primary coccidioidomycosis, progressive fibrocavitary disease, transient cavities that develop in areas of pulmonary consolidation, and empyema that follows rupture of a cavity into the pleural space. Some cavities persist, are thin walled and peripheral, and cause no symptoms; occasionally there is mild hemoptysis, and rarely there is serious hemorrhage. Rarely, acute respiratory insufficiency occurs following intense exposure; this is associated with high mortality rates.

**Residual Pulmonary Coccidioidomycosis**

Residual pulmonary coccidioidomycosis includes fibrosis as well as persisting pulmonary nodules. Nodules are present in 5-7% of infections and sometimes require differentiation from malignancy.

**Disseminated (Extrapulmonary) Infection**

Clinically apparent dissemination occurs in 0.5% of patients. Its incidence is increased in infants; men; persons of Filipino, African, and Latin American ancestry; and persons from other Asian backgrounds. Primary or acquired disorders of cellular immunity (Table 240-1) markedly increase the risk of dissemination.

Symptoms usually occur within 6 mo of primary infection. Prolonged fever, toxicity, skin lesions, subcutaneous and/or osseous cold abscesses, and laryngeal lesions can herald the onset. Organism-specific skin lesions have a predilection for the nasolabial area and appear initially as papules, which evolve to form pustules, plaques, abscesses, and verrucous plaques. Biopsy of these lesions demonstrates spherules. Basilar meningitis is the most common manifestation and may be accompanied by ventriculitis, ependymitis, cerebral vasculitis, abscess, and syringomyelia. Headache, vomiting, meningismus, and cranial nerve dysfunction are often present. Untreated meningitis is almost invariably fatal. Bone infections account for 20-50% of extrapulmonary manifestations, are often multifocal, and can affect adjacent structures. Miliary dissemination and peritonitis can mimic tuberculosis.

**Figure 240-2** Chest radiograph of a 19 yr old man with acute primary coccidioidomycosis. There is prominent hilar lymphadenopathy and mediastinal widening.
Immunoglobulin (Ig) M–specific antibody becomes measurable in 50% of infected patients 1 wk after onset and in 90% of infected patients by 3 wk. EIA is sensitive and can detect IgM and IgG antibody; it is less specific than other methods, and confirmation with immunodiffusion or CF may be needed. IgG antibodies measured by CF appear between the 2nd and 3rd wk but can take several months; follow-up testing is needed if tests are negative and clinical suspicion persists. In the presence of CF titers of 1:2 or 1:4, a positive immunodiffusion test can help corroborate significance. IgG-specific antibody can persist for months, with titers elevated in proportion to the severity of illness. CF titers >1:16 are suggestive of dissemination. Direct comparison of the results of CF (IgG) antibody tests measured by different methodologies should be interpreted with caution. IgG antibody titers used to monitor disease activity should be tested concurrently with serum samples taken earlier in the illness using the same methodology.

_C. immitis_ antibody is present in CSF in 95% of patients with meningitis and is usually diagnostic. Rarely, “spillover” in patients without meningitis but with high IgG titers in serum can be present in CSF. Isolation of _Coccidioides_ from CSF culture of patients with meningitis is uncommon, although culture of large volumes of CSF may improve sensitivity.

**Imaging Procedures**

During primary infection, chest radiography may be normal or demonstrate consolidation, single or multiple circumscribed lesions, or soft pulmonary densities. Hilar and subcarinal lymphadenopathy is often present (see Fig. 240-2). Cavities tend to be thin walled (Fig. 240-3). Pleural effusions vary in size. The presence of miliary or reticulonodular lesions is prognostically unfavorable. Isolated or multiple osseous lesions are usually lytic and often affect cancellous bone. Lesions can affect adjacent structures, and vertebral lesions can impact the spinal cord.

**TREATMENT**

Based on the few rigorous clinical trials performed in adults and the opinions of experts in the management of coccidioidomycosis, consensus treatment guidelines have been developed (Table 240-2). Consultation with experts in an area of endemicity should be considered when formulating a plan of management.

Patients should be followed closely because late relapse can occur, especially in patients who are immunosuppressed or have severe manifestations. Treatment is recommended for all HIV-infected patients.
with active coccidioidomycosis and CD4 counts <250/µL. Following successful treatment, antifungals may be stopped if the CD4 count exceeds 250/µL. Treatment should be continued if the CD4 count remains less than 250/µL and should be given indefinitely in all HIV-infected patients with coccidioidal meningitis.

First-line agents include oral and intravenous preparations of fluconazole (6-12 mg/kg/day IV or PO) and itraconazole (5-10 mg/kg/day). Serum levels of itraconazole should be monitored.

Amphotericin B is preferred for initial treatment of severe infections. Amphotericin B deoxycholate is less costly than lipid formulations and is often well tolerated in children. Once a daily dose of amphotericin B deoxycholate of 1-1.5 mg/kg/day is achieved, the frequency of administration can be reduced to 3 times weekly. The recommended total dosage ranges from 15 mg/kg to 45 mg/kg and is determined by the clinical response. Lipid formulations of amphotericin are recommended for patients with impaired renal function, patients receiving other nephrotoxic agents, or if amphotericin B deoxycholate is not tolerated. Some experts prefer liposomal amphotericin to treat central nervous system infections because it achieves higher levels in brain parenchyma. Amphotericin B preparations do not cross the blood–brain barrier to effectively treat Coccidioides spp., but they can mask the signs of meningitis. Infections during pregnancy should be treated with amphotericin B, because the azoles are potentially teratogenic. Voriconazole and posaconazole have been used successfully as salvage therapy in infections failing the standard agents.

**Primary Pulmonary Infection**
Primary pulmonary coccidioidomycosis resolves in 95% of patients without risk factors for dissemination; antifungal therapy does not lessen the frequency of dissemination or pulmonary residua. When it is elected to defer antifungal therapy, visits are recommended at 3-6 mo intervals for 2 yr and as needed.

Patients with significant or prolonged symptoms are more likely to incur benefit from antifungal agents, but there are no established criteria upon which to base the decision. Table 240-2 summarizes commonly used indicators in adults. A treatment trial in adults with primary respiratory infections examined outcomes of antifungal therapy prescribed on the basis of severity and compared them to an untreated group with less-severe symptoms; complications occurred only in patients in the treatment group and only in those in whom treatment was stopped. If treatment is elected, a 3-6 mo course of fluconazole (6-12 mg/kg/day) or itraconazole (5-10 mg/kg/day) is recommended.

**Diffuse Pneumonia**
Diffuse reticulonodular densities or miliary infiltrates, sometimes accompanied by severe illness, can occur in dissemination or follow exposure to a large fungal inoculum. In this setting, amphotericin B is recommended for initial treatment, followed thereafter by extended treatment with high-dose fluconazole (see Table 240-2).

**Disseminated (Extrapulmonary) Infection**
For nonmeningeal infection (see Table 240-2), oral fluconazole and itraconazole are effective for treating disseminated coccidioidomycosis that is not extensive, is not progressing rapidly, and has not affected the central nervous system. Some experts recommend higher doses for adults than were used in clinical trials. A subgroup analysis showed a tendency for improved response of skeletal infections that were treated with itraconazole. Amphotericin B deoxycholate is used as an alternative, especially if there is rapid worsening and lesions are in critical locations. Voriconazole has been used successfully as salvage therapy. The optimal duration of therapy with the azoles has not been clearly defined. Late relapses have occurred after lengthy treatment and favorable clinical response.

**Meningitis**
Therapy with oral fluconazole is currently preferred for coccidioidal meningitis. In adults, a dosage >400 mg/day is recommended by some experts. Itraconazole at a dosage of 400-600 mg/day in adults is reported to have a comparable effect. Some experts use intrathecal, intraventricular, or intracisternally administered amphotericin B in addition to an azole, believing that the clinical response may be faster. Patients who respond to the azole should continue treatment indefinitely. Hydrocephalus is a common occurrence and is not necessarily a marker of treatment failure. In the event of treatment failure with azoles, intrathecal therapy with amphotericin B deoxycholate is indicated, with or without the azole treatment. Cerebral vasculitis can occur and can predispose to cerebral ischemia, infarction, or hemorrhage. The efficacy of steroids in high dosage is unresolved. Salvage therapy with voriconazole has been found to be effective.

**Surgical Management**
If a cavity is located peripherally or there is recurrent bleeding or pleural extension, excision may be needed.Infrequently, bronchopleural fistula or recurrent cavitation occurs as a surgical complication; rarely, dissemination can result. Perioperative intravenous therapy with amphotericin B may be considered. Drainage of cold abscesses, synovectomy, and curettage or excision of osseous lesions is sometimes needed. Local and systemic administration of amphotericin B can be used to treat coccidioidal arthritic disease.

**PREVENTION**
Prevention relies on education about ways to reduce exposure. Physicians practicing in nonendemic regions should incorporate careful travel histories when evaluating patients with symptoms compatible with coccidioidomycosis.

*Bibliography is available at Expert Consult.*
Bibliography

**ETIOLOGY**

Paracoccidioidomycosis (South American or Brazilian blastomycosis, Lutz-Splendore-Almeida disease) is an uncommon fungal infection endemic in South America, with cases reported in Central America and Mexico. Brazil accounts for more than 80% of all reported cases. The etiologic agent, *Paracoccidioides brasiliensis*, is a thermally dimorphic fungus found in the environment in the mycelial (mold) form and in tissues as yeast.

**EPIDEMIOLOGY**

*P. brasiliensis*, a soil-inhabiting microorganism, is ecologically unique to Central and South America. Endemic outbreaks occur mainly in the tropical rain forests of Brazil, with cases scattered in Argentina, Colombia, and Venezuela. There is an increased incidence in areas with moderately high altitude, with high humidity and rainfall, and where coffee and tobacco are grown. Armadillos appear to be a natural reservoir for *P. brasiliensis*. The most common route of infection is by inhalation of conidia. The disease is not usually thought to be contagious, and person-to-person transmission has not been confirmed. Paracoccidioidomycosis is more common among boys after puberty because of the role of estrogen in preventing the transition of conidia to the yeast form. Children account for <10% of the total number of cases.

**PATHOGENESIS**

The entry route into the body is via the respiratory tract, and the lungs are the site of primary infection, although not all patients have respiratory symptoms. Once the conidia reach the alveoli, yeast
transformation takes place. The infection then spreads to the mucous membranes of the nose, mouth, and gastrointestinal tract. Cell-mediated immunity, specifically a T-helper type 2-type response, is crucial to containing the infection. Tumor necrosis factor-α and interferon-γ activated macrophages are responsible for intracellular killing of *P. brasiliensis*. The yeast can disseminate by the lymphohematogenous route to skin, lymph nodes, and other organs and remain dormant in lymph nodes, producing a latent infection with reactivation occurring later on in life. There are cases of patients who developed disease 30 or more years after leaving an endemic region.

Histopathologically, the yeast-like cells are round, with the parent cell being quite large and surrounded by small buds, giving it the appearance of a ship’s wheel. A mixed suppurrative and granulomatous inflammatory reaction with areas of necrosis is seen in pulmonary infections. In chronic infections fibrosis and calcification may be seen. Mucocutaneous infections are typified by ulceration and pseudoepitheliomatous hyperplasia.

**CLINICAL MANIFESTATIONS**

There are 2 clinical forms of disease. The acute form is rare, occurs almost exclusively in children and persons with impaired immunity, and targets the reticuloendothelial system. Pulmonary symptoms may be absent, although chest radiographs often show patchy, confluent, or nodular densities. Patients typically present acutely with fever, malaise, wasting, lymphadenopathy, and abdominal enlargement from intraabdominal lymphadenopathy. Hepatomegaly and splenomegaly are nearly constant. Localized bony lesions have been reported in children and can progress to systemic disease. Multifocal osteomyelitis, arthritis, and pericardial effusions can also occur. Nonspecific laboratory findings include anemia, eosinophilia, and hypergammaglobulinemia. Acute paracoccidioidomycosis has a 25% mortality rate.

Adults develop a chronic, progressive illness that manifests initially with flu-like symptoms, fever, and weight loss. Pulmonary infection develops with dyspnea, cough, chest pain, and hemoptyis. Findings on physical examination are scant, although chest radiographs can show infiltrates that are disproportionate with mild clinical findings. Mucositis involving the mouth and its structures as well as the nose can manifest as localized pain, change in voice, or dysphagia. Lesions can extend beyond the oral cavity onto the skin. Generalized lymphadenopathy, hepatosplenomegaly, and adrenal involvement (seen in 15-50% of cases) can lead to Addison disease. Meningoencephalitis and central nervous system granulomas can occur as presenting or secondary symptoms. Adults with extensive exposure to soil, such as farmers, are most likely to develop the chronic form of the disease.

**DIAGNOSIS**

Demonstration of the fungus by direct wet mount (potassium hydroxide) preparation of sputum, exudate, or pus supports the diagnosis in many cases. Histopathologic examination of biopsy specimens using special fungal staining techniques is also diagnostic. Immunohistochemistry using monoclonal antibodies to specific glycoproteins can also be done on tissue sections. Culture of the fungus on Sabouraud-dextrose or yeast extract agar confirms the diagnosis. Antibodies to *P. brasiliensis* can be demonstrated in most patients. Serial antibody titers and lymphocyte proliferative responses to fungal antigens are useful for monitoring the response to therapy. The 43 kDa glycoprotein (gp43) is present in sera of more than 90% of patients with paracoccidioidomycosis by immunodiffusion (the most commonly used diagnostic test) and in 100% by immunoblotting. A latex particle agglutination test using pooled crude fungal exoantigens is being developed for the detection of anti-*P. brasiliensis* antibodies and has shown 92% agreement with the double immunodiffusion test. Newer diagnostic methods that might prove to be very useful in the future include polymerase chain reaction, detection of gp43, and capture enzyme-linked immunosorbent assay to detect specific immunoglobulin E in patient sera. Skin testing with paracoccidioidin is not reliable, because 30-50% of patients with active disease are nonreactive initially and a positive test indicates previous exposure but not necessarily active disease.

**TREATMENT**

Itraconazole (5-10 mg/kg/day with maximum dosage of 400 mg/day) orally for 6 mo is the treatment of choice for paracoccidioidomycosis. Fluconazole has also been used, but high doses (≥600 mg/day) and longer treatment periods are required. Terbinafine, an allylamine, has potent in vitro activity against *P. brasiliensis* and has been used for successful treatment of paracoccidioidomycosis unresponsive to treatment with trimethoprim-sulfamethoxazole (TMP-SMX) (8-10 mg/kg/day). Amphotericin B is recommended for disseminated disease and if other therapies fail. Therapy with sulfonamide compounds, including sulfadiazine, TMP-SMX, and dapsone, have been used historically and are generally less expensive than the newer azoles and allylamines. The primary disadvantage is that the treatment course is very long, lasting months to years, depending on the agent selected. Relapse can occur following any form of therapy, including with amphotericin B.

Two therapies currently under investigation include the use of curcumin, an antioxidant found in the Indian spice turmeric, and the calcineurin inhibitor cyclosporine. Curcumin was found to have more antifungal activity than fluconazole against *P. brasiliensis* when studied in vitro using human buccal epithelial cells. Cyclosporine blocks the thermomorphism of *P. brasiliensis*. Animal models demonstrate that fungal whole cells, purified antigens, peptides, and DNA vaccines have great potential toward the development of a vaccine for use in humans.

Bibliography is available at Expert Consult.
Bibliography

ETIOLOGY
Sporotrichosis is a rare fungal infection that occurs worldwide both sporadically and in outbreaks. The etiologic agent, Sporothrix schenckii, exhibits temperature dimorphism, existing as a mold at environmental temperatures (25-30°C [77-86°F]) and as a yeast in vivo (37°C [98.6°F]).

EPIDEMIOLOGY
S. schenckii is found throughout the world, but most cases of sporotrichosis are reported from North and South America and Japan. In the United States, the majority of cases have occurred in the Midwest, particularly in areas along the Mississippi and Missouri rivers. The fungus is found in decaying vegetation and has been isolated most commonly from sphagnum moss, rosebushes, barberry, straw, and some types of hay. Sporotrichosis can occur as an occupational disease among farmers, gardeners, veterinarians, and laboratory workers. Transmission from bites and scratches of animals, most commonly cats and armadillos, has occurred. Reports of human-to-human transmission are rare. Sporotrichosis has rarely been reported in infants. The mechanism of transmission in children may be zoonotic but usually is unclear. In 1 endemic area of Peru, the incidence of infection in children is greater than adults; risk factors for infection in these children were playing in crop fields, living in houses with dirt floors, and owning a cat.

PATHOGENESIS
Disease in humans usually follows cutaneous inoculation of the fungus into a minor wound. Pulmonary infection can result from the
inhalation of large numbers of spores. Disseminated infection is unusual but can occur in immunocompromised patients following ingestion or inhalation of spores. The cellular immune response to *S. schenckii* infection is both neutrophilic and monocytic. Histologically, the coexistence of noncaseating granulomas and microabscess formation is characteristic. T-cell–mediated immunity appears to be important in limiting infection, and antibody does not protect against infection. As a result of the paucity of organisms, it is usually difficult to demonstrate the fungi in biopsy specimens.

**CLINICAL MANIFESTATIONS**

Cutaneous sporotrichosis is the most common form of disease in all age groups. Cutaneous disease may either be lymphocutaneous or fixed cutaneous, the former being much more common. Lymphocutaneous sporotrichosis accounts for more than 75% of reported cases in children and occurs after traumatic subcutaneous inoculation. After a variable and often prolonged incubation period (1-12 wk), an isolated, painless erythematous papule develops at the inoculation site. The initial lesion is usually on an extremity in adults but is often on the face in children. The original papule enlarges and ulcerates. Although the infection might remain limited to the inoculation site (fixed cutaneous form), satellite lesions follow lymphangitic spread and appear as multiple tender subcutaneous nodules tracking along the lymphatic channels that drain the lesion. These secondary nodules are subcutaneous granulomas that adhere to the overlying skin and subsequently ulcerate. Sporotrichosis does not heal spontaneously, and these ulcerative lesions can persist for years if they are untreated. Systemic signs and symptoms are uncommon.

Extracutaneous sporotrichosis is rare in children, and most cases are reported in adults with underlying medical conditions, including AIDS and other immunosuppressing diseases. The most common form of extracutaneous sporotrichosis involves infection of the bones and joints. Pulmonary sporotrichosis usually manifests as a chronic pneumonitis similar to the presentation of pulmonary tuberculosis.

**DIAGNOSIS**

Cutaneous and lymphocutaneous sporotrichosis must be differentiated from other causes of nodular lymphangitis, including atypical mycobacterial infection, nocardiosis, leishmaniasis, tularemia, melioidosis, cutaneous anthrax, and other systemic mycoses, including coccidioidomycosis. Definitive diagnosis requires isolation of the fungus from the site of infection by culture. Special histologic staining such as periodic acid–Schiff and methenamine silver is required to identify yeast forms in tissues. In spite of special staining techniques, diagnostic yield from biopsy specimens is low because of the small number of organisms present in the tissues. In cases of disseminated disease, demonstration of serum antibody against *S. schenckii*–related antigens can be diagnostically useful. Serologic testing is not commercially available, but it is offered by specialized laboratories including the Centers for Disease Control and Prevention in the United States.

**TREATMENT**

Although comparative trials and extensive experience in children are not available, itraconazole is the recommended treatment of choice for infections outside the central nervous system. The recommended dosage for children is 5-10 mg/kg/day orally, with a target of 200 mg daily. Dosing may be increased up to 400 mg daily if there is no initial response. Alternatively, younger children with cutaneous disease only may be treated with a saturated solution of potassium iodide given orally once daily beginning at 5-10 drops 3 times per day. The dose is gradually advanced to 25-40 drops 3 times per day for children or 40-50 drops 3 times per day for adolescents and adults. Adverse reactions, usually in the form of nausea and vomiting, should be managed with temporary cessation of therapy and reinstitution at a lower dosage. Therapy is continued until the cutaneous lesions have resolved, which usually takes 6-12 wk. Terbinafine, an allylamine, also has been used successfully to treat cutaneous sporotrichosis. Further clinical efficacy data are needed to routinely recommend its use. Amphotericin B is the treatment of choice for pulmonary infections, disseminated infections, central nervous system disease, and infections in immunocompromised persons.

Therapy with azoles or a saturated solution of potassium iodide should not be used in pregnant women. Amphotericin B can safely be used for cases of pulmonary or disseminated disease in pregnancy. Pregnant patients with cutaneous disease can be treated with local hyperthermia, or therapy can be delayed until the pregnancy is completed. Hyperthermia, in which the affected area is heated to 42-45°C (107.6-113°F) using water baths or heating pads, inhibits growth of the fungus. Dissemination to the fetus does not occur, and the disease is not worsened by pregnancy. Surgical debridement has a role in the treatment of some cases of sporotrichosis, particularly in osteoarticular disease.

*Bibliography is available at Expert Consult.*
Bibliography

Chapter 243
Zygomycosis
(Mucormycosis)
Jane M. Gould and Stephen C. Aronoff

ETIOLOGY
Zygomycosis refers to a group of opportunistic fungal infections caused by dimorphic fungi of the class Zygomycetes, which are primitive, fast-growing fungi that are largely saprophytic and ubiquitous. These organisms are found commonly in soil, in decaying plant and animal matter, and on moldy cheese, fruit, and bread.

This class is subdivided into 2 orders, Mucorales and Entomophthorales, each containing human pathogens. The term mucormycosis refers only to infections caused by Mucorales, which includes the genera *Absidia*, *Apophysomyces*, *Mucor*, *Rhizomucor*, and *Rhizopus* and represents the more-common cause of zygomycosis in humans. Infections caused by organisms of the genera *Cunninghamella*, *Saksenaea*, and *Cokeromyces* are seen less often. Mucorales disease in humans is characterized by a rapidly evolving course, tissue necrosis, and blood vessel invasion in addition to subcutaneous infection. These infections are most acute and fulminant in debilitated patients. Genera of the order Entomophthorales causing infection in humans include *Conidiobolus* and *Basidiobolus*. These agents typically cause indolent sinus or subcutaneous infections in immunocompetent persons.

EPIDEMIOLOGY
Zygomycosis is primarily a disease of persons with underlying conditions that impair host immunity. Predisposing factors include diabetes, hematologic malignancies, persistent acidosis, corticosteroid or deferoxamine therapy, organ transplantation, prematurity, and, less commonly, AIDS. Fungi that are pathogenic in humans grow on almost any carbohydrate substrate and are able to grow at temperatures >37°C (98.6°F). Acidosis diminishes the phagocytic and chemotactic ability of neutrophils while increasing the availability of unbound iron. Deferoxamine-bound iron can also be used by the fungus to enhance its growth.

PATHOGENESIS
Macrophages and neutrophils are the main host defense against Zygomycetes and other filamentous fungi and provide almost complete immunity against Zygomycetes by phagocytosis and oxidative killing.
of spores, perhaps explaining the predilection for zygomycosis in patients with neutropenia or neutrophil dysfunction. Many of the Zygomycetes have virulence mechanisms that scavenge iron, an element essential for cell growth, from the host. The primary route of infection from Zygomycetes is inhalation of spores from the environment. In immunocompromised persons, if spores are not cleared by macrophages they germinate into hyphae, resulting in local invasion and tissue destruction. Cutaneous or percutaneous routes of infection can lead to cutaneous and subcutaneous zygomycosis. Ingestion of contaminated food or drinks has been linked to gastrointestinal disease. Typically these infections are characterized by extensive angioinvasion resulting in thrombosis, infarction, and tissue necrosis, which can limit the delivery of antifungal agents and leukocytes to the site of infection and contribute to dissemination of the organism to other organs.

**CLINICAL MANIFESTATIONS**

There are no unique signs or symptoms of zygomycosis. It can occur as any of several clinical syndromes, including sinus/rhinocerebral, pulmonary, gastrointestinal, disseminated, or cutaneous or subcutaneous disease.

Sinus and rhinocerebral infection are the most common forms of zygomycosis and occur primarily in persons with diabetes mellitus or who are immunocompromised. Infection typically originates in the paranasal sinuses. Initial symptoms are consistent with sinusitis and include headache, retroorbital pain, fever, and nasal discharge. Infection can evolve rapidly or be slowly progressive. Orbital involvement manifesting as periorbital edema, proptosis, ptosis, and ophthalmoplegia can occur early in the disease. The nasal discharge is often dark and bloody; examination of the nasal mucosa reveals the hallmark finding of black, necrotic areas; however, its absence does not exclude the diagnosis. Extension beyond the nasal cavity into the mouth is common. Involved tissues become red, then violaceous, and then black as vessel thrombosis and tissue necrosis occur. Direct bony involvement is common as a result of contiguous pressure effects or because of direct invasion and infarction. Destructive paranasal sinusitis with intracranial extension can be demonstrated by CT or MRI. Cases complicated by cavernous sinus thrombosis and thrombosis of the internal carotid artery have been reported. Brain abscesses can occur in patients with rhinocerebral infection that extends directly from the nasal cavity and sinuses, usually to the frontal or frontotemporal lobes. In patients with disseminated disease, abscesses can involve the occipital lobe or brainstem.

Pulmonary zygomycosis infection usually occurs in severely neutropenic patients and is characterized by fever, tachypnea, and productive cough with pleuritic chest pain and hemoptysis. A wide range of pulmonary radiologic findings, including solitary pulmonary nodule, segmental or lobar consolidation, and cavitary and bronchopneumonic changes, are recognized. Gastrointestinal zygomycosis is uncommon. Often the diagnosis is delayed; only 25% of cases are diagnosed antemortem, and the subsequent mortality is as high as 85%. It can occur as a complication of disseminated disease or as an isolated intestinal infection in diabetics, immunosuppressed or malnourished children, or preterm infants. Any part of the gastrointestinal tract can be involved, with the stomach followed by colon and ileum being the most commonly affected. Abdominal pain and distention with hematemesis, hematochezia, or melena can occur. Stomach or bowel wall perforation is not uncommon.

Disseminated zygomycosis is associated with a very high mortality rate, especially among immunocompromised persons. Pulmonary involvement is most common, but infection can originate from any of the primary sites of infection. A metastatic skin lesion is an important clue to early diagnosis.

Cutaneous and soft tissue zygomycosis can complicate burns or surgical wounds. An outbreak occurred among preterm infants following the use of contaminated wooden tongue depressors to immobilize the extremities. Primary cutaneous disease may be invasive locally, progressing through all tissue layers, including muscle, fascia, and bone. Necrotizing fasciitis may occur. Infection manifests as an erythematous papule that ulcerates, leaving a black necrotic center. The skin lesions are painful, and affected patients may be febrile. Cutaneous lesions from hematogenous seeding tend to be nodular, with minimal destruction of the epidermis.

**DIAGNOSIS**

The diagnosis relies on direct morphologic identification of mycotic elements and recovery of Zygomycetes in culture or by biopsy identification in specimens obtained at the site of presumed involvement. To identify the fungus from scrapings, sputum, and exudates under direct microscopy, the use of calcifluor white or 10% potassium hydroxide and Parker ink is recommended. In lung and other tissue biopsy specimens, demonstration of fungal elements with fungal specific stains is recommended. Mucorales appear as broad (5-25 µm in diameter), infrequently septate, thin-walled hyphae, branching irregularly at right angles when stained with Gomori methenamine silver or hematoxylin and eosin. Secondary to their thin-walled structure and lack of regular septation, they often appear twisted, collapsed, or folded. Angiopropidism is a hallmark of zygomycosis. The fungi can be cultured on standard laboratory media from sputum, bronchoalveolar lavage fluid, skin lesions, or biopsy material. Mucorales are common culture contaminants. Serologic tests for detecting zygomycosis are not clinically useful. Real-time quantitative polymerase chain reaction assay targeting the 28S rRNA gene has been tested in a rabbit model of experimental pulmonary zygomycosis and shows great promise as a rapid, sensitive, and specific diagnostic test. Additionally, direct sequencing of cultured organisms or formalin fixed tissue and fluorescence in situ hybridization are methods that show great promise to increase the sensitivity, specificity, and speed of laboratory-based diagnostics.

**TREATMENT**

All forms of the disease can be aggressive and difficult to treat, with high fatality rates. The optimal therapy for zygomycosis in children requires early diagnosis and prompt institution of medical therapy combined with extensive surgical debridement of all devitalized tissue. Correction of the underlying disease, if possible, is an essential component of management. Use of granulocyte colony-stimulating factor or granulocytemacrophage colony-stimulating factor to reverse immunosuppression is recommended in conjunction with antifungal agents. Amphotericin B deoxycholate (1-1.5 mg/kg/day to a total dose of 70 mg/kg or 3-4 g over several weeks) or amphotericin B lipid complex (3-5 mg/kg/day) has been successful in treating infection. Anecdotal reports suggest that higher total doses of amphotericin B lipid complex (15-20 mg/kg/day) are associated with better outcomes in invasive infection. Pulmonary and cutaneous disease has been successfully treated with intermediate dosages of amphotericin B (30 mg/kg total dose). Surveillance in the United States suggests an association between use of voriconazole prophylaxis and the emergence of zygomycosis in transplant patients, which might represent increased patient survival or selection of resistant organisms. Voriconazole is inactive against the Zygomycetes. Posaconazole appears to be active against most of the Zygomycetes both in vitro and in vivo and together with surgery has been associated with dramatic clinical responses and holds promise as a therapeutic agent for mucormycosis. Caspofungin has limited or no in vitro activity against Zygomycetes; however, when combined with amphotericin lipid complex, caspofungin has been found to be more active than lipid complex alone or caspofungin alone for the treatment of experimental zygomycosis in diabetic mice. Caspofungin has been shown to uncover β-glucan in the cell wall of Rhizopus, which results in an increase in neutrophil activity. Hyperbaric oxygen has been used anecdotally as an adjunctive therapy, and iron chelation with deferasirox has been tried as salvage therapy in refractory mucormycosis.

**Bibliography is available at Expert Consult.**
Bibliography


Pneumocystis jiroveci pneumonia (interstitial cell pneumonitis) in an immunocompromised person is a life-threatening infection. Primary infection in the immunocompetent person is usually subclinical and goes unrecognized. The disease most likely results from new or repeat acquisition of the organism rather than reactivation of latent organisms. Even in the most severe cases, with rare exceptions, the organisms remain localized to the lungs.

**Etiology**

P. jiroveci is a common extracellular parasite found worldwide in the lungs of mammals. The taxonomic placement of this organism has not been unequivocally established, but nucleic acid homologies place it closest to fungi despite sharing morphologic features and drug susceptibility with protozoa. Detailed studies of the basic biology of the organism are not possible because of the inability to maintain P. jiroveci in culture. Phenotypic and genotypic analyses demonstrate that each mammalian species is infected by a unique strain (or possibly species) of Pneumocystis. A biologic correlate of these differences is evidenced by animal experiments that have shown organisms are not transmissible from one mammalian species to another. These observations have led to the suggestion that organisms be renamed, with those infecting humans renamed P. jiroveci. Alternative acceptable nomenclature retains the use of Pneumocystis carinii but uses the annotation forma specialis to designate the host of origin such that P. carinii infecting humans, rats, or mice would carry the forma specialis designation hominis, ratti, or muris, respectively. Both nomenclatures appear in the medical literature.

**Epidemiology**

Serologic surveys show that most humans are infected with P. jiroveci before 4 yr of age. In the immunocompetent child, these infections are usually asymptomatic. P. jiroveci DNA can occasionally be detected in nasopharyngeal aspirates of normal infants. Pneumonia caused by P. jiroveci occurs almost exclusively in severely immunocompromised hosts, including those with congenital or acquired immunodeficiency disorders, malignancies, or transplanted organs. Patients with primary immunodeficiency diseases at risk for infection include severe immunodeficiency disease, X-linked CD40 ligand deficiency, major histocompatibility complex class II deficiency, nuclear factor kappa B essential modulator deficiency, dedicator of cytokinesis 8 deficiency, Wiskott-Aldrich syndrome, and caspase recruitment domain 11 deficiency. Small numbers of P. jiroveci can be found in the lungs of infants who have died with the diagnosis of sudden infant death syndrome. This observation could indicate a cause-and-effect relationship or simply that there is overlap in the timing of the primary infection with P. jiroveci and sudden infant death syndrome.

Without chemoprophylaxis, approximately 40% of infants and children with AIDS, 70% of adults with AIDS, 12% of children with leukemia, and 10% of patients with organ transplants experience P. jiroveci pneumonia. Epidemics that occurred among debilitated infants in Europe during and after World War II are attributed to malnutrition. The use of new biologic immunosuppressive agents has expanded at-risk populations. The addition of tumor necrosis factor-α inhibitors to the management of patients with inflammatory bowel disease has resulted in a demonstrable increase in P. jiroveci pneumonia in this patient population as has the use of rituximab in patients with hematologic malignancies.

The natural habitat and mode of transmission to humans are unknown, but animal studies clearly demonstrate airborne transmission. Animal-to-human transmission is unlikely because of the host specificity of P. jiroveci. Thus, person-to-person transmission is likely but has not been conclusively demonstrated.

**Pathogenesis**

Two forms of P. jiroveci are found in the alveolar spaces: cysts, which are 5-8 µm in diameter and contain up to 8 pleomorphic intracystic sporozoites (or intracystic bodies), and extracystic trophozoites (or trophic forms), which are 2-5 µm cells derived from excysted sporozoites. The terminology of sporozoite and trophozoite is based on the morphologic similarities to protozoa, because there are no exact correlates for these forms of the organism among the fungi. P. jiroveci attaches to type I alveolar epithelial cells, possibly by adhesive proteins such as fibronectin and or mannose-dependent ligands.

Control of infection depends on intact cell-mediated immunity. Studies in patients with AIDS show an increased incidence of P. jiroveci pneumonia with markedly decreased CD4⁺ T-lymphocyte counts. The CD4⁺ cell count provides a useful indicator in both older children and adults of the need for prophylaxis for P. jiroveci pneumonia. Although normally functioning CD4⁺ T cells are central to controlling infection by P. jiroveci, the final effector pathway for destruction of P. jiroveci is poorly understood but likely depends on alveolar macrophages. A role for CD4⁺ T cells could be to provide help for the production of specific antibody that is then involved in the clearance of organisms through interaction with complement, phagocytes, or T cells or through direct activation of alveolar macrophages.

In the absence of an adaptive immune response, as can be modeled in severe combined immunodeficient mice, infection with P. jiroveci produces little alteration in lung histology or function until late in the course of the disease. If functional lymphocytes are given to severe combined immunodeficient mice infected with P. jiroveci, there is a rapid onset of an inflammatory response that results in an intense cellular infiltrate, markedly reduced lung compliance, and significant hypoxia, which are the characteristic changes of P. jiroveci pneumonia in humans. These inflammatory changes are also associated with marked disruption of surfactant function. T-cell subset analysis has shown that CD4⁺ T cells produce an inflammatory response that clears the organisms but also results in lung injury. CD8⁺ T cells are ineffective in the eradication of P. jiroveci. CD8⁺ T cells do help modulate the inflammation produced by CD4⁺ T cells, but in the absence of CD4⁺ T cells the ineffectual inflammatory response of CD8⁺ T cells contributes significantly to lung injury. These various T-cell effects are likely responsible for the variations in presentation and outcome of P. jiroveci pneumonia observed in different patient populations.

**Pathology**

The histopathologic features of P. jiroveci pneumonia are of 2 types. The first type is infantile interstitial plasma cell pneumonitis, which was seen in epidemic outbreaks in debilitated infants 3-6 mo of age. Extensive infiltration with thickening of the alveolar septum occurs, and plasma cells are prominent. The second type is a diffuse desquamative alveolar pneumonitis found in immunocompromised children and adults. The alveoli contain large numbers of P. jiroveci in a foamy exudate with alveolar macrophages active in the phagocytosis of organisms. The alveolar septum is not infiltrated to the extent it is in the infantile type, and plasma cells are usually absent.

**Clinical Manifestations**

There are at least 3 distinct clinical presentations of P. jiroveci pneumonia. In patients with profound congenital immunodeficiency or in AIDS patients with very few CD4⁺ T cells, the onset of hypoxia and symptoms is subtle, with tachypnea progressing to nasal flaring, often without fever; intercostal, suprasternal, and infrastrernal retractions; and cyanosis in severe cases. In cases of P. jiroveci pneumonia occurring in children and adults with immunodeficiency resulting from immunosuppressive medications, the onset of hypoxia and symptoms is often more abrupt, with fever, tachypnea, dyspnea, and cough, progressing to severe respiratory compromise. This type accounts for the
majority of cases, although the severity of clinical expression can vary. Rales are usually not detected on physical examination. The third pattern of disease is seen in severely immunocompromised patients with \textit{P. jiroveci} pneumonia who appear to be responding to therapy but then have an acute and seemingly paradoxical deterioration thought to be associated with return of immune function. This condition is referred to as \textit{immune restitution inflammatory syndrome} and is most commonly seen in patients with newly diagnosed AIDS who present with \textit{P. jiroveci} pneumonia and who have a rapid response to antiretroviral therapy that is instituted at the same time as anti-\textit{Pneumocystis} therapy. It can also occur in stem cell transplant recipients who engraft while infected with \textit{P. jiroveci}.

\textbf{LABORATORY FINDINGS}

The chest radiograph reveals bilateral diffuse alveolar disease with a granular pattern. The earliest densities are perihilar, and progression proceeds peripherally, sparing the apical areas until last. The arterial oxygen tension (\textit{PoaO}) is invariably decreased. The major role of the laboratory in establishing a diagnosis of \textit{P. jiroveci} pneumonia is in identifying organisms in lung specimens by a variety of methods. Once obtained, the specimens are typically stained with 1 of 4 commonly used stains: Grocott-Gomori silver stain and toluidine blue stain for the cyst form, polychrome stains such as Giemsa stain for the trophozoites and sporozoites, and the fluorescein-labeled monoclonal antibody stains for both trophozoites and cysts. Polymerase chain reaction analysis of respiratory specimens offers promise as a rapid diagnostic method, but a standardized system for clinical use has not been established.

\textbf{DIAGNOSIS}

Definitive diagnosis requires demonstration of \textit{P. jiroveci} in the lung in the presence of clinical signs and symptoms of the infection. Organisms can be detected in specimens collected by bronchoalveolar lavage (BAL), tracheal aspirate, transbronchial lung biopsy, bronchial brushings, percutaneous transthoracic needle aspiration, and open lung biopsy. Hypertonic saline–induced sputum samples are helpful if \textit{P. jiroveci} is found, but the absence of the organisms in induced sputum does not exclude the infection and BAL should be performed. Open lung biopsy is the most reliable method, although BAL is more practical in most cases. Estimates of the diagnostic yield of the various specimens are 20–40% for induced sputum, 50–60% for tracheal aspirate, 75–95% for BAL, 75–85% for transbronchial biopsy, and 90–100% for open lung biopsy.

\textbf{TREATMENT}

The recommended therapy for \textit{P. jiroveci} pneumonia is trimethoprim-sulfamethoxazole (TMP-SMX) (15–20 mg TMP and 75–100 mg SMX/ kg/day in 4 divided doses) administered intravenously, or orally if there is mild disease and no malabsorption or diarrhea. The duration of treatment is 3 wk for patients with AIDS and 2 wk for other patients. Unfortunately, adverse reactions often occur with TMP-SMX, especially rash and neutropenia in patients with AIDS. For patients who cannot tolerate or who fail to respond to TMP-SMX after 5–7 days, pentamidine isethionate (4 mg/kg/day as a single dose IV) may be used. Adverse reactions are frequent and include renal and hepatic dysfunction, hyperglycemia or hypoglycemia, rash, and thrombocytopenia. Atovaquone (750 mg twice daily with food, for patients >13 yr of age) is an alternative treatment that has been used primarily in adults with mild to moderate disease. Limited experience is available for younger children. Pharmacokinetic studies of atovaquone show that a dose of 30 mg/kg/day PO in 2 divided doses for children 0–3 mo of age and older than 2 yr of age is adequate and safe; a dose of 45 mg/kg/day PO in 2 divided doses is needed for children between 4 mo and 2 yr of age. Other effective therapies include trimetrexate glucuronate or combinations of trimethoprim plus dapsone or clindamycin plus primaquine.

Some studies in adults suggest that administration of corticosteroids as adjunctive therapy to suppress the inflammatory response increases the chances for survival in moderate and severe cases of \textit{P. jiroveci} pneumonia. The recommended regimen of corticosteroids for adolescents older than 13 yr of age and for adults is oral prednisone, 80 mg/day PO in 2 divided doses on days 1–5, 40 mg/day PO once daily on days 6–10, and 20 mg/day PO once daily on days 11–21. A reasonable regimen for children is oral prednisone, 2 mg/kg/day for the 1st 7–10 days, followed by a tapering regimen for the next 10–14 days.

\textbf{SUPPORTIVE CARE}

Basic supportive care is dictated by the condition of the patient, with careful attention to maintain appropriate hydration and oxygenation. Only 5–10% of AIDS patients require mechanical ventilation compared to 50–60% of patients without AIDS, consistent with the hypothesis that the patient’s ability to mount an inflammatory response correlates with severity and outcome. There are anecdotal reports of giving surfactant to children with severe \textit{P. jiroveci} pneumonia, although the use of surfactant to treat adult-type respiratory distress syndrome is controversial.

\textbf{COMPLICATIONS}

Most complications occur as adverse events associated with the drugs used or the mechanical ventilation used for treatment. The most severe pulmonary complication of \textit{P. jiroveci} pneumonia is adult-type respiratory distress syndrome. Rarely, \textit{P. jiroveci} infection affects extrapulmonary sites (e.g., retina, spleen, and bone marrow), but such infections are usually not symptomatic and also respond to treatment.

\textbf{PROGNOSIS}

Without treatment, \textit{P. jiroveci} pneumonitis is fatal in almost all immunocompromised hosts within 3–4 wk of onset. The mortality rate varies with patient population and is related to inflammatory response rather than organism burden. AIDS patients have a mortality rate of 5–10%, and patients with other diseases such as malignancies have mortality rates as high as 20–25%. Patients who require mechanical ventilation have mortality rates of 60–90%. Patients remain at risk for \textit{P. jiroveci} pneumonia as long as they are immunocompromised. Continuous prophylaxis should be initiated or reinstituted at the end of therapy for patients with AIDS (see Chapter 276).

\textbf{PREVENTION}

Patients at high risk for \textit{P. jiroveci} pneumonia should be placed on chemoprophylaxis. Prophylaxis in infants born to HIV-infected mothers and for HIV-infected infants and children is based on age and CD4 cell counts (see Chapter 276). Patients with severe combined immunodeficiency syndrome, patients receiving intensive immunosuppressive therapy for cancer or other diseases, and organ transplant recipients are also candidates for prophylaxis. TMP-SMX (5 mg/kg TMP and 25 mg SMX/kg PO once daily or divided into 2 doses daily) is the drug of choice and may be given for 3 consecutive days each week, or, alternatively, each day. Alternatives for prophylaxis include dapsone (2 mg/kg/day PO, maximum: 100 mg/dose; or 4 mg/kg PO once weekly, maximum: 200 mg/dose), atovaquone (30 mg/kg/day PO for infants 1–3 mo and ≥24 mo of age; 45 mg/kg/day for infants and toddlers 4–23 mo of age), and aerosolized pentamidine (300 mg monthly by Respigrad II nebulizer), but all of these agents are inferior to TMP-SMX. Finally, limited clinical experience suggests that pentamidine can be given intravenously once monthly to prevent \textit{P. jiroveci} pneumonia. Prophylaxis must be continued as long as the patient remains immunocompromised. Some AIDS patients who reconstitute adequate immune response during highly active antiretroviral therapy may have prophylaxis withdrawn.

\textit{Bibliography is available at Expert Consult.}
Bibliography


Section 13
Viral Infections

Chapter 245
Principles of Antiviral Therapy
Mark R. Schleiss

Antiviral chemotherapy typically requires a delicate balance between targeting critical steps in viral replication without interfering with host cellular function. Because viruses require cellular functions to complete replication, many antiviral agents exert significant host cellular toxicity, a limitation that has hindered antiviral drug development. In spite of this limitation, a number of agents are licensed for use against viruses, particularly herpesviruses, respiratory viruses, and hepatitis viruses (Table 245-1).

In making the decision to commence antiviral drugs, it is important for the clinician to obtain appropriate diagnostic specimens, which can help clarify the antiviral of choice. The choice of a specific antiviral is based on the recommended agent of choice for a particular clinical condition, pharmacokinetics, toxicities, cost, and the potential for development of resistance (Table 245-2). Intercurrent conditions in the patient, such as renal insufficiency, should also be considered. Clinicians must monitor antiviral therapy closely for adverse events or toxicities, both anticipated and unanticipated.

In vitro sensitivity testing of virus isolates to antiviral compounds usually involves a complex tissue culture system. The potency of an antiviral is determined by the 50% inhibitory dose (ID$_{50}$), which is the antiviral concentration required to inhibit the growth in cell culture of a standardized viral inoculum by 50%. Because of the complexity of these assays, the results vary widely, and the actual relationship between antiviral sensitivity testing and antiviral therapy outcomes is sometimes unclear. Moreover, these assays are often not readily available and take considerable time to complete, limiting their utility and value in clinical practice. Fortunately, genotypic analysis of antiviral resistance mutations is increasingly available for clinical testing, based on identification by molecular techniques of known mutations associated with antiviral resistance.

Knowledge of the precise status of a patient’s immune system, particularly cell-mediated immunity, is important in the decision making for using an antiviral agent. Treatment of cytomegalovirus (CMV) infection in an immunocompromised patient is seldom necessary, whereas antiviral therapy may be lifesaving when administered to an immunocompromised solid organ transplant (SOT) or hematopoietic stem cell transplant (HSCT) patient. Antivirals can be employed with a variety of clinical goals in mind. Antivirals can be used for treatment of active end-organ disease, as prophylaxis to prevent viral infection or disease, or as preemptive therapy of viral infection to prevent viral disease. In preemptive therapy, a patient will demonstrate evidence of an active infection, usually by molecular means such as polymerase chain reaction–based identification of viral nucleic acids in clinical samples (blood or body fluids), but may have no symptoms. However, SOT and HSCT patients are at high risk of developing disease in this setting (particularly CMV infection), a scenario that warrants preemptive

Table 245-1 Currently Licensed Antiviral Drugs*

<table>
<thead>
<tr>
<th>ANTIVIRAL</th>
<th>TRADE NAME</th>
<th>MECHANISM OF ACTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acyclovir</td>
<td>Zovirax</td>
<td>Inhibits viral DNA polymerase</td>
</tr>
<tr>
<td>Adefovir</td>
<td>Hepsera</td>
<td>Nucleotide reverse transcriptase inhibitor</td>
</tr>
<tr>
<td>Amantadine</td>
<td>Symmetrel</td>
<td>Blocks M2 protein ion channel</td>
</tr>
<tr>
<td>Cidofovir</td>
<td>Vistide</td>
<td>Inhibits viral DNA polymerase</td>
</tr>
<tr>
<td>Famiclovir</td>
<td>Famvir</td>
<td>Inhibits viral DNA polymerase</td>
</tr>
<tr>
<td>Fomivirsen</td>
<td>Vitavirame</td>
<td>Phosphorothioate oligonucleotide inhibits viral replication via antisense mechanism</td>
</tr>
<tr>
<td>Foscarnet</td>
<td>Foscavir</td>
<td>Inhibits viral DNA polymerase and reverse transcriptase at pyrophosphate-binding site</td>
</tr>
<tr>
<td>Ganciclovir</td>
<td>Cytovene</td>
<td>Inhibits viral DNA polymerase</td>
</tr>
<tr>
<td>Idoxuridine</td>
<td>Herplex</td>
<td>Inhibits viral DNA polymerase</td>
</tr>
<tr>
<td>Interferon-α</td>
<td>Intro-A (interferon-α2b)</td>
<td>Produces multiple effector proteins that exert antiviral effects; also directly interacts with immune system components</td>
</tr>
<tr>
<td>Interferon-α2b plus ribavirin</td>
<td>Rebetron</td>
<td>Not established</td>
</tr>
<tr>
<td>Lamivudine</td>
<td>Epivir</td>
<td>Inhibits viral DNA polymerase and reverse transcriptase Neuraminidase inhibitor; interference with deaggregation and release of viral progeny</td>
</tr>
<tr>
<td>Oseltamivir</td>
<td>Tamiflu</td>
<td>Same as interferon; Inhibits viral DNA polymerase Interference with viral messenger RNA Blocks M2 protein ion channel</td>
</tr>
<tr>
<td>Pegylated interferon</td>
<td>PEG-Intron (α2b), Pegasis (α2a)</td>
<td>Same as interferon; Inhibits viral DNA polymerase Same as acyclovir</td>
</tr>
<tr>
<td>Penciclovir</td>
<td>Denavir</td>
<td>Same as interferon; Inhibits viral DNA polymerase Similar to acyclovir</td>
</tr>
<tr>
<td>Ribavirin</td>
<td>Virazole, Rebetol, Copegus</td>
<td>Same as ganciclovir; Inhibits viral DNA polymerase and to lesser extent, cellular DNA polymerase</td>
</tr>
<tr>
<td>Rimantadine</td>
<td>Flumadine</td>
<td>Neuraminidase inhibitor; interference with deaggregation and release of viral progeny</td>
</tr>
<tr>
<td>Trifluridine</td>
<td>Viroptic</td>
<td></td>
</tr>
<tr>
<td>Valacyclovir</td>
<td>Valtrex</td>
<td></td>
</tr>
<tr>
<td>Valganciclovir</td>
<td>Valcyte</td>
<td></td>
</tr>
<tr>
<td>Vidarabine</td>
<td>ara-A</td>
<td></td>
</tr>
<tr>
<td>Zanamivir</td>
<td>Relenza</td>
<td></td>
</tr>
</tbody>
</table>

FDA-APPROVED COMBINATION THERAPIES

- Interferon-α2b + ribavirin: Rebetron (Intron-A plus Rebetol)
- Interferon-α2a + ribavirin: Roferon-A + ribavirin
- Pegylated interferon-α2b + ribavirin: PEG-Intron + Rebetol
- Pegylated interferon-α2a + ribavirin: Pegasis + Copegus

*See Chapter 276 for antiretroviral drugs.
Principles of Antiviral Therapy

An understudied and underappreciated issue in antiviral therapy is emergence of resistance, particularly in the setting of high viral load, high intrinsic viral mutation rate, and prolonged or repeated courses of antiviral therapy. Resistant viruses are more likely to develop in or be selected for immunocompromised patients, because these patients are more likely to have multiple or long-term exposures to an antiviral agent.

ANTIVIRALS USED FOR HERPESVIRUSES

The herpesviruses are important pediatric pathogens, particularly in newborns and immunocompromised children. Most of the licensed antivirals are nucleoside analogs that inhibit viral DNA polymerase, treatment with an antiviral agent. In contrast, prophylaxis is administered to seropositive patients who are at risk to reactivate latent viral infection but do not yet have evidence of active viral replication or shedding.

A fundamental concept important in the understanding of the mechanism of action of most antivirals is that viruses must use host cell components to replicate. Thus, mechanisms of action for antiviral compounds must be selective to virus-specific functions whenever possible, and antiviral agents may have significant toxicities to the host if these compounds impact cellular physiology. Many of the approved antiviral drugs active against the herpesviruses are analogs of deoxynucleosides and subsequently inhibit viral DNA polymerase. Some of the more commonly targeted sites of action for antiviral agents include viral entry, absorption, penetration, and uncoating (amantadine, rimantadine); transcription or replication of the viral genome (acyclovir, valacyclovir, cidofovir, famciclovir, penciclovir, foscarnet, ganciclovir, valganciclovir, ribavirin, trifluridine); viral protein synthesis (interferons); and viral assembly, release, or deaggregation (oseltamivir, zanamivir, interferons).

Table 245-2  Antiviral Therapies for Non-HIV Clinical Conditions

<table>
<thead>
<tr>
<th>VIRUS</th>
<th>CLINICAL SYNDROME</th>
<th>ANTIVIRAL AGENT OF CHOICE</th>
<th>ALTERNATIVE ANTIVIRAL AGENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Influenza A</td>
<td>Treatment</td>
<td>Oseltamivir (&gt;1 yr old)</td>
<td>Rimantadine</td>
</tr>
<tr>
<td></td>
<td>Prophylaxis</td>
<td>Oseltamivir (&gt;1 yr old)</td>
<td>Amantadine, Zanamivir (&gt;7 yr old)</td>
</tr>
<tr>
<td>Influenza B</td>
<td>Treatment</td>
<td>Oseltamivir</td>
<td>Zanamivir (&gt;7 yr old)</td>
</tr>
<tr>
<td>Respiratory syncytial virus</td>
<td>Bronchiolitis or pneumonia in high-risk host</td>
<td>Ribavirin aerosol</td>
<td></td>
</tr>
<tr>
<td>Cyto megalovirus (CMV)</td>
<td>Congenital CMV infection</td>
<td>Ganciclovir (IV)</td>
<td>Valganciclovir (oral therapy appropriate; long-term oral valganciclovir investigational but may improve developmental and hearing outcomes)</td>
</tr>
<tr>
<td></td>
<td>Retinitis in AIDS patients</td>
<td>Valganciclovir</td>
<td>Ganciclovir, Cidofovir, Foscarnet, Ganciclovir ocular insert, Foscarnet, Cidofovir, Valganciclovir</td>
</tr>
<tr>
<td></td>
<td>Pneumonitis, colitis, esophagitis in immunocompromised patients</td>
<td>Ganciclovir (IV)</td>
<td></td>
</tr>
<tr>
<td>Herpes simplex virus (HSV)</td>
<td>Neonatal herpes</td>
<td>Acyclovir (IV)</td>
<td>Acyclovir (PO)</td>
</tr>
<tr>
<td></td>
<td>Suppressive therapy following neonatal herpes with central nervous system involvement</td>
<td>Acyclovir (IV)</td>
<td>Acyclovir (IV)</td>
</tr>
<tr>
<td></td>
<td>HSV encephalitis</td>
<td>Acyclovir (PO)</td>
<td>Acyclovir (IV)</td>
</tr>
<tr>
<td></td>
<td>HSV gingivostomatitis</td>
<td>Acyclovir (PO)</td>
<td>Acyclovir (IV)</td>
</tr>
<tr>
<td></td>
<td>First episode genital infection</td>
<td>Acyclovir (IV)</td>
<td>Acyclovir (IV)</td>
</tr>
<tr>
<td></td>
<td>Recurrent genital herpes</td>
<td>Acyclovir (PO)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Suppression of genital herpes</td>
<td>Acyclovir (PO)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cutaneous HSV (whitlow, herpes gladiatorum)</td>
<td>Acyclovir (PO)</td>
<td>Acyclovir (PO)</td>
</tr>
<tr>
<td></td>
<td>Eczema herpeticum</td>
<td>Acyclovir (PO)</td>
<td>Acyclovir (PO)</td>
</tr>
<tr>
<td></td>
<td>Mucocutaneous infection in immunocompromised host (mild)</td>
<td>Acyclovir (IV)</td>
<td>Acyclovir (IV)</td>
</tr>
<tr>
<td></td>
<td>Mucocutaneous infection in immunocompromised host (moderate to severe)</td>
<td>Acyclovir (IV)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Prophylaxis in bone marrow transplant recipients</td>
<td>Acyclovir (IV)</td>
<td>Valacyclovir</td>
</tr>
<tr>
<td></td>
<td>Acyclovir-resistant HSV</td>
<td>Foscarnet</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Keratitis or keratoconjunctivitis</td>
<td>Trifluridine</td>
<td></td>
</tr>
<tr>
<td>Varicella-zoster virus</td>
<td>Chickenpox, healthy child</td>
<td>Supportive care</td>
<td>Acyclovir (PO)</td>
</tr>
<tr>
<td></td>
<td>Chickenpox, immunocompromised child</td>
<td>Acyclovir (IV)</td>
<td>Acyclovir (PO)</td>
</tr>
<tr>
<td></td>
<td>Zoster (not ophthalmic branch of trigeminal nerve), healthy child</td>
<td>Supportive care</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Zoster (ophthalmic branch of trigeminal nerve), healthy child</td>
<td>Acyclovir (IV)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Zoster, immunocompromised child</td>
<td>Acyclovir (IV)</td>
<td>Valacyclovir</td>
</tr>
</tbody>
</table>

inducing premature chain termination during viral DNA synthesis in infected cells.

**Acyclovir**

Acyclovir is a safe and effective therapy for herpes simplex virus (HSV) infections. The favorable safety profile of acyclovir derives from its requirement for activation to its active form via phosphorylation by a viral enzyme, thymidine kinase (TK). Thus, acyclovir can only be activated in cells already infected with HSV that express the viral TK enzyme, a strategy that maximizes selectivity and reduces the potential for cellular toxicity in uninfected cells. Acyclovir is most active against HSV and also is active against varicella-zoster virus (VZV); therapy is indicated for infections with these viruses in a variety of clinical settings. Activity of acyclovir against CMV is less pronounced, and activity against Epstein-Barr virus is modest, both in vitro and clinically. Therefore, under most circumstances acyclovir should not be used to treat CMV or Epstein-Barr virus infections.

The biggest impact of acyclovir in clinical practice is in the treatment of primary and recurrent genital HSV infections. Oral nucleoside therapy plays an important role in the management of acute primary genital herpes, treatment of episodic symptomatic reactivations, and prophylaxis against reactivation. Acyclovir is also indicated in the management of suspected or proven HSV encephalitis in patients of all ages, and for treatment of neonatal HSV infection, with or without central nervous system (CNS) involvement. With respect to neonatal HSV infection, the routine use of acyclovir as empiric therapy against HSV infection in infants admitted with fever of unknown origin in the first 4-8 wk of life is controversial. Acyclovir should be routinely empirically used in infants born to women with risk factors for primary genital herpes or infants presenting with any combination of vesicular lesions, seizures, meningoencephalitis, hepatitis, pneumonia, or disseminated intravascular coagulation. Some advocate initiation of acyclovir in all febrile infants pending the collection and analysis of viral culture and polymerase chain reaction studies. Others have argued that a selective approach based on the history and physical exam is more appropriate when making decisions about the use of acyclovir in febrile infants. Given the safety of the drug, prudence would dictate the use of acyclovir in such patients if HSV infection cannot be excluded. In neonates with HSV infection including CNS involvement, the use of suppressive therapy with oral acyclovir for 6 mo has been demonstrated to improve neurodevelopmental outcome.

Acyclovir is indicated for the treatment of primary HSV gingivostomatitis and for primary genital HSV infection. Long-term suppressive therapy for genital HSV and for recurrent oropharyngeal infections (herpes labialis) is also effective. Acyclovir is also recommended for less-commonly encountered HSV infections, including herpetic aphthous ulcer, eczema herpeticum, and herpes gladiatorum. In addition, acyclovir is commonly used for prophylaxis against HSV reactivation in SOT and HSCT transplant patients. Severe end-organ HSV disease, typically with valacyclovir (see “Valacyclovir” below), has become standard of care among many obstetricians. One uncommon but important complication of long-term use of acyclovir is the selection for acyclovir-resistant HSV strains, which usually occurs from mutations in the HSV TK gene. Resistance is rarely observed in pediatric practice but should be considered in any patient who has been on long-term antiviral therapy and who has an HSV or VZV infection that fails to clinically respond to acyclovir therapy.

**Valacyclovir**

Valacyclovir is the l-valyl ester of acyclovir and is rapidly converted to acyclovir following oral administration. This agent has a safety and activity profile similar to that of acyclovir, but it has a bioavailability of >50%, 3-5-fold greater than that of acyclovir. Plasma concentrations approach those observed with intravenous acyclovir. Valacyclovir is only available for oral administration. A suspension formulation is not commercially available, but an oral suspension (25 mg/mL or 50 mg/mL) may be prepared extemporaneously from 500-mg caplets for use in pediatric patients for whom a solid dosage form is not appropriate. Suppressive therapy with valacyclovir is commonly prescribed in the 2nd and 3rd trimesters of pregnancy in women who have a clinical history of recurrent genital herpes. It is important to be aware that perinatal transmission of HSV can occur, leading to symptomatic disease in spite of maternal antenatal antiviral prophylaxis. In such settings, the possibility of emergence of acyclovir-resistant virus should be considered.

**Penciclovir and Famciclovir**

Penciclovir is an acyclic nucleoside analog that, like acyclovir, inhibits the viral DNA polymerase following phosphorylation to its active form. Compared with acyclovir, penciclovir has a substantially longer intracellular half-life, which in theory can confer superior antiviral activity at the intracellular level; however, there is no evidence that this effect confers clinical superiority. Penciclovir is licensed only as a topical formulation (1% penciclovir cream), and this formulation is indicated for therapy of cutaneous HSV infections. Topical therapy for primary or recurrent herpes labialis or cutaneous HSV infection is an appropriate use of penciclovir in children older than 2 yr of age.

Famciclovir is the prodrug formulation (diacetyl ester) of penciclovir. In contrast to penciclovir, famciclovir may be administered orally and has bioavailability of approximately 70%. Following oral administration, famciclovir is deacetylated to the parent drug, penciclovir. The efficacy of famciclovir for HSV and VZV infections appears equivalent to that of acyclovir, although the pharmacokinetic profile is more favorable. Famciclovir is indicated for oral therapy of HSV and VZV infections. There is currently no liquid or suspension formulation available. The toxicity profile is identical to that of acyclovir. In a clinical trial, valacyclovir was found to be superior to famciclovir in prevention of reactivation and reduction of viral shedding in the setting of recurrent genital HSV infection.

**Ganciclovir**

Ganciclovir is a nucleoside analog with structural similarity to acyclovir. Like acyclovir, ganciclovir must be phosphorylated for antiviral activity, which is targeted against the viral polymerase. The gene responsible for
activity against other DNA viruses, most notably the poxviruses. Cidofovir is actively broad-spectrum directed against herpesviruses, cidofovir also exhibits broad-spectrum activity against other DNA viruses, most notably the poxviruses. Cidofovir is an acyclic nucleotide analog that requires phosphorylation to its active form, cidofovir diphosphate, to exert its antiviral effect. Cidofovir is also of benefit for newborns with symptomatic congenital CMV infection and may be of value in partially ameliorating the sensorineural hearing loss and developmental disibilities that are common complications of congenital CMV infection.

Ganciclovir is supplied as parenteral and oral formulations. Ganciclovir ocular implants are also available for the management of CMV retinitis. The bioavailability of oral ganciclovir is poor, <10%. An oral prodrug, valganciclovir, is well absorbed from the gastrointestinal tract and quickly converted to ganciclovir by intestinal or hepatic metabolism. Bioavailability of ganciclovir (from valganciclovir) is approximately 60% from tablet and solution formulations. Significant concentrations are found in aqueous humor, subretinal fluid, cerebrospinal fluid, and brain tissue (enough to inhibit susceptible strains of CMV). Subretinal concentrations are comparable to plasma concentrations, but intravitreal concentrations are lower. Drug concentrations in the CNS range from 24-70% of plasma concentrations. The main route of elimination is renal, and dosage adjustments are necessary for renal insufficiency. Dose reduction is proportional to the creatinine clearance. Hemodialysis efficiently eliminates ganciclovir, so administration of additional doses after dialysis is necessary.

Ganciclovir has several important toxicities. Reversible myelosuppression is the most important toxicity associated with ganciclovir therapy and commonly requires either discontinuation of therapy or the intercurrent administration of granulocyte colony-stimulating factor. There are also the theoretical risks for carcinogenicity and gonadal toxicity; although these effects have been observed in some animal models, they have never been observed in patients. The decision to administer ganciclovir to a pediatric patient is complex and should be made in consultation with a pediatric infectious diseases specialist.

Foscarnet

Foscarnet has a unique profile, insofar as it is not a nucleoside analog but rather a pyrophosphate analog. The drug has broad activity against most herpesviruses. Like the nucleoside analogs, foscarnet inhibits viral DNA polymerase. On the other hand, foscarnet does not require phosphorylation to exert its antiviral activity, thus differing from the nucleoside analogs. It binds to a different site on the viral DNA polymerase. On the other hand, foscarnet does not require phosphorylation to exert its antiviral activity, thus differing from the nucleoside analogs. It binds to a different site on the viral DNA polymerase.

Cidofovir has activity against the BK virus, a polyomavirus, and therapy may be warranted in some settings of BK reactivation post-HSCT and SOT. Cidofovir is also useful in the management of CMV disease caused by strains with documented ganciclovir resistance.

Cidofovir is administered intravenously and is cleared renally by tubular secretion. Extensive prehydration and coadministration of probenecid are recommended. Nephrotoxicity is commonly encountered, even with appropriate prehydration; cidofovir must be coadministered with other nephrotoxic medications with care. Other potential toxicities include reproductive toxicity and carcinogenesis.

Trifluridine

Trifluridine is a pyrimidine nucleoside analog with activity against HSV, CMV, and adenovirus. It is formulated as a 1% ophthalmic solution and approved for topical use in the treatment of HSV keratitis and keratoconjunctivitis. Trifluridine is the treatment of choice for HSV keratitis, a disease that should always be managed in consultation with an ophthalmologist.

Vidarabine

Vidarabine is a nucleoside analog that has activity against HSV. It was the first parenteral antiviral agent for HSV infection, although it is no longer available for intravenous administration. A topical preparation remains available to treat HSV keratitis and is considered a second-line agent for this indication.

Fomivirsen

Fomivirsen is a novel anti-CMV compound that is used as a second-line agent for CMV retinitis by direct injection into the vitreous space. It is an antisense 21-mer DNA oligonucleotide that binds directly to complementary messenger RNA. This agent was the first antisense antiviral agent approved by the FDA. The standard dosage is 330 µg via intravitreal injection every 2 wk for 2 doses followed by maintenance therapy of 330 µg every 4 wk. There is no systemic absorption following intravitreal injection.

New Agents

There is a major need for development of new, nontoxic antivirals for HSV infection. Two new agents are approaching licensure that will be very useful in the management of HSCT and SOT patients. The oral lipid conjugate prodrug of cidofovir, CMX001, has improved activity against herpesviruses compared to parenterally administered cidofovir and a markedly reduced risk of nephrotoxicity. Another novel agent, etermlovir (AIC246), is highly orally bioavailable and has a novel mechanism of action, exerting its antiviral effect by interfering with the viral terminase complex. This agent demonstrates substantial promise as an alternative to more toxic antivirals in patients at high risk for CMV disease, particularly in the transplantation setting. It is also active against BK virus and poxviruses.

Ribavirin

Ribavirin is a guanosine analog that has broad-spectrum activity against a variety of viruses, particularly RNA viruses. Its precise mechanism of action is incompletely understood but is probably related to interference with viral messenger RNA processing and translation. Ribavirin is available in oral, parenteral, and aerosolized formulations. Although intravenous ribavirin is highly effective in the management of Lassa fever and other hemorrhagic fevers, this formulation is not licensed for use in the United States. The only licensed formulations in the United States are an aqueous formulation for aerosol administration (indicated for RSV infection) and an oral formulation that is combined with interferon-α for the treatment of hepatitis C. (For more information about antivirals
for hepatitis, see Chapter 358.) Administration of ribavirin by aerosol should be considered for serious RSV lower respiratory tract disease in immunocompromised children, young infants with serious RSV-associated illness, and high-risk infants and children (children with chronic lung disease or cyanotic congenital heart disease). In vitro testing and uncontrolled clinical studies also suggest efficacy of aerosolized ribavirin for parainfluenza, influenza, and measles infections.

Ribavirin is generally nontoxic, particularly when administered by aerosol. Ribavirin and its metabolites concentrate in red blood cells and can persist for several weeks and, in rare instances, may be associated with anemia. Conjunctivitis and bronchospasm have been reported following exposure to aerosolized drug. Care must be taken when using aerosolized ribavirin in children undergoing mechanical ventilation to avoid precipitation of particles in ventilator tubing: the drug is not formally approved for use in the mechanically ventilated patient, although there is published experience with this approach and it can be considered for mechanically ventilated patients, particularly in a “high-dose, short-duration” regimen. Concerns regarding potential teratogenicity from animal studies have not been borne out in clinical practice, although care should be taken to prevent inadvertent exposure to aerosolized drug in pregnant healthcare providers.

**Amantadine and Rimantadine**

Amantadine and rimantadine are tricyclic amines that are highly similar to each other, both structurally and functionally. Both are indicated for the prophylaxis and therapy of influenza A, and neither has discernible activity against influenza B or any other respiratory viruses. For maximal therapeutic efficacy, therapy should begin as soon as possible and within 48 hr of the onset of symptoms. Influenza immunization is a greatly preferred method of disease control, but these agents can be useful for prophylaxis, particularly in unimmunized, high-risk persons during annual seasonal epidemics of influenza.

The mechanism of action of the tricyclic amines against influenza A virus is unclear, but they appear to exert their antiviral effect at the level of uncoating of the virus. Both agents are extremely well absorbed after oral administration and are eliminated via the kidneys (90% of the dose is unchanged), necessitating dosage adjustments for renal insufficiency. The toxicities of the tricyclic amines are modest and include CNS adverse effects such as anxiety, difficulty concentrating, and lightheadedness and gastrointestinal adverse effects such as nausea and loss of appetite. Adverse effects are less common with rimantadine than with amantadine.

**Oseltamivir, Zanamivir, and Peramivir**

Oseltamivir and zanamivir are active against both influenza A and B, although the importance of this broader spectrum of antiflu activity in disease control is modest because influenza B infection is typically a much milder illness. Emerging strains of influenza, including H5N1 and the 2009-2010 pandemic strain, H1N1 (swine flu), are susceptible to oseltamivir and zanamivir but resistant to amantadine. Therefore, these agents are emerging as the antivirals of choice for influenza infection. Neither agent has appreciable activity against other respiratory viruses. The mechanism of antiviral activity of these agents is via inhibition of the influenza neuraminidase.

Zanamivir has poor oral bioavailability and is licensed only for inhalational administration. With inhaled administration, >75% of the dose is deposited in the oropharynx and much of it is swallowed. The actual amount distributed to the airways and lungs depends on factors such as the patient’s inspiratory flow. Approximately 13% of the dose appears to be distributed to the airways and lungs, with approximately 10% of the inhaled dose distributed systemically. Local respiratory mucosal drug concentrations greatly exceed the drug concentration needed to inhibit influenza A and B viruses. Elimination is via the kidneys, and no dosage adjustment is necessary with renal insufficiency, because the amount that is systemically absorbed is low.

Oseltamivir is administered as an esterified prodrug that has high oral bioavailability. It is eliminated by tubular secretion, and dosage adjustment is required for patients with renal insufficiency. Gastrointestinal adverse effects, including nausea and vomiting, are occasionally observed. The drug is indicated for both treatment and prophylaxis. The usual adult dosage for treatment of influenza is 75 mg twice daily for 5 days. Treatment should be initiated within 2 days of the appearance of symptoms. Recommended treatment dosages for children vary by age and weight. The recommended dose for children younger than 1 yr of age is 3 mg/kg/dose twice a day. For children older than 1 yr of age, doses are 30 mg twice a day for children weighing ≤15 kg, 45 mg twice a day for children weighing 15-23 kg, 60 mg twice a day for those weighing 23–40 kg, and 75 mg twice a day for children weighing ≥40 kg. Dosages for chemoprophylaxis are the same for each weight group in children older than 1 yr of age, but the drug should be administered only once daily rather than twice daily. Oseltamivir is FDA-approved for therapy of influenza A and B treatment in children 2 wk of age and older, whereas zanamivir is recommended for treatment of children 7 yr of age and older. Current treatment and dosage recommendations for treatment of influenza in children and for chemoprophylaxis are available at: [http://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm](http://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm). Oseltamivir has been described to produce neuropsychiatric (narcolepsy) and psychologic (suicidal events) side effects in some patient populations; the drug should be discontinued if behavioral or psychiatric side effects are observed. In late 2014 the FDA approved another neuraminidase inhibitor, peramivir, for treatment of influenza. It is available as a single-dose, intravenous option. The standard adult dose is 600 mg IV in a single, one-time dose. The drug is currently approved for use only in adults.

**Antiviral immune globulins**

Immune globulins are useful adjuncts in the management of viral disease. However, they are most useful when administered as prophylaxis against infection and disease in high-risk patients; their value as therapeutic agents in the setting of established infection is less clear. Varicella-zoster immune globulin (human) is valuable for prophylaxis against VZV in high-risk children, particularly newborns and immunocompromised children (see Chapter 255). Cytomegalovirus immune globulin is warranted for children at high risk for CMV disease, particularly SOT and HSCT patients, and can play a role in preventing injury to the infected fetus when administered to the pregnant patient (see Chapter 255). Palivizumab, a monoclonal antibody with anti-RSV activity, is effective for preventing severe RSV lower respiratory tract disease in high-risk premature infants and has replaced RSV immune globulin (see Chapter 260). Hepatitis B immune globulin is indicated in infants born to hepatitis B surface antigen-positive mothers (see Chapter 358).

**Bibliography is available at Expert Consult.**
Bibliography


Measles is highly contagious but owing to widespread vaccination, endemic transmission has been interrupted in the United States; indigenous or imported cases (in children or adults) have occasionally resulted in epidemics in the United States in unimmunized or partially immunized American or foreign-born children (adopted children, refugees, returning tourists). In some areas of the world, measles remains a serious threat to children.

**ETIOLOGY**

Measles virus is a single-stranded, lipid-enveloped RNA virus in the family Paramyxoviridae and genus *Morbillivirus*. Other members of the genus *Morbillivirus* affect a variety of mammals, such as rinderpest virus in cattle and distemper virus in dogs, but humans are
the only host of measles virus. Of the 6 major structural proteins of measles virus, the 2 most important in terms of induction of immunity are the hemagglutinin (H) protein and the fusion (F) protein. The neutralizing antibodies are directed against the H protein, and antibodies to the F protein limit proliferation of the virus during infection. Small variations in genetic composition have also been identified that result in no effect on protective immunity but provide molecular markers that can distinguish between viral types. Related genotypes have been grouped by clades, and the World Health Organization recognizes 8 clades, A-H, and 23 genotypes. These markers have been useful in the evaluation of endemic and epidemic spread of measles.

**EPIDEMIOLOGY**

The measles vaccine has changed the epidemiology of measles dramatically. Once worldwide in distribution, endemic transmission of measles has been interrupted in many countries where there is widespread vaccine coverage. Historically, measles caused universal infection in childhood in the United States, with 90% of children acquiring the infection before 15 yr of age. Morbidity and mortality associated with measles decreased prior to the introduction of the vaccine as a result of improvements in healthcare and nutrition. However, the incidence declined dramatically following the introduction of the measles vaccine in 1963. The attack rate fell from 313 cases per 100,000 population in 1956-1960 to 1.3 cases per 100,000 in 1982-1988.

A nationwide indigenous measles outbreak occurred in the United States in 1989-1991, resulting in more than 55,000 cases, 11,000 hospitalizations, and 123 deaths, demonstrating that the infection had not yet been conquered. This resurgence was attributed to vaccine failure in a small number of school-age children, low coverage of preschool-age children, and more rapid waning of maternal antibodies in infants born to mothers who had never experienced wild-type measles infection. Implementation of the 2 dose vaccine policy and more intensive immunization strategies resulted in interruption of endemic transmission in the United States in 1993. The current rate is <1 case per 1,000,000 population.

Measles continues to be imported into the United States from abroad; therefore, continued maintenance of >90% immunity through vaccination is necessary to prevent widespread outbreaks from occurring (Fig. 246-1).

In 2011, 222 cases of measles were reported to the U.S. Centers for Disease Control and Prevention (CDC), an incidence rate of 0.7 per 1,000,000 population. There were 17 outbreaks reported compared to a median of 4 outbreaks reported annually during 2001-2010. Of the 222 cases, 200 were associated with importations from other countries (returning tourists, adoptees, refugees) and 112 were associated with outbreaks. Measles rates remain high in the World Health Organization European Region, which reported more than 30,000 cases in 2011. Almost half of the measles importations to the United States were from this World Health Organization region.

High measles vaccination coverage rates early in life are essential to maintain the endemic spread of measles in the United States (>90% 1 dose coverage at 12-15 mo and >95% 2 dose coverage in school-age children.) While measles-mumps-rubella coverage was high (median: 94.8%) in the 2011-2012 school year, pockets of lower coverage rates exist because of reluctance of parents to vaccinate their children because of personal beliefs. This variability in vaccination has contributed to outbreaks among school-age children in recent years. In addition, measles may occur more often in children receiving the first dose at age 12-13 mo when compared to those immunized at age 15 mo and older.

**TRANSMISSION**

The portal of entry of measles virus is through the respiratory tract or conjunctivae following contact with large droplets or small-droplet aerosols in which the virus is suspended. Patients are infectious from 3 days before to up to 4-6 days after the onset of rash. Approximately 90% of exposed susceptible individuals experience measles. Face-to-face contact is not necessary, because viable virus may be suspended in air for as long as 1 hr after the patient with the source case leaves a room. Secondary cases from spread of aerosolized virus have been reported in airplanes, physicians' offices, and hospitals.

**PATHOLOGY**

Measles infection causes necrosis of the respiratory tract epithelium and an accompanying lymphocytic infiltrate. Measles produces a small-vessel vasculitis on the skin and on the oral mucous membranes. Histology of the rash and exanthem reveals intracellular edema and dyskeratosis associated with formation of epidermal syncytiot giant cells with up to 26 nuclei. Viral particles have been identified within these giant cells. In lymphoreticular tissue, lymphoid hyperplasia is prominent. Fusion of infected cells results in multinucleated giant cells, the Warthin-Finkeldey giant cells that are pathognomonic for measles, with up to 100 nuclei and intracytoplasmic and intranuclear inclusions.

**PATHOGENESIS**

Measles consists of 4 phases: incubation period, prodromal illness, exanthematosus phase, and recovery. During incubation, measles virus migrates to regional lymph nodes. A primary viremia ensues that disseminates the virus to the reticuloendothelial system. A secondary viremia spreads virus to body surfaces. The prodromal illness begins after the secondary viremia and is associated with epithelial necrosis and giant cell formation in body tissues. Cells are killed by cell-to-cell plasma membrane fusion associated with viral replication that occurs in many body tissues, including cells of the central nervous system. Virus shedding begins in the prodromal phase. With onset of the rash, antibody production begins, and viral replication and symptoms begin to subside. Measles virus also infects CD4+ T cells, resulting in suppression of the Th1 immune response and a multitude of other immunosuppressive effects.

Recent research has clarified the pathogenesis of disease caused by measles virus. Unlike other Paramyxoviridae members that utilize sialic acid molecules on the virus surface to enter cells, measles virus attaches to specific cell receptors to infect host cells. Studies in primates show that the initial targets for measles virus are alveolar macrophages, dendritic cells, and lymphocytes. The cell receptor used appears to be the signaling lymphocyte activating molecule or more properly CD150. Subsequently, respiratory epithelial cells become infected but do not express CD150. The mechanism of infection of respiratory tissues is attachment to the PVR4 receptor (Nectin4) that is expressed on cells in the trachea, oral mucosa, nasopharynx, and lungs. These 2 receptors, CD150 and PVR4, account for the lymphotropic and epitheliotropic nature of natural measles virus infection, and along with the prolonged immunosuppressive effects of measles, suggest that it is more characteristic of human immunodeficiency virus infection than a respiratory illness.

![Figure 246-1 Number of measles cases—United States, 1962–2011.](https://example.com/figure246-1)

Measles data provided were reported voluntarily to Centers for Disease Control and Prevention (CDC) from state health departments. (From McLean HQ, Fiebelkorn AP, Temte JL, Wallace GS; Centers for Disease Control and Prevention: Prevention of measles, rubella, congenital rubella syndrome, and mumps, 2013: summary recommendations of the Advisory Committee on Immunization Practices (ACIP); MMWR Recomm Rep 62(RR-04):1–34, 2013, Fig. 1.)
CLINICAL MANIFESTATIONS
Measles is a serious infection characterized by high fever, an enanthem, cough, coryza, conjunctivitis, and a prominent exanthem. After an incubation period of 8-12 days, the prodromal phase begins with a mild fever followed by the onset of conjunctivitis with photophobia, coryza, a prominent cough, and increasing fever. Koplik spots represent the enanthem and are the pathognomonic sign of measles, appearing 1-4 days prior to the onset of the rash (Fig. 246-2). They first appear as discrete red lesions with bluish white spots in the center on the inner aspects of the cheeks at the level of the premolars. They may spread to involve the lips, hard palate, and gingiva. They also may occur in conjunctival folds and in the vaginal mucosa. Koplik spots have been reported in 50-70% of measles cases but probably occur in the great majority.

Symptoms increase in intensity for 2-4 days until the 1st day of the rash. The rash begins on the forehead (around the hairline), behind the ears, and on the upper neck as a red maculopapular eruption. It then spreads downward to the torso and extremities, reaching the palms and soles in up to 50% of cases. The exanthem frequently becomes confluent on the face and upper trunk (Fig. 246-3).

With the onset of the rash, symptoms begin to subside. The rash fades over about 7 days in the same progression as it evolved, often leaving a fine desquamation of skin in its wake. Of the major symptoms of measles, the cough lasts the longest, often up to 10 days. In more severe cases, generalized lymphadenopathy may be present, with cervical and occipital lymph nodes especially prominent.

INAPPARENT MEASLES INFECTION
In individuals with passively acquired antibody, such as infants and recipients of blood products, a subclinical form of measles may occur. The rash may be indistinct, brief, or, rarely, entirely absent. Likewise, some individuals who have received vaccine, when exposed to measles, may have a rash but few other symptoms. Persons with inapparent or subclinical measles do not shed measles virus and do not transmit infection to household contacts.

LABORATORY FINDINGS
The diagnosis of measles is almost always based on clinical and epidemiologic findings. Laboratory findings in the acute phase include reduction in the total white blood cell count, with lymphocytes decreased more than neutrophils. Absolute neutropenia has been known to occur, however. In measles not complicated by bacterial infection, the erythrocyte sedimentation rate and C-reactive protein level are normal.

DIAGNOSIS
In the absence of a recognized measles outbreak, confirmation of the clinical diagnosis is often recommended. Serologic confirmation is most conveniently made by identification of immunoglobulin (Ig) M antibody in serum. IgM antibody appears 1-2 days after the onset of the rash and remains detectable for about 1 mo. If a serum specimen is collected <72 hr after onset of rash and is negative for measles antibody, a second specimen should be obtained. Serologic confirmation may also be made by demonstration of a 4-fold rise in IgG antibodies in acute and convalescent specimens collected 2-4 wk apart. Viral isolation from blood, urine, or respiratory secretions can be accomplished by culture at the CDC or local or state laboratories. Molecular detection by polymerase chain reaction is available through some state and local health departments and through the CDC.

DIFFERENTIAL DIAGNOSIS
Typical measles is unlikely to be confused with other illnesses, especially if Koplik spots are observed. Measles in the later stages or inapparent or subclinical infections may be confused with a number of other exanthematous immune-mediated illnesses and infections, including rubella, adenovirus infection, enterovirus infection, and Epstein-Barr virus infection. Exanthem subitum (in infants) and erythema infectiosum (in older children) may also be confused with measles. Mycoplasma pneumoniae and group A streptococcus may also produce rashes similar to that of measles. Kawasaki syndrome can cause many of the same findings as measles but lacks discrete intraoral lesions (Koplik spots) and a severe prodromal cough, and typically leads to elevations of neutrophils and acute-phase reactants. In addition, the characteristic thrombocytosis of Kawasaki syndrome is absent in measles (see Chapter 166). Drug eruptions may occasionally be mistaken for measles.

COMPLICATIONS
Complications of measles are largely attributable to the pathogenic effects of the virus on the respiratory tract and immune system (Table 246-1). Several factors make complications more likely. Morbidity and mortality from measles are greatest in patients younger than 5 yr of age (especially <1 yr of age) and older than 20 yr of age. In developing countries, higher case fatality rates have been associated with crowding, possibly attributable to larger inoculum doses after household exposure. Severe malnutrition in children results in a suboptimal
Table 246-1  Complications By Age for Reported Measles Cases, United States, 1987-2000

<table>
<thead>
<tr>
<th>COMPLICATION</th>
<th>OVERALL (67,032 CASES WITH AGE INFORMATION)</th>
<th>&lt;5 YR (N = 28,730)</th>
<th>5-9 YR (N = 6,492)</th>
<th>10-19 YR (N = 18,580)</th>
<th>20-29 YR (N = 9,161)</th>
<th>&lt;30 YR (N = 4,069)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any</td>
<td>19,480 (29.1)</td>
<td>11,883 (41.4)</td>
<td>1,173 (18.1)</td>
<td>2,369 (12.8)</td>
<td>2,656 (29.0)</td>
<td>1,399 (34.4)</td>
</tr>
<tr>
<td>Death</td>
<td>177 (0.3)</td>
<td>97 (0.3)</td>
<td>9 (0.1)</td>
<td>18 (0.1)</td>
<td>26 (0.3)</td>
<td>27 (0.7)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>5,482 (8.2)</td>
<td>3,294 (11.5)</td>
<td>408 (6.3)</td>
<td>627 (3.4)</td>
<td>767 (8.4)</td>
<td>386 (9.5)</td>
</tr>
<tr>
<td>Encephalitis</td>
<td>97 (0.1)</td>
<td>43 (0.2)</td>
<td>9 (0.1)</td>
<td>13 (0.1)</td>
<td>21 (0.2)</td>
<td>11 (0.3)</td>
</tr>
<tr>
<td>Hospitalization</td>
<td>12,876 (19.2)</td>
<td>7,470 (26.0)</td>
<td>612 (9.4)</td>
<td>1,612 (8.7)</td>
<td>2,075 (22.7)</td>
<td>1,107 (27.2)</td>
</tr>
<tr>
<td>Otitis media</td>
<td>4,879 (7.3)</td>
<td>4,009 (14.0)</td>
<td>305 (4.7)</td>
<td>338 (1.8)</td>
<td>157 (1.7)</td>
<td>70 (1.7)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>3,959 (5.9)</td>
<td>2,480 (8.6)</td>
<td>183 (2.8)</td>
<td>363 (2.0)</td>
<td>554 (6.1)</td>
<td>379 (9.3)</td>
</tr>
</tbody>
</table>


immune response and higher morbidity and mortality with measles infection. Low serum retinol levels in children with measles are associated with higher measles morbidity and mortality in developing countries and in the United States. Measles infection lowers serum retinol concentrations, so subclinical cases of hyporetninemia may be made symptomatic during measles. Measles infection in immunocompromised persons is associated with increased morbidity and mortality. Among patients with malignancy in whom measles develops, pneumonitis occurs in 58% and encephalitis occurs in 20%.

Pneumonia is the most common cause of death in measles. It may manifest as giant cell pneumonia caused directly by the viral infection or as superimposed bacterial infection. The most common bacterial pathogens are Streptococcus pneumoniae, Haemophilus influenzae, and Staphylococcus aureus. Following severe measles pneumonia, the final common pathway to a fatal outcome is often the development of bronchiolitis obliterans.

Croup, tracheitis, and bronchiolitis are common complications in infants and toddlers with measles. The clinical severity of these complications frequently requires intubation and ventilatory support until the infection resolves.

Acute otitis media is the most common complication of measles and was of particularly high incidence during the epidemic of the late 1980s and early 1990s because of the relatively young age of affected children. Sinusitis and mastoiditis also occur as complications. Viral and/or bacterial tracheitis is seen and can be life-threatening. Rhabdomyoneal abscess has also been reported.

Measles infection is known to suppress skin test responsiveness to purified tuberculin antigen. There may be a higher rate of activation of pulmonary tubercules in populations of individuals infected with Mycobacterium tuberculosis who are then exposed to measles.

Diarrhea and vomiting are common symptoms associated with acute measles, and diffuse giant cell formation is found in the epithelium in the gastrointestinal tract. Dehydration is a common consequence, especially in young infants and children. Appendicitis or bacterial tracheitis is seen and can be life-threatening. Rhabdomyoneal abscess has also been reported.

Measles is a long-associated complication, often with an unfavorable outcome. Rates of 1-3 per 1,000 cases of measles have been reported, with greater numbers occurring in adolescents and adults than in preschool- or school-age children. Encephalitis is a postinfectious, immunologically mediated process and is not the result of a direct effect by the virus. Clinical onset begins during the exanthem and manifests as seizures (56%), lethargy (46%), coma (28%), and irritability (26%). Findings in cerebrospinal fluid include lymphocytic pleocytosis in 85% of cases and elevated protein concentrations. Approximately 15% of patients with measles encephalitis die. Another 20-40% of patients suffer long-term sequelae, including mental retardation, motor disabilities, and deafness.

Measles encephalitis in immunocompromised patients results from direct damage to the brain by the virus. Subacute measles encephalitis manifests 1-10 mo after measles in immunocompromised patients, particularly those with AIDS, lymphoreticular malignancies, and immunosuppression. Signs and symptoms include seizures, myoclonus, stupor, and coma. In addition to intracellular inclusions, abundant viral nucleocapsids and viral antigens are seen in brain tissue. Progressive disease and death rarely almost always occur.

A severe form of measles rarely seen now is hemorrhagic measles or “black measles.” It manifested as a hemorrhagic skin eruption and was often fatal. Keratitis, appearing as multiple punctate epithelial foci, resolved with recovery from the infection. Thrombocytopenia sometimes occurred following measles.

Myocarditis is a rare complication of measles. Miscellaneous bacterial infections have been reported, including bacteremia, cellulitis, and toxic shock syndrome. Measles during pregnancy is associated with high rates of maternal morbidity, fetal wastage, and stillbirths with and congenital malformations in 3% of liveborn infants.

Subacute Sclerosing Panencephalitis
Subacute sclerosing panencephalitis (SSPE) is a chronic complication of measles with a delayed onset and an outcome that is nearly always fatal. It appears to result from a persistent infection with an altered measles virus that is harbored intracellularly in the central nervous system for several years. After 7-10 yr the virus apparently regains virulence and attacks the cells in the central nervous system that offered the virus protection. This “slow virus infection” results in inflammation and cell death, leading to an inexorable neurodegenerative process.

SSPE is a rare disease and generally follows the prevalence of measles in a population. The incidence in the United States in 1960 was 0.61 cases per million persons younger than age 20 yr. By 1980 the rate had fallen to 0.06 cases per million. Between 1956 and 1982 a total of 634 cases of SSPE had been reported to the national SSPE registry. After 1982 approximately 5 cases/yr were reported annually in the United States, and only 2-3 cases/yr were reported in the early 1990s. However, between 1995 and 2000, reported cases in the United States increased and 13 cases were reported in 2000. Nine of the 13 cases occurred in foreign-born individuals. This “resurgence” may be the result of an increased incidence of measles between 1989 and 1991. Although the age of onset ranges from <1 yr to <30 yr, the illness is primarily one of children and adolescents. Measles at an early age favors the development of SSPE: 50% of patients with SSPE had primary measles before 2 yr of age, and 75% had measles before 4 yr of age. Males are affected twice as often as females, and there appear to be more cases reported from rural than urban populations. Recent observations from the registry indicate a higher prevalence among children of Hispanic origin.

The pathogenesis of SSPE remains enigmatic. Factors that seem to be involved include defective measles virus and interaction with a defective or immature immune system. The virus isolated from brain tissue of patients with SSPE is missing 1 of the 6 structural proteins, the matrix or M protein. This protein is responsible for assembly, orientation, and alignment of the virus in preparation for budding during...
viral replication. Immature virus may be able to reside, and possibly propagate, within neuronal cells for long periods. The fact that most patients with SSPE were exposed at a young age suggests that immune immaturity is involved in pathogenesis. In addition, the intracellular location of the virus sequesters it from the immune system, especially from humoral immunity.

Clinical manifestations of SSPE begin insidiously 7-13 yr after primary measles infection. Subtle changes in behavior or school performance appear, including irritability, reduced attention span, and temper outbursts. The initial phase (stage I) may at times be missed because of brevity or mildness of the symptoms. Fever, headache, and other signs of encephalitis are absent. The hallmark of the 2nd stage is massive myoclonus, which coincides with extension of the inflammatory process site to deeper structures in the brain, including the basal ganglia. Involuntary movements and repetitive myoclonic jerks begin in single muscle groups but give way to massive spasms and jerks involving both axial and appendicular muscles. Consciousness is maintained. In the 3rd stage, involuntary movements disappear and are replaced by choreathetosis, immobility, dystonia, and lead pipe rigidity that result from destruction of deeper centers in the basal ganglia. The sensorium deteriorates into dementia, stupor, and then coma. The 4th stage is characterized by loss of critical centers that support breathing, heart rate, and blood pressure. Death soon ensues. Progression through the clinical stages may follow courses characterized as acute, subacute, or chronic progressive.

The diagnosis of SSPE can be established through documentation of a compatible clinical course and at least 1 of the following supporting findings: (1) measles antibody detected in cerebrospinal fluid, (2) characteristic electroencephalographic findings, and (3) typical histologic findings in and/or isolation of virus or viral antigen from brain tissue obtained by biopsy or postmortem examination.

Cerebrospinal fluid analysis reveals normal cells but elevated IgG and IgM antibody titers in dilutions >1:8. Electroencephalographic patterns are normal in stage I, but in the myoclonic phase, suppression-burst episodes are seen that are characteristic of, but not pathognomonic for, SSPE. Brain biopsy is no longer routinely indicated for diagnosis of SSPE.

Management of SSPE is primarily supportive and similar to care provided to patients with other neurodegenerative diseases. Clinical trials using isoprinosine with or without interferon suggest significant benefit (30-34% remission rate) compared to patients without treatment (5-10% with spontaneous remissions).

It is recognized that carbamazepine is of significant benefit in the control of myoclonic jerks in the early stages of the illness. Virtually all patients eventually succumb to SSPE. Most die within 1-3 yr of onset from infection or loss of autonomic control mechanisms. Prevention of SSPE depends on prevention of primary measles infection through vaccination. SSPE has been described in patients who have no history of measles infection and only exposure to the virus. Vitamin A should be administered once daily for 2 days at doses of 200,000 IU for children 12 mo of age or older; 100,000 IU for infants 6 mo through 11 mo of age; and 50,000 IU for infants younger than 6 mo of age.

In children with signs and symptoms of vitamin A deficiency, a 3rd age-appropriate dose is recommended 2 through 4 wk after the 2nd dose.

**Vitamin A**

Vitamin A deficiency in children in developing countries has long been known to be associated with increased mortality from a variety of infectious diseases, including measles. In the United States, studies in the early 1990s documented that 22-72% of children with measles had low retinol levels. In addition, 1 study demonstrated an inverse correlation between the level of retinol and severity of illness. Several randomized controlled trials of vitamin A therapy in the developing world and the United States have demonstrated reduced morbidity and mortality from measles. Vitamin A therapy is indicated for all patients with measles. Vitamin A should be administered once daily for 2 days at doses of 200,000 IU for children 12 mo of age or older; 100,000 IU for infants 6 mo through 11 mo of age; and 50,000 IU for infants younger than 6 mo of age.

**PROGNOSIS**

In the early 20th century, deaths from measles in the United States varied between 2,000 and 10,000 per year, or about 10 deaths per 1,000 cases of measles. With improvements in healthcare and antimicrobial therapy, better nutrition, and decreased crowding, the death:case ratio fell to 1 per 1,000 cases. Between 1982 and 2002, the CDC estimated that there were 259 deaths caused by measles in the United States, with a death:case ratio of 2.5-2.8 per 1,000 cases of measles. Pneumonia and encephalitis were complications in most of the fatal cases, and immunodeficiency conditions were identified in 14-16% of deaths. In 2011, of the 222 cases reported in the United States, 70 (32%) were hospitalized, including 17 (24%) with diarrhea, 15 (21%) with dehydration, and 12 (17%) with pneumonia. No cases of encephalitis or deaths were reported.

**PREVENTION**

Patients shed measles virus from 7 days after exposure to 4-6 days after the onset of rash. Exposure of susceptible individuals to patients with measles should be avoided during this period. In hospitals, standard and airborne precautions should be observed for this period. Immunocompromised patients with measles will shed virus for the duration of the illness, so isolation should be maintained throughout the disease.

**Vaccine**

Measles vaccine in the United States is available as a monovalent preparation or combined with the measles-rubella or measles-mumps-rubella vaccine, the last of which is the recommended form in most circumstances (Table 246-2). Following the measles resurgence of 1989-1991, a 2nd dose of measles vaccine was added to the schedule. The current recommendations include a 1st dose at 12-15 mo of age, followed by a 2nd dose at 4-6 yr of age. Seroconversion is slightly lower in children who receive the 1st dose before or at 12 mo of age (87% at 9 mo, 95% at 12 mo, and 98% at 15 mo) because of persisting maternal antibody. For children who have not received 2 doses by 11-12 yr of age, a 2nd dose should be provided. Infants who receive a dose before 12 mo of age should be given 2 additional doses at 12-15 mo and 4-6 yr of age.

Adverse events from the measles-mumps-rubella vaccine include fever (usually 6-12 days following vaccination), rash in approximately 5% of vaccinated persons, and, rarely, transient thrombocytopenia. Children prone to febrile seizures may experience an event following vaccination, so the risks and benefits of vaccination should be discussed with parents. Encephalopathy and autism have not been shown to be causally associated with the measles-mumps-rubella vaccine or vaccine constituents.

A review of the effect of measles vaccination on the epidemiology of SSPE has demonstrated that measles vaccination protects against SSPE and does not accelerate the course of SSPE or trigger the disease in those already infected with wild measles virus.

Passively administered immune globulin may inhibit the immune response to live measles vaccine, and administration should be delayed for variable amounts of time based on the dose of immune globulin (Table 246-3).
### Table 246-2  Recommendations for Measles Immunization

<table>
<thead>
<tr>
<th>CATEGORY</th>
<th>RECOMMENDATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unimmunized, no history of measles (12-15 mo of age)</td>
<td>A 2 dose schedule (with MMR) is recommended. The 1st dose is recommended at 12-15 mo of age; the 2nd is recommended at 4-6 yr of age</td>
</tr>
<tr>
<td>Children 6-11 mo of age in epidemic situations or prior to international travel</td>
<td>Immunize with MMR vaccine, but this dose is not considered valid, and 2 valid doses administered on or after the 1st birthday are required. The 1st valid dose should be administered at 12-15 mo of age. The 2nd valid dose is recommended at least 28 days later and is given at 4 through 6 yr of age</td>
</tr>
<tr>
<td>Students in kindergarten or elementary, middle, and high school who have received 1 dose of measles vaccine at 12 mo of age or older</td>
<td>Administer the 2nd dose</td>
</tr>
<tr>
<td>Students in college and other post–high school institutions who have received 1 dose of measles vaccine at ≥12 mo of age</td>
<td>Administer the 2nd dose</td>
</tr>
<tr>
<td>History of immunization before the 1st birthday</td>
<td>Do not consider valid and immunize (2 doses)</td>
</tr>
<tr>
<td>History of receipt of inactivated measles vaccine or unknown type of vaccine, 1963-1967</td>
<td>Do not consider valid and immunize (2 doses)</td>
</tr>
<tr>
<td>Further attenuated or unknown vaccine given with Ig</td>
<td>Do not consider valid and immunize (2 doses)</td>
</tr>
<tr>
<td>Allergy to eggs</td>
<td>Immunize; no reactions likely</td>
</tr>
<tr>
<td>Neomycin allergy, nonanaphylactic</td>
<td>Immunize; no reactions likely</td>
</tr>
<tr>
<td>Severe hypersensitivity (anaphylaxis) to neomycin or gelatin</td>
<td>Avoid immunization</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>Immunize; if patient has untreated tuberculosis disease, start antituberculosis therapy before immunizing</td>
</tr>
<tr>
<td>Measles exposure</td>
<td>Immunize and/or give Ig, depending on circumstances</td>
</tr>
<tr>
<td>HIV-infected</td>
<td>Immunize (2 doses) unless severely immunocompromised, and give Ig if exposed to measles</td>
</tr>
<tr>
<td>Personal or family history of seizures</td>
<td>Immunize; advise parents of slightly increased risk of seizures</td>
</tr>
<tr>
<td>Ig or blood recipient</td>
<td>Immunize at the appropriate interval (see Table 246-3)</td>
</tr>
</tbody>
</table>

Ig, immunoglobulin; MMR, measles-mumps-rubella vaccine.


### Table 246-3  Suggested Intervals Between Immunoglobulin Administration and Measles Immunization

<table>
<thead>
<tr>
<th>INDICATION FOR IMMUNOGLOBULIN</th>
<th>ROUTE</th>
<th>UNITS (U) OR MILLILITERS (mL)</th>
<th>mg IgG/kg</th>
<th>INTERVAL (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tetanus (as tetanus Ig)</td>
<td>IM</td>
<td>250 U</td>
<td>10</td>
<td>3</td>
</tr>
<tr>
<td>Hepatitis A prophylaxis (as Ig):</td>
<td>IM</td>
<td>0.02 mL/kg</td>
<td>3.3</td>
<td>3</td>
</tr>
<tr>
<td>Contact prophylaxis</td>
<td>IM</td>
<td>0.06 mL/kg</td>
<td>10</td>
<td>3</td>
</tr>
<tr>
<td>International travel</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatitis B prophylaxis (as hepatitis B Ig)</td>
<td>IM</td>
<td>0.06 mL/kg</td>
<td>10</td>
<td>3</td>
</tr>
<tr>
<td>Rabies prophylaxis (as rabies Ig)</td>
<td>IM</td>
<td>20 IU/kg</td>
<td>22</td>
<td>4</td>
</tr>
<tr>
<td>Varicella prophylaxis (as VarizIG)</td>
<td>IM</td>
<td>125 U/10 kg (maximum 625 U)</td>
<td>20-40</td>
<td>5</td>
</tr>
<tr>
<td>Measles prophylaxis (as Ig):</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standard</td>
<td>IM</td>
<td>0.25 mL/kg</td>
<td>40</td>
<td>5</td>
</tr>
<tr>
<td>Immunocompromised host</td>
<td>IM</td>
<td>0.50 mL/kg</td>
<td>80</td>
<td>6</td>
</tr>
<tr>
<td>Respiratory syncytial virus prophylaxis (palivizumab monoclonal antibody)</td>
<td>IM</td>
<td>—</td>
<td>15 mg/kg (monoclonal)</td>
<td>None</td>
</tr>
<tr>
<td>Cytomegalovirus immune globulin</td>
<td>IV</td>
<td>3 mL/kg</td>
<td>150</td>
<td>6</td>
</tr>
<tr>
<td>Blood transfusion:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Washed RBCs</td>
<td>IV</td>
<td>10 mL/kg</td>
<td>Negligible</td>
<td>0</td>
</tr>
<tr>
<td>RBCs, adenine-saline added</td>
<td>IV</td>
<td>10 mL/kg</td>
<td>10</td>
<td>3</td>
</tr>
<tr>
<td>Packed RBCs</td>
<td>IV</td>
<td>10 mL/kg</td>
<td>20-60</td>
<td>5</td>
</tr>
<tr>
<td>Whole blood</td>
<td>IV</td>
<td>10 mL/kg</td>
<td>80-100</td>
<td>6</td>
</tr>
<tr>
<td>Plasma or platelet products</td>
<td>IV</td>
<td>10 mL/kg</td>
<td>160</td>
<td>7</td>
</tr>
</tbody>
</table>

Continued
### Table 246-3  Suggested Intervals Between Immunoglobulin Administration and Measles Immunization*—cont’d

<table>
<thead>
<tr>
<th>INDICATION FOR IMMUNOGLOBULIN</th>
<th>ROUTE</th>
<th>UNITS (U) OR MILLILITERS (mL)</th>
<th>mg IgG/kg</th>
<th>INTERVAL (mo)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Replacement (or therapy) of immune deficiencies (as IVIG)</td>
<td>IV</td>
<td>—</td>
<td>300-400</td>
<td>8</td>
</tr>
<tr>
<td>ITP (as IVIG)</td>
<td>IV</td>
<td>—</td>
<td>400</td>
<td>8</td>
</tr>
<tr>
<td>ITP</td>
<td>IV</td>
<td>—</td>
<td>1,000</td>
<td>10</td>
</tr>
<tr>
<td>ITP or Kawasaki disease</td>
<td>IV</td>
<td>—</td>
<td>1,600-2,000</td>
<td>11</td>
</tr>
</tbody>
</table>

*Immunization in the form of measles-mumps-rubella (MMR), measles-mumps-rubella-varicella (MMRV), or monovalent measles vaccine.
†These intervals should provide sufficient time for decreases in passive antibodies in all children to allow for an adequate response to measles vaccine. Physicians should not assume that children are fully protected against measles during these intervals. Additional doses of Ig or measles vaccine may be indicated after exposure to measles (see text).
‡Monoclonal antibodies, such as palivizumab, do not interfere with the immune response to vaccines.

| Ig, immunoglobulin; IgG, immunoglobulin G; ITP, immune (formerly termed “idiopathic”) thrombocytopenic purpura; IVIG, intravenous Ig; RBCs, red blood cells. |


Live vaccines should not be administered to pregnant women or to immunodeficient or immunosuppressed patients. However, patients with HIV who are not severely immunocompromised should be immunized. Because measles virus may suppress the cutaneous response to tuberculosis antigen, skin testing for tuberculosis should be performed before or at the same time as administration of the vaccine. Individuals infected with *M. tuberculosis* should be receiving appropriate treatment at the time of administration of measles vaccine.

**Postexposure Prophylaxis**

Susceptible individuals exposed to measles may be protected from infection by either vaccine administration or immunization with immune globulin. The vaccine is effective in prevention or modification of measles if given within 72 hr of exposure. Immune globulin may be given up to 6 days after exposure to prevent or modify infection. Immunocompetent children should receive 0.25 mL/kg intramuscularly, and immunocompromised children should receive 0.5 mL/kg (maximum dose in both cases is 15 mL/kg). Immune globulin is indicated for susceptible household contacts of measles patients, especially infants younger than 6 mo of age, pregnant women, and immunocompromised persons.

*Bibliography is available at Expert Consult.*
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Rubella (German measles or 3 day measles) is a mild, often exanthematous disease of infants and children that is typically more severe and associated with more complications in adults. Its major clinical significance is transplacental infection and fetal damage as part of the congenital rubella syndrome (CRS).

**ETIOLOGY**

Rubella virus is a member of the family Togaviridae and is the only species of the genus Rubivirus. It is a single-stranded RNA virus with a lipid envelope and 3 structural proteins, including a nucleocapsid protein that is associated with the nucleus and 2 glycoproteins, E1 and E2, that are associated with the envelope. The virus is sensitive to heat, ultraviolet light, and extremes of pH but is relatively stable at cold temperatures. Humans are the only known host.

**EPIDEMILOGY**

In the prevaccine era, rubella appeared to occur in major epidemics every 6-9 yr, with smaller peaks interspersed every 3-4 yr, and was most common in preschool-age and school-age children. During the rubella epidemic of 1964-1965 there were an estimated 12.5 million cases of rubella associated with 2,000 cases of encephalitis, more than 13,000 abortions or perinatal deaths, and 20,000 cases of CRS. Following introduction of the rubella vaccine in 1969, the incidence of rubella fell 78% by 1976 and CRS cases fell 69% (Fig. 247-1). Further decline in rubella and CRS cases occurred when certain at-risk populations were added to those for whom rubella immunization is indicated, including adolescents and college students. After years of decline, a resurgence of rubella and CRS cases occurred during 1989-1991 in association with the epidemic of measles during that period (Fig. 247-1). Subsequently, a 2 dose recommendation for rubella vaccine was implemented and resulted in a decrease in incidence of rubella from 0.45 per 100,000 population in 1990 to 0.1 per 100,000 in 1999 and a corresponding decrease of CRS, with an average of 6 infants with CRS reported annually from 1992-2004. Mothers of these infants tended to be young, Hispanic, or foreign born. The number of reported cases of rubella continued to decline through the 1990s and first decade of this century.

The endemic spread of rubella has been eliminated in the United States; elimination of transmission of rubella in the Americas also may have been achieved. However, cases of rubella continue to be imported...
into the United States from countries where it remains endemic. From 2004-2012 there were 79 cases of rubella and 6 cases of CRS, all of which were imported cases of unknown source. Three of the CRS cases were acquired in Africa. Between January 1 and May 1, 2013, 5,442 cases of rubella and 10 cases of CRS were reported, demonstrating that the elimination of rubella internationally has not been achieved and continued vigilance and maintenance of high levels of immunity in the United States are necessary.

PATHOLOGY
Little information is available on the pathologic findings in rubella occurring postnatally. The few reported studies of biopsy or autopsy material from cases of rubella revealed only nonspecific findings of lymphoreticular inflammation and mononuclear perivascular and meningeal infiltration. The pathologic findings for CRS are often severe and may involve nearly every organ system (Table 247-1).

PATHOGENESIS
The viral mechanisms for cell injury and death in postnatal or congenital rubella are not well understood. Following infection, the virus replicates in the respiratory epithelium and then spreads to regional lymph nodes (Fig. 247-2). Viremia ensues and is most intense from 10-17 days after infection. Viral shedding from the nasopharynx begins approximately 10 days after infection and may be detected up to 2 wk following onset of the rash. The period of highest communicability is from 5 days before to 6 days after the appearance of the rash.

The most important risk factor for severe congenital defects is the stage of gestation at the time of infection. Maternal infection during the 1st 8 wk of gestation results in the most severe and widespread defects. The risk for congenital defects has been estimated at 90% for maternal infection before 11 wk of gestation, 33% at 11-12 wk, 11% at 13-14 wk, and 24% at 15-16 wk. Defects occurring after 16 wk of gestation are uncommon, even if fetal infection occurs.

Causes of cellular and tissue damage in the infected fetus may include tissue necrosis due to vascular insufficiency, reduced cellular multiplication time, chromosomal breaks, and production of a protein inhibitor causing mitotic arrests in certain cell types. The most distinctive feature of congenital rubella is chronicity. Once the fetus is infected early in gestation, the virus persists in fetal tissue until well beyond delivery. Persistence suggests the possibility of ongoing tissue damage and reactivation, most notably in the brain.

CLINICAL MANIFESTATIONS
Postnatal infection with rubella is a mild disease not easily discernible from other viral infections, especially in children. Following an incubation period of 14-21 days, a prodrome consisting of low-grade fever, sore throat, red eyes with or without eye pain, headache, malaise, anorexia, and lymphadenopathy begins. Suboccipital, postauricular, and anterior cervical lymph nodes are most prominent. In children, the first manifestation of rubella is usually the rash, which is variable and not distinctive. It begins on the face and neck as small, irregular pink macules that coalesce, and it spreads centrifugally to involve the torso and extremities, where it tends to occur as discrete macules (Fig. 247-3). About the time of onset of the rash, examination of the oropharynx may reveal tiny, rose-colored lesions (Forchheimer spots).

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Table 247-1. Pathologic Findings in Congenital Rubella Syndrome

<table>
<thead>
<tr>
<th>SYSTEM</th>
<th>PATHOLOGIC FINDINGS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular</td>
<td>Patent ductus arteriosus, Pulmonary artery stenosis, Ventriculoseptal defect, Myocarditis</td>
</tr>
<tr>
<td>Central nervous system</td>
<td>Chronic meningitis, Parenchymal necrosis, Vasculitis with calcification</td>
</tr>
<tr>
<td>Eye</td>
<td>Microphthalmia, Cataract, Iridocyclitis, Ciliary body necrosis, Glaucoma, Retinopathy</td>
</tr>
<tr>
<td>Ear</td>
<td>Cochlear hemorrhage, Endothelial necrosis</td>
</tr>
<tr>
<td>Lung</td>
<td>Chronic mononuclear interstitial pneumonitis</td>
</tr>
<tr>
<td>Liver</td>
<td>Hepatic giant cell transformation, Fibrosis, Lobular disarray, Bile stasis</td>
</tr>
<tr>
<td>Kidney</td>
<td>Interstitial nephritis</td>
</tr>
<tr>
<td>Adrenal gland</td>
<td>Cortical cytomegaly</td>
</tr>
<tr>
<td>Bone</td>
<td>Malformed osteoid, Poor mineralization of osteoid, Thinning cartilage</td>
</tr>
<tr>
<td>Spleen, lymph node</td>
<td>Extramedullary hematopoiesis</td>
</tr>
<tr>
<td>Thymus</td>
<td>Histiocytic reaction, Absence of germinal centers</td>
</tr>
<tr>
<td>Skin</td>
<td>Erythropoiesis in dermis</td>
</tr>
</tbody>
</table>

Figure 247-2. Pathophysiologic events in postnatally acquired rubella virus infection. *Possible complications include arthralgia and/or arthritis, thrombocytopenic purpura, and encephalitis. CF, complement fixation titer; HI, hemagglutination-inhibition titer. (From Lamprecht CL: Rubella virus. In Beshe RB, editor: Textbook of human virology, ed 2, Littleton, MA, 1990, PSG Publishing, p. 685.)
or petechial hemorrhages on the soft palate. The rash fades from the face as it extends to the rest of the body so that the whole body may not be involved at any one time. The duration of the rash is generally 3 days, and it usually resolves without desquamation. Subclinical infections are common, and 25-40% of children may not have a rash.

LABORATORY FINDINGS

Leukopenia, neutropenia, and mild thrombocytopenia have been described during postnatal rubella.

DIAGNOSES

A specific diagnosis of rubella is important for epidemiologic reasons, for diagnosis of infection in pregnant women, and for confirmation of the diagnosis of congenital rubella. The most common diagnostic test is rubella immunoglobulin (Ig) M enzyme immunsorbent assay. As with any serologic test, the positive predictive value of testing decreases in populations with low prevalence of disease. Tests should be performed in the context of a supportive history of exposure or consistent clinical findings. The relative sensitivity and specificity of commercial kits used in most laboratories range from 96-99% and 86-97%, respectively. A caveat for testing of congenitally infected infants early in infancy is that false-negative results may occur owing to competing IgG antibodies circulating in these patients. In such patients, an IgM capture assay, reverse transcriptase polymerase chain reaction test, or viral culture should be performed for confirmation.

DIFFERENTIAL DIAGNOSES

Rubella may manifest as distinctive features suggesting the diagnosis. It is frequently confused with other infections because it is uncommon, similar to other viral exanthematous diseases, and demonstrates variability in the presence of typical findings. In severe cases, it may resemble measles. The absence of Koplik spots and a severe prodrome as well as a shorter course allow for differentiation from measles. Other diseases frequently confused with rubella include infections caused by adenoviruses, parvovirus B19 (erythema infectiosum), Epstein-Barr virus, enteroviruses, and *Mycoplasma pneumoniae*.

COMPLICATIONS

Complications following postnatal infection with rubella are infrequent and generally not life-threatening.

Postinfectious *thrombocytopenia* occurs in approximately 1 in 3,000 cases of rubella and occurs more frequently among children and in girls. It manifests about 2 wk following the onset of the rash as petechiae, epistaxis, gastrointestinal bleeding, and hematuria. It is usually self-limited.

*Arthritis* following rubella occurs more commonly among adults, especially women. It begins within 1 wk of onset of the exanthem and classically involves the small joints of the hands. It also is self-limited and resolves within weeks without sequelae. There are anecdotal reports and some serologic evidence linking rubella with rheumatoid arthritis, but a true causal association remains speculative.

*Encephalitis* is the most serious complication of postnatal rubella. It occurs in 2 forms: a postinfectious syndrome following acute rubella and a rare progressive panencephalitis manifesting as a neurodegenerative disorder years following rubella.

Postinfectious encephalitis is uncommon, occurring in 1 in 5,000 cases of rubella. It appears within 7 days after onset of the rash, consisting of headache, seizures, confusion, coma, focal neurologic signs, and ataxia. Fever may recrudesce with the onset of neurologic symptoms. Cerebrospinal fluid may be normal or have a mild mononuclear pleocytosis and/or elevated protein concentration. Virus is rarely, if ever, isolated from cerebrospinal fluid or brain, suggesting a noninfectious pathogenesis. Most patients recover completely, but mortality rates of 20% and long-term neurologic sequelae have been reported.

Progressive rubella panencephalitis (PRP) is an extremely rare complication of either acquired rubella or CRS. It has an onset and course similar to those of the subacute sclerosing panencephalitis associated with measles (see Chapter 246). Unlike in the postinfectious form of rubella encephalitis, however, rubella virus may be isolated from brain tissue of the patient with PRP, suggesting an infectious pathogenesis, albeit a “slow” one. The clinical findings and course are indistinguishable from those of subacute sclerosing panencephalitis and transmissible spongiform encephalopathies (see Chapter 278). Death occurs 2-5 yr after onset.

Other neurologic syndromes rarely reported with rubella include Guillain-Barré syndrome and peripheral neuritis. Myocarditis is a rare complication.

**Congenital Rubella Syndrome**

In 1941, an ophthalmologist first described a syndrome of cataracts and congenital heart disease that he correctly associated with rubella infections in the mothers during early pregnancy (Table 247-2). Shortly after the first description, hearing loss was recognized as a common

**Table 247-2 Clinical Manifestations of Congenital Rubella Syndrome in 376 Children Following Maternal Rubella**

<table>
<thead>
<tr>
<th>MANIFESTATION</th>
<th>RATE (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Otar deafness</td>
<td>67</td>
</tr>
<tr>
<td>Ocular</td>
<td>71</td>
</tr>
<tr>
<td>Cataracts</td>
<td>29</td>
</tr>
<tr>
<td>Retinopathy</td>
<td>39</td>
</tr>
<tr>
<td>Heart disease*</td>
<td>48</td>
</tr>
<tr>
<td>Patent ductus arteriosus</td>
<td>78</td>
</tr>
<tr>
<td>Right pulmonary artery stenosis</td>
<td>70</td>
</tr>
<tr>
<td>Left pulmonary artery stenosis</td>
<td>56</td>
</tr>
<tr>
<td>Valvular pulmonic stenosis</td>
<td>40</td>
</tr>
<tr>
<td>Low birthweight</td>
<td>60</td>
</tr>
<tr>
<td>Psychomotor retardation</td>
<td>45</td>
</tr>
<tr>
<td>Neonatal purpura</td>
<td>23</td>
</tr>
<tr>
<td>Death</td>
<td>35</td>
</tr>
</tbody>
</table>

*Other findings: hepatitis, linear streaking of bone, hazy cornea, congenital glaucoma, delayed growth.

†Findings in 87 patients with congenital rubella syndrome and heart disease who underwent cardiac angiography.

finding often associated with microcephaly. In 1964-1965 a pandemic of rubella occurred, with 20,000 cases reported in the United States, leading to more than 11,000 spontaneous or therapeutic abortions and 2,100 neonatal deaths. From this experience emerged the expanded definition of CRS that includes numerous other transient or permanent abnormalities.

Nerve deafness is the single most common finding among infants with CRS. Most infants have some degree of intrauterine growth restriction. Retinal findings described as salt-and-pepper retinopathy are the most common ocular abnormality but have little early effect on vision. Unilateral or bilateral cataracts are the most serious eye finding, occurring in about a third of infants (Fig. 247-4). Cardiac abnormalities occur in half of the children infected during the 1st 8 wk of gestation. Patent ductus arteriosus is the most frequently reported cardiac defect, followed by lesions of the pulmonary arteries and valvular disease. Interstitial pneumonitis leading to death in some cases has been reported. Neurologic abnormalities are common and may progress following birth. Meningoencephalitis is present in 10-20% of infants with CRS and may persist for up to 12 mo. Longitudinal follow-up through 9-12 yr of infants without initial retardation revealed progressive development of additional sensory, motor, and behavioral abnormalities, including hearing loss and autism. PRP has also been recognized rarely after CRS. Subsequent postnatal growth retardation and ultimate short stature have been reported in a minority of cases. Rare reports of immunologic deficiency syndromes have also been described.

A variety of late-onset manifestations of CRS have been recognized. In addition to PRP, they include diabetes mellitus (20%), thyroid dysfunction (5%), and glaucoma and visual abnormalities associated with the retinopathy, which had previously been considered benign.

TREATMENT
There is no specific treatment available for either acquired rubella or CRS.

SUPPORTIVE CARE
Postnatal rubella is generally a mild illness that requires no care beyond antipyretics and analgesics. Intravenous immunoglobulin or corticosteroids can be considered for severe, nonremitting thrombocytopenia.

Management of children with CRS is more complex and requires pediatric, cardiac, audiologic, ophthalmologic, and neurologic evaluation and follow-up because many manifestations may not be readily apparent initially or may worsen with time. Hearing screening is of special importance, because early intervention may improve outcomes in children with hearing problems caused by CRS.

PROGNOSIS
Postnatal infection with rubella has an excellent prognosis. Long-term outcomes of CRS are less favorable and somewhat variable. In an Australian cohort evaluated 50 yr after infection, many had chronic conditions but most were married and had made good social adjustments. A cohort from New York from the mid-1960s epidemic had less-favorable outcomes, with 30% leading normal lives, 30% in dependent situations but functional, and 30% requiring institutionalization and continuous care.

Reinfection with wild virus occurs postnataally in both individuals who were previously infected with wild-virus rubella and in vaccinated individuals. Reinfection is defined serologically as a significant increase in IgG antibody level and/or an IgM response in an individual who has a documented preexisting rubella-specific IgG above an accepted cutoff. Reinfection may result in an anamnestic IgG response, an IgM and IgG response, or clinical rubella. There are 29 reports of CRS following maternal reinfection in the literature. Reinfection with serious adverse outcomes to adults or children is rare and of unknown significance.

PREVENTION
Patients with postnatal infection should be isolated from susceptible individuals for 7 days after onset of the rash. Standard plus droplet precautions are recommended for hospitalized patients. Children with CRS may excrete the virus in respiratory secretions up to 1 yr of age, so contact precautions should be maintained for them until then, unless repeated cultures of urine and pharyngeal secretions have negative results. Similar precautions apply to patients with CRS with regard to attendance in school and out-of-home childcare.

Exposure of susceptible pregnant women poses a potential risk to the fetus. For pregnant women exposed to rubella, a blood specimen should be obtained as soon as possible for rubella IgG-specific antibody testing; a frozen aliquot also should be saved for later testing. If the rubella antibody test result is positive, the mother is likely immune. If the rubella antibody test is negative, a 2nd specimen should be obtained 2-3 wk later and tested concurrently with the saved specimen. If both of these test negative, a 3rd specimen should be obtained 6 wk after exposure and tested concurrently with the saved specimen. If both the 2nd and 3rd specimens test negative, infection has not occurred. A negative 1st specimen and a positive test result in either the 2nd and 3rd specimens indicate that seroconversion has occurred in the mother, suggesting recent infection. Counseling should be provided about the risks and benefits of termination of pregnancy. The routine use of immunoglobulin for susceptible pregnant women exposed to rubella is not recommended and is considered only if termination of pregnancy is not an option because of maternal preferences. In such circumstances, immunoglobulin 0.55 mL/kg IM may be given with the understanding that prophylaxis may reduce the risk for clinically apparent infection but does not guarantee prevention of fetal infection.

VACCINATION
Rubella vaccine in the United States consists of the attenuated Wistar RA 27/3 strain that is usually administered in combination with measles and mumps (MMR) or also with varicella (MMRV) in a 2 dose regimen at 12-15 mo and 4-6 yr of age. It theoretically may be effective as postexposure prophylaxis if administered within 3 days of exposure. Vaccine should not be administered to severely immunocompromised patients (e.g., transplant recipients). Patients with HIV infection who are not severely immunocompromised may benefit from vaccination. Fever is not a contraindication, but if a more serious illness is suspected, immunization should be delayed. Immunoglobulin preparations may inhibit the serologic response to the vaccine (see Chapter 172). Vaccine should not be administered during pregnancy. If pregnancy occurs within 28 days of immunization, the patient should be counseled on the theoretical risks to the fetus. Studies of more than 200 women who had been inadvertently immunized with rubella vaccine during pregnancy showed that none of their offspring developed CRS. Therefore, interruption of pregnancy is probably not warranted.

Following a single dose of rubella RA 27/3 vaccine, 95% of persons 12 mo of age and older develop serologic immunity, and after 2 doses 99% have detectable antibody. Rubella RA 27/3 vaccine is highly protective as 97% of those vaccinated are protected from clinical disease after
1 dose. Detectable antibodies remain for 15 yr in most individuals vaccinated following 1 dose, and 91% to 100% had antibodies after 12-15 yr after 2 doses. Although antibody levels may wane, especially after 1 dose of vaccine, increased susceptibility to rubella disease does not occur.

Adverse reactions to rubella vaccination are uncommon in children. MMR administration is associated with fever in 5-15% of vaccinees and with rash in approximately 5% of vaccinees. Arthralgia and arthritis are more common following rubella vaccination in adults. Approximately 25% of postpubertal women experience arthralgia, and 10% experience arthritis.Peripheral neuropathies and transient thrombocytopenia may also occur.

As part of the worldwide effort to eliminate endemic rubella virus transmission and occurrence of CRS, maintaining high population immunity through vaccination coverage and high-quality integrated measles-rubella surveillance have been emphasized as being vital to its success.

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Mumps is an acute self-limited infection that was once commonplace but is now unusual in developed countries because of widespread use of vaccination. It is characterized by fever, bilateral or unilateral parotid swelling and tenderness, and the frequent occurrence of meningoencephalitis and orchitis. Although no longer common in countries with extensive vaccination programs, mumps remains endemic in the rest of the world, warranting continued vaccine protection.

ETIOLOGY
Mumps virus is in the family Paramyxoviridae and the genus Rubulavirus. It is a single-stranded pleomorphic RNA virus encapsulated in a lipoprotein envelope and possessing 7 structural proteins. Surface glycoproteins called HN (hemagglutinin-neuraminidase) and F (fusion) mediate absorption of the virus to host cells and penetration of the virus into cells, respectively. Both of these proteins stimulate production of protective antibodies. Mumps virus exists as a single immunotype, and humans are the only natural host.

EPIDEMIOLOGY
In the prevaccine era, mumps occurred primarily in young children between the ages of 5 and 9 yr and in epidemics about every 4 yr. Mumps infection occurred more often in the winter and spring months. In 1968, just after the introduction of the mumps vaccine, 185,691 cases were reported in the United States. The following recommendation for routine use of mumps vaccine in 1977, the incidence of mumps fell dramatically in young children (Fig. 248-1) and shifted instead to older children, adolescents, and young adults. Outbreaks continued to occur even in highly vaccinated populations as a result of vaccine failure and also because of undervaccination of susceptible persons. After implementation of the 2-dose recommendation for the measles-mumps-rubella (MMR) vaccine for measles control in 1989, the number of mumps cases declined further. During 2001-2003, fewer than 300 mumps cases were reported each year. In 2006, the largest mumps epidemic in the last 20 yr occurred in the United States. A total of 6,584 cases occurred, 85% of them in 8 midwestern states. Twenty-nine percent of the cases occurred in patients 18-24 yr old, most of whom were attending college. An analysis of 4,039 patients with mumps seen in the 1st 7 mo of the epidemic indicated that 63% had received more than 2 doses of the MMR vaccine. Subsequently, several outbreaks of mumps have been documented in highly vaccinated populations in the Northeast United States, in a large public university in the Western United States, and in Guam.

Figure 248-1 Mumps cases in the United States from 1967, when the live mumps vaccine was introduced, to 2011. There was a steady decline following introduction of the vaccine and recommendation for routine vaccination in 1977 (arrow). Note national increases in activity in 1986-1987 and 2006. Mumps data provided were reported voluntarily to Centers for Disease Control and Prevention from state health departments. (From McLean HQ, Fiebelkorn AP, Temple JL, Wallace GS: Prevention of measles, rubella, congenital rubella syndrome and mumps, 2013, MMWR Recomm Rep 62(RR-04):1-34, 2013.)

Mumps is spread from person to person by respiratory droplets. Virus appears in the saliva from up to 7 days before to as long as 7 days after onset of parotid swelling. The period of maximum infectiousness is 1-2 days before to 5 days after onset of parotid swelling. Viral shedding before onset of symptoms and in asymptomatic infected individuals impairs efforts to contain the infection in susceptible populations. The U.S. Centers for Disease Control and Prevention, the American Academy of Pediatrics, and the Health Infection Control Practices Advisory Committee recommend an isolation period of 5 days after onset of parotiditis for patients with mumps in both community and healthcare settings.

PATHOLOGY AND PATHOGENESIS
Mumps virus targets the salivary glands, central nervous system (CNS), pancreas, testes, and, to a lesser extent, thyroid, ovaries, heart, kidneys, liver, and joint synovia.

Following infection, initial viral replication occurs in the epithelium of the upper respiratory tract. Infection spreads to the adjacent lymph nodes by the lymphatic drainage, and viremia ensues, spreading the virus to targeted tissues. Mumps virus causes necrosis of infected cells and is associated with a lymphocytic inflammatory infiltrate. Salivary gland ducts are lined with necrotic epithelium, and the interstitium is infiltrated with lymphocytes. Swelling of tissue within the testes may result in focal ischemic infarcts. The cerebrospinal fluid (CSF) frequently contains a mononuclear pleocytosis, even in individuals without clinical signs of meningitis.

CLINICAL MANIFESTATIONS
The incubation period for mumps ranges from 12-25 days but is usually 16-18 days. Mumps virus infection may result in clinical presentation ranging from asymptomatic or nonspecific symptoms to the typical illness associated with parotitis with or without complications involving several body systems. The typical patient presents with a prodrome lasting 1-2 days and consisting of fever, headache, vomiting, and achiness. Parotitis then appears and may be unilateral initially but becomes bilateral in approximately 70% of cases (Fig. 248-2). The parotid gland is tender, and parotitis may be preceded or accompanied by ear pain on the ipsilateral side. Ingestion of sour or acidic foods or liquids may enhance pain in the parotid area. As swelling progresses, the angle of the jaw is obscured and the ear lobe may be lifted upward and outward (Figs. 248-2 and 248-3). The opening of the Stensen duct may be red and edematous. The parotid swelling peaks in approximately 3 days and then gradually subsides over 7 days. Fever and the
DIFFERENTIAL DIAGNOSIS
Parotid swelling may be caused by many other infectious and noninfectious conditions. Viruses that cause parotitis include parainfluenza 1 and parainfluenza 3 viruses, influenza A virus, cytomegalovirus, Epstein-Barr virus, enteroviruses, lymphocytic choriomeningitis virus, and HIV. Purulent parotitis, usually caused by Staphylococcus aureus, is unilateral, is extremely tender, is associated with an elevated white blood cell count, and may involve purulent drainage from the Stensen duct. Submandibular or anterior cervical adenitis from a variety of pathogens may also be confused with parotitis. Other noninfectious causes of parotid swelling include obstruction of the Stensen duct, collagen vascular diseases such as Sjögren syndrome, systemic lupus erythematosus, and tumor.

COMPLICATIONS
The most common complications of mumps are meningitis, with or without encephalitis, and gonadal involvement. Uncommon complications include conjunctivitis, optic neuritis, pneumonia, nephritis, pancreatitis, and thrombocytopenia. Maternal infection with mumps during the 1st trimester of pregnancy results in increased fetal wastage. No fetal malformations have been associated with intrauterine mumps infection. However, perinatal mumps disease has been reported in infants born to mothers who acquired mumps late in gestation.

Meningitis and Meningoencephalitis
Mumps virus is neurotropic and is thought to enter the CNS via the choroid plexus and infect the choroidal epithelium and ependymal cells, both of which can be found in CSF along with mononuclear leukocytes. Symptomatic CNS involvement occurs in 10-30% of infected individuals, but CSF pleocytosis has been found in 40-60% of patients with mumps parotitis. The meningooencephalitis may occur before, along with, or following the parotitis. It most commonly manifests 5 days after the parotitis. Clinical findings vary with age. Infants and young children have fever, malaise, and lethargy, whereas older children, adolescents, and adults complain of headache and demonstrate meningeal signs. In 1 series of children with mumps and meningoencephalitis, findings were fever in 94%, vomiting in 84%, headache in 47%, parotitis in 47%, neck stiffness in 71%, lethargy in 69%, and seizures in 18%. In typical cases, symptoms resolve in 7-10 days. CSF in mumps meningitis has a white blood cell pleocytosis of 200-600/µL with a predominance of lymphocytes. The CSF glucose content is normal in most patients, but a moderate hypoglycrrachia (glucose content 20-40 mg/dL) may be seen in 10-20% of patients. The CSF protein content is normal or mildly elevated. Less-common CNS complications of mumps include transverse myelitis, aqueductal stenosis, and facial palsy. Sensorineural hearing loss is rare and has been estimated to occur in 0.5-5.0 in 100,000 cases of mumps. There is some evidence that this sequela is more likely in patients with meningooencephalitis.

Orchitis and Oophoritis
In adolescent and adult males, orchitis is second only to parotitis as a common finding in mumps. Involvement in prepubescent boys is extremely rare, but after puberty, orchitis occurs in 30-40% of males. It begins within days following onset of parotitis in the majority of cases and is associated with moderate to high fever, chills, and exquisite pain and swelling of the testes. In 30% or less of cases, the orchitis is bilateral. Atrophy of the testes may occur, but sterility is rare even with bilateral involvement.
Oophoritis is uncommon in postpubertal females but may cause severe pain and may be confused with appendicitis when located on the right side.

**Pancreatitis**

Pancreatitis may occur in mumps with or without parotid involvement. Severe disease is rare, but fever, epigastric pain, and vomiting are suggestive. Epidemiologic studies have suggested that mumps may be associated with the subsequent development of diabetes mellitus, but a causal link has not been established.

**Cardiac Involvement**

Myocarditis has been reported in mumps, and molecular studies have identified mumps virus in heart tissue taken from patients with endocardial fibroelastosis.

**Arthritis**

Arthralgia, monoarthritis, and migratory polyarthritis have been reported in mumps. Arthritis is seen with or without parotitis and usually occurs within 3 wk of onset of parotid swelling. It is generally mild and self-limited.

**Thyroiditis**

Thyroiditis is rare following mumps. It has not been reported without parotitis and may occur weeks after the acute infection. Most cases resolve, but some become relapsing and result in hypothyroidism.

**TREATMENT**

No specific antiviral therapy is available for mumps. Management should be aimed at reducing the pain associated with meningitis or orchitis and maintaining adequate hydration. Antipyretics may be given for fever.

**PROGNOSIS**

The outcome of mumps is nearly always excellent, even when the disease is complicated by encephalitis, although fatal cases from CNS involvement or myocarditis have been reported.

**PREVENTION**

Immunization with the live mumps vaccine is the primary mode of prevention used in the United States. It is given as part of the MMR 2 dose vaccine schedule, at 12-15 mo of age for the 1st dose and 4-6 yr of age for the 2nd dose. If not given at 4-6 yr, the 2nd dose should be given before children enter puberty. Antibody develops in 94% (range: 89-97%) of vaccinees after 1 dose. Antibody levels achieved following vaccination are lower than following natural infection.

The median vaccine effectiveness of mumps vaccine after 1 dose of vaccine is 78% (range: 49-92%) and after 2 doses is 88% (range: 66-95%). Duration of effectiveness is ≥10 yr after 1 dose and ≥15 yr after 2 doses.

As a live-virus vaccine, MMR should not be administered to pregnant women or to severely immunodeficient or immunosuppressed individuals. HIV-infected patients who are not severely immunocompromised may receive the vaccine, because the risk for severe infection with mumps outweighs the risk for serious reaction to the vaccine. Individuals with anaphylactoid reactions to egg or neomycin may be at risk for immediate-type hypersensitivity reactions to the vaccine. Persons with other types of reactions to egg or reactions to other components of the vaccine are not restricted from receiving the vaccine.

In 2006, in response to the multistate outbreak in the United States, evidence of immunity to mumps through vaccination was redefined. Acceptable presumptive evidence of immunity to mumps now consists of 1 of the following: (1) documentation of adequate vaccination at age 12 mo or older, (2) laboratory evidence of immunity, (3) birth before 1957, and (4) documentation of physician-diagnosed mumps. Evidence of immunity through documentation of adequate vaccination is now defined as 1 dose of a live mumps virus vaccine for preschool-age children and adults not at high risk and 2 doses for school-age children (i.e., grades K-12) and for adults at high risk (e.g., healthcare workers, international travelers, and students at post–high school educational institutions).

All persons who work in healthcare facilities should be immune to mumps. Adequate mumps vaccination for healthcare workers born during or after 1957 consists of 2 doses of a live mumps virus vaccine. Healthcare workers with no history of mumps vaccination and no other evidence of immunity should receive 2 doses, with >28 days between doses. Healthcare workers who have received only 1 dose previously should receive a 2nd dose. Because birth before 1957 is only presumptive evidence of immunity, healthcare facilities should consider recommending 1 dose of a live mumps virus vaccine for unvaccinated workers born before 1957 who do not have a history of physician-diagnosed mumps or laboratory evidence of mumps immunity. During an outbreak, healthcare facilities should strongly consider recommending 2 doses of a live mumps virus vaccine to unvaccinated workers born before 1957 who do not have evidence of mumps immunity.

**Adverse reactions** to mumps virus vaccine are rare. Parotitis and orchitis have been reported rarely. Other reactions, such as febrile seizures, deafness, rash, purpura, encephalitis, and meningitis, may not be causally related to the strain of mumps virus vaccine used for immunization in the United States. Higher rates of aseptic meningitis following vaccination for mumps are associated with vaccine strains used elsewhere in the world, including the Leningrad 3 and Urabe Am 9 strains. Transient suppression of reactivity to tuberculin skin testing has been reported after mumps vaccination.

In 2005, the quadrivalent measles, mumps, rubella, and varicella vaccine (MMRV) was made available. However, in 2010 studies showed a greater risk of febrile seizures in children 12-23 mo of age 5-12 days following administration of the vaccine. No increased risk of seizures was seen in children receiving the 1st dose of the MMRV at older than 48 mo of age. As a result, the American Academy of Pediatrics currently recommends either the MMR vaccine and separate varicella vaccine or the MMRV vaccine in children 12 through 47 mo of age. After 48 mo of age, the MMRV is generally preferred.

*Bibliography is available at Expert Consult.*
Bibliography
ETIOLOGY
The polioviruses are nonenveloped, positive-stranded RNA viruses belonging to the Picornaviridae family, in the genus Enterovirus, and consist of 3 antigenically distinct serotypes (types 1, 2, and 3). Polioviruses spread from the intestinal tract to the central nervous system (CNS), where they cause aseptic meningitis and poliomyelitis, or polio. The polioviruses are extremely hardy and can retain infectivity for several days at room temperature.

EPIDEMIOLOGY
The most devastating result of poliovirus infection is paralysis, although 90-95% of infections are inapparent but induce protective immunity. Clinically apparent but nonparalytic illness occurs in approximately 5% of all infections, with paralytic polio occurring in approximately 1 in 1,000 infections among infants to approximately 1 in 100 infections among adolescents. In developed countries prior to universal vaccination, epidemics of paralytic poliomyelitis occurred primarily in adolescents. Conversely, in developing countries with poor sanitation, infection early in life results in infantile paralysis. Improved sanitation explains the virtual eradication of polio from the United States in the early 1960s, when only approximately 65% of the population was immunized with the Salk vaccine, which contributed to the disappearance of circulating wild-type poliovirus in the United States and
Europe. Poor sanitation and crowding have permitted the continued transmission of poliovirus in certain poor countries in Africa and Asia, despite massive global efforts to eradicate polio, which in some areas involve an average of 12-13 doses of polio vaccine administered to children in the 1st 5 yr of life (Fig. 249-1).

TRANSMISSION
Humans are the only known reservoir for the polioviruses, which are spread by the fecal-oral route. Poliovirus has been isolated from feces for longer than 2 wk before paralysis to several weeks after the onset of symptoms.

PATHOGENESIS
Polioviruses infect cells by adsorbing to the genetically determined poliovirus receptor. The virus penetrates the cell, is uncoated, and releases viral RNA. The RNA is translated to produce proteins responsible for replication of the RNA, shutoff of host cell protein synthesis, and synthesis of structural elements that compose the capsid. Mature virus particles are produced in 6-8 hr and are released into the environment by disruption of the cell.

In the contact host, wild-type and vaccine strains of polioviruses gain host entry via the gastrointestinal tract. The primary site of replication is in the M cells lining the mucosa of the small intestine. Regional lymph nodes are infected, and primary viremia occurs after 2-3 days. The virus seeds multiple sites, including the reticuloendothelial system, brown fat deposits, and skeletal muscle. Wild-type poliovirus probably accesses the CNS along peripheral nerves. Vaccine strains of polioviruses do not replicate in the CNS, a feature that accounts for the safety of the live-attenuated vaccine. Occasional revertants (by nucleotide substitution) of these vaccine strains develop a neuroviral phenotype and cause vaccine-associated paralytic poliomyelitis (VAPP). Reversion occurs in the small intestine and probably accesses the CNS via the peripheral nerves. Because poliovirus replicates in endothelial cells, the theory of viremic spread to the CNS was favored; however, poliovirus has almost never been cultured from the cerebrospinal fluid (CSF) of patients with paralytic disease, and patients with aseptic meningitis caused by poliovirus have never have paralytic disease. With the first appearance of non-CNS symptoms, a secondary viremia probably occurs as a result of enormous viral replication in the reticuloendothelial system.

The exact mechanism of entry into the CNS is not known. However, once entry is gained the virus may traverse neural pathways, and multiple sites within the CNS are often affected. The effect on motor and vegetative neurons is most striking and correlates with the clinical manifestations. Perineuronal inflammation, a mixed inflammatory reaction with both polymorphonuclear leukocytes and lymphocytes, is associated with extensive neuronal destruction. Petechial hemorrhages and considerable inflammatory edema also occur in areas of poliovirus infection. The poliovirus primarily infects motor neuron cells in the spinal cord (the anterior horn cells) and the medulla oblongata (the cranial nerve nuclei). Because of the overlap in muscle innervation by 2-3 adjacent segments of the spinal cord, clinical signs of weakness in the limbs develop when more than 50% of motor neurons are destroyed. In the medulla, less-extensive lesions cause paralysis, and involvement of the reticular formation that contains the vital centers controlling respiration and circulation may have a catastrophic outcome. Involvement of the intermediate and dorsal areas of the horn and the dorsal root ganglia in the spinal cord results in hyperesthesia and myalgias that are typical of acute poliomyelitis. Other neurons affected are the nuclei in the roof and vermis of the cerebellum, the substantia nigra, and, occasionally, the red nucleus in the pons; there may be variable involvement of thalamic, hypothalamic, and pallidal nuclei and the motor cortex.

Apart from the histopathology of the CNS, inflammatory changes occur generally in the reticuloendothelial system. Inflammatory edema and sparse lymphocytic infiltration are prominently associated with hyperplastic lymphocytic follicles.

Infants acquire immunity transplacentally from their mothers. Transplacental immunity disappears at a variable rate during the 1st 4-6 mo of life. Active immunity after natural infection is probably lifelong but protects against the infecting serotype only; infections with other serotypes are possible. Poliovirus neutralizing antibodies develop within several days after exposure as a result of replication of the virus in the M cells in the intestinal tract and deep lymphatic tissues. This early production of circulating immunoglobulin (Ig) G antibodies protects against CNS invasion. Local (mucosal) immunity, conferred mainly by secretory IgA, is an important defense against subsequent reinfection of the gastrointestinal tract.

CLINICAL MANIFESTATIONS
The incubation period of poliovirus from contact to initial clinical symptoms is usually considered to be 8-12 days, with a range of 5-35 days. Poliovirus infections with wild-type virus may follow 1 of several courses: inapparent infection, which occurs in 90-95% of cases and causes no disease and no sequelae; abortive poliomyelitis; nonparalytic
hour small spotulas, and spasms) may develop. On physical examination the sensory and motor phenomena (e.g., paresthesia, hyperesthesia, fas

Involvement of one leg is most common, followed by involvement of the proximal areas of the extremities. Tendon reflexes are absent with paralysis. Muscle tenderness, may precede weakness by 12-24 hr. The superficial reflexes, unless paralysis supervenes. Changes in reflexes, either increased or decreased, may precede weakness by 12-24 hr. The superficial reflexes, the cremasteric and abdominal reflexes, and the reflexes of the spinal and gluteal muscles are usually the first to diminish. The spinal and gluteal reflexes may disappear before the abdominal and cremasteric reflexes. Changes in the deep tendon reflexes generally occur 8-24 hr after the superficial reflexes are depressed and indicate impending paresis of the extremities. Tendon reflexes are absent with paralysis. Sensory defects do not occur in poliomyelitis.

Paralytic Poliomyelitis
Paralytic poliomyelitis develops in approximately 0.1% of persons infected with poliovirus, causing 3 clinically recognizable syndromes that represent a continuum of infection differentiated only by the portion of the CNS most severely affected. These are (1) spinal paralytic poliomyelitis, (2) bulbar poliomyelitis, and (3) polioencephalitis.

Spinal paralytic poliomyelitis may occur as the 2nd phase of a biphasic illness, the 1st phase of which corresponds to abortive poliomyelitis. The patient then appears to recover and feels better for 2-5 days, after which severe headache and fever occur with exacerbation of the previous systemic symptoms. Severe muscle pain is present, and sensory and motor phenomena (e.g., paresthesia, hyperesthesia, fasciculations, and spasms) may develop. On physical examination the distribution of paralysis is characteristically spotty. Single muscles, multiple muscles, or groups of muscles may be involved in any pattern. Within 1-2 days, asymmetric flaccid paralysis or paresis occurs. Involvement of one leg is most common, followed by involvement of one arm. The proximal areas of the extremities tend to be involved to a greater extent than the distal areas. To detect mild muscular weakness, it is often necessary to apply gentle resistance in opposition to the muscle group being tested. Examination at this point may reveal nuchal stiffness or rigidity, muscle tenderness, initially hyperactive deep tendon reflexes (for a short period) followed by absence or diminution of reflexes, and paresis or flaccid paralysis. In the spinal form, there is weakness of some of the muscles of the neck, abdomen, trunk, diaphragm, thorax, or extremities. Sensation is intact; sensory disturbances, if present, suggest a disease other than poliomyelitis.

The paralytic phase of poliomyelitis is extremely variable; some patients progress during observation from paresis to paralysis, whereas others recover, either slowly or rapidly. The extent of paresis or paralysis is directly related to the extent of neuronal involvement; paralysis occurs if 50-60% of the neurons supplying the muscles are destroyed. The extent of involvement is usually obvious within 2-3 days; only rarely does progression occur beyond this interval. Bowel and bladder dysfunction ranging from transient incontinence to paralysis with constipation and urinary retention often accompany paralysis of the lower limbs.

The onset and course of paralysis are variable in developing countries. The biphasic course is rare; typically the disease manifests in a single phase in which prodromal symptoms and paralysis occur in a continuous fashion. In developing countries, where a history of intra-muscular injections precedes paralytic poliomyelitis in approximately 50-60% of patients, patients may present initially with fever and paralysis (provocation paralysis). The degree and duration of muscle pain are also variable, ranging from a few days usually to a week. Occasionally spasm and increased muscle tone with a transient increase in deep tendon reflexes occur in some patients, whereas in most patients, flaccid paralysis occurs abruptly. Once the temperature returns to normal, progression of paralytic manifestations stops. Little recovery from paralysis is noted in the 1st days or weeks, but, if it is to occur, it is usually evident within 6 mo. The return of strength and reflexes is slow and may continue to improve for as long as 18 mo after the acute disease. Lack of improvement from paralysis within the 1st several weeks or months after onset is usually evidence of permanent paralysis. Atrophy of the limb, failure of growth, and deformity are common and are especially evident in the growing child.

Bulbar poliomyelitis may occur as a clinical entity without apparent involvement of the spinal cord. Infection is a continuum, and designation of the disease as bulbar implies only dominance of the clinical manifestations by dysfunctions of the cranial nerves and medullary centers. The clinical findings seen with bulbar poliomyelitis with respiratory difficulty (other than paralysis of extracelular, facial, and masticatory muscles) include (1) nasal twang to the voice or cry caused by palatal and pharyngeal weakness (hard-consonant words such as “cookie” and “candy” bring this feature out best); (2) inability to swallow smoothly, resulting in accumulation of saliva in the pharynx, indicating partial immobility (holding the larynx lightly and asking the patient to swallow will confirm such immobility); (3) accumulated pharyngeal secretions, which may cause irregular respirations that appear interrupted and abnormal even to the point of falsely simulating intercostal or diaphragmatic weakness; (4) absence of effective coughing, shown by constant fatiguing efforts to clear the throat; (5) nasal regurgitation of saliva and fluids as a result of palatal paralysis, with inability to separate the oropharynx from the nasopharynx during swallowing; (6) deviation of the palate, uvula, or tongue; (7) involvement of vital centers in the medulla, which manifest as irregularities in rate, depth, and rhythm of respiration; as cardiovascular alterations, including blood pressure changes (especially increased blood pressure), alternate flushing and mottling of the skin, and cardiac arrhythmias; and as rapid changes in body temperature; (8) paralysis of 1 or both vocal cords, causing hoarseness, aponia, and, ultimately, asphyxia unless the problem is recognized on laryngoscopy and managed by immediate tracheostomy; and (9) the rope sign, an acute angulation between the chin and larynx caused by weakness of the hyoid muscles (the hyoid bone is pulled posteriorly, narrowing the hypopharyngeal inlet).

Uncommonly, bulbar disease may culminate in an ascending paralysis (Landry type), in which there is progression cephalad from initial involvement of the lower extremities. Hypertension and other
autonomic disturbances are common in bulbar involvement and may persist for a week or more or may be transient. Occasionally, hypertension is followed by hypotension and shock and is associated with irregular or failed respiratory effort, delirium, or coma. This kind of bulbar disease may be rapidly fatal.

The course of bulbar disease is variable; some patients die as a result of extensive, severe involvement of the various centers in the medulla; others recover partially but require ongoing respiratory support, and others recover completely. Cranial nerve involvement is seldom permanent. Atrophy of muscles may be evident, patients immobilized for long periods may experience pneumonia, and renal stones may form as a result of hypercalcemia and hypercalciuria secondary to bone resorption.

**Poliencephalitis** is a rare form of the disease in which higher centers of the brain are severely involved. Seizures, coma, and spastic paralysis with increased reflexes may be observed. Irritability, disorientation, drowsiness, and coarse tremors are often present with peripheral or cranial nerve paralysis that coexist or ensues. Hypoxia and hypercapnia caused by inadequate ventilation due to respiratory insufficiency may produce disorientation without true encephalitis. The manifestations are common to encephalitis of any cause and can be attributed to polioviruses only with specific viral diagnosis or if accompanied by flaccid paralysis.

**Paralytic poliomyelitis with ventilatory insufficiency** results from several components acting together to produce ventilatory insufficiency resulting in hypoxia and hypercapnia. It may have profound effects on many other systems. Because respiratory insufficiency may develop rapidly, close continued clinical evaluation is essential. Despite weakness of the respiratory muscles, the patient may respond with so much respiratory effort associated with anxiety and fear that overventilation may occur at the outset, resulting in respiratory alkalosis. Such effort is fatiguing and contributes to respiratory failure.

There are certain characteristic patterns of disease. Pure spinal poliomyelitis with respiratory insufficiency involves tightness, weakness, or paralysis of the respiratory muscles (chiefly the diaphragm and intercostals) without discernible clinical involvement of the cranial nerves or vital centers that control respiration, circulation, and body temperature. The cervical and thoracic spinal cord segments are chiefly affected. Pure bulbar poliomyelitis involves paralysis of the motor cranial nerve nuclei with or without involvement of the vital centers. Involvement of the 9th, 10th, and 12th cranial nerves results in paralysis of the pharynx, tongue, and larynx with consequent airway obstruction. Bulbospinal poliomyelitis with respiratory insufficiency affects the respiratory muscles and results in coexisting bulbar paralysis.

The clinical findings associated with involvement of the respiratory muscles include (1) anxious expression; (2) inability to speak without frequent pauses, resulting in short, jerky, “breathless” sentences; (3) increased respiratory rate; (4) movement of the ala nasi and of the accessory muscles of respiration; (5) inability to cough or sniff with full depth; (6) paradoxical abdominal movements caused by diaphragmatic immobility caused by spasm or weakness of 1 or both leaves; and (7) relative immobility of the intercostal spaces, which may be segmental, unilateral, or bilateral. When the arms are weak, and especially when deltoid paralysis occurs, there may be impending respiratory paralysis because the phrenic nerve nuclei are in adjacent areas of the spinal cord. Observation of the patient’s capacity for thoracic breathing while the abdominal muscles are splinted manually indicates minor degrees of paresis. Light manual splinting of the thoracic cage helps assess the effectiveness of diaphragmatic movement.

**DIAGNOSIS**

Poliomyelitis should be considered in any unimmunized or incompletely immunized child with paralytic disease. While this guideline is most applicable in poliomyelitis endemic countries (Afghanistan, Pakistan, and Nigeria), the spread of polio in 2013 from endemic countries to many nonendemic countries (Niger, Chad, Cameroon, Ethiopia, Kenya, Somalia, and Syria) and the isolation of wild poliovirus type 1 in Israel suggest that the diagnosis of polio should still be entertained in all countries. VAPP should be considered in any child with paralytic disease occurring 7-14 days after receiving the orally administered polio vaccine (OPV). VAPP can occur at later times after administration and should be considered in any child with paralytic disease in countries or regions where wild-type poliovirus has been eradicated and the OPV has been administered to the child or a contact. The combination of fever, headache, neck and back pain, asymmetric flaccid paralysis without sensory loss, and pleocytosis does not regularly occur in any other illness.

The World Health Organization (WHO) recommends that the laboratory diagnosis of poliomyelitis be confirmed by isolation and identification of poliovirus in the stool, with specific identification of wild-type and vaccine-type strains. In suspected cases of acute flaccid paralysis, 2 stool specimens should be collected 24-48 hr apart as soon as possible after the diagnosis of poliomyelitis is suspected. Poliovirus concentrations are high in the stool in the 1st wk after the onset of paralysis, which is the optimal time for collection of stool specimens. Polioviruses may be isolated from 80-90% of specimens from acutely ill patients, whereas <20% of specimens from such patients may yield virus within 3-4 wk after onset of paralysis. Because most children with spinal or bulbospinal poliomyelitis have constipation, rectal stabs may be used to obtain specimens; ideally a minimum of 8-10 g of stool should be collected. In laboratories that can isolate poliovirus, isolates should be sent to either the U.S. Centers for Disease Control and Prevention or to one of the WHO-certified poliomyelitis laboratories where DNA sequence analysis can be performed to distinguish between wild poliovirus and neurovirulent, revertant OPV strains. With the current WHO plan for global eradication of poliomyelitis, most regions of the world (the Americas, Europe, Australia) have been certified wild-poliovirus free; in these areas, poliomyelitis is most often caused by vaccine strains. Hence it is critical to differentiate between wild-type and revertant vaccine-type strains.

The CSF is often normal during the minor illness and typically contains a pleocytosis with 20-300 cells/μL with CNS involvement. The cells in the CSF may be polymorphonuclear early during the course of the disease but shift to mononuclear cells soon afterward. By the 2nd wk of major illness, the CSF cell count falls to near-normal values. In contrast, the CSF protein content is normal or only slightly elevated at the outset of CNS disease but usually rises to 50-100 mg/dL by the 2nd wk of illness. In poliencephalitis, the CSF may remain normal or show minor changes. Serologic testing demonstrates seroconversion or a 4-fold or greater increase in antibody titers from the acute phase of illness to 3-6 wk later.

**DIFFERENTIAL DIAGNOSIS**

Poliomyelitis should be considered in the differential diagnosis of any case of paralysis, and is only 1 of many causes of acute flaccid paralysis in children and adults. There are numerous other causes of acute flaccid paralysis (Table 249-1). In most conditions, the clinical features are sufficient to differentiate between these various causes, but in some cases nerve conduction studies and electromyograms, in addition to muscle biopsies, may be required.

The possibility of polio should be considered in any case of acute flaccid paralysis, even in countries where polio has been eradicated. The diagnoses most often confused with polio are VAPP, West Nile virus infection, infections caused by other enteroviruses, as well as Guillain-Barré syndrome, transverse myelitis, and traumatic paralysis. In Guillain-Barré syndrome, which is the most difficult to distinguish from poliomyelitis, the paralysis is characteristically symmetric, and sensory changes and pyramidal tract signs are common, contrasting with poliomyelitis. Fever, headache, and meningeal signs are less notable, and the CSF has few cells but an elevated protein content. Transverse myelitis progresses rapidly over hours to days, causing an acute symmetric paralysis of the lower limbs with concomitant anesthetic and diminished sensory perception. Autonomic signs of hypotension in the affected limbs are common, and there is bladder dysfunction. The CSF is usually normal. Traumatic neuritis occurs from a few hours to a few days after the traumatic event, is asymmetric, is acute, and affects only 1 limb. Muscle tone and deep tendon reflexes are reduced or absent in the affected limb with pain in the gluteus. The CSF is normal.
Table 249-1  Differential Diagnosis of Acute Flaccid Paralysis

<table>
<thead>
<tr>
<th>SITE, CONDITION, FACTOR, OR AGENT</th>
<th>CLINICAL FINDINGS</th>
<th>ONSET OF PARALYSIS</th>
<th>PROGRESSION OF PARALYSIS</th>
<th>SENSORY SIGNS AND SYMPTOMS</th>
<th>REDUCTION OR ABSENCE OF DEEP TENDON REFLEXES</th>
<th>RESIDUAL PARALYSIS</th>
<th>PLEOCYTOSIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANTERIOR HORN CELLS OF SPINAL CORD</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Poliomyelitis (wild and vaccine-associated paralytic poliomyelitis)</td>
<td>Paralysis</td>
<td>Incubation period 7-14 days (range: 4-35 days)</td>
<td>24-48 hr to onset of full paralysis; proximal → distal, asymmetric</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Aseptic meningitis (moderate polymorphonuclear leukocytes at 2-3 days)</td>
</tr>
<tr>
<td>Nonpolio enteroviruses</td>
<td>Hand-foot-and-mouth disease, aseptic meningitis, acute hemorrhagic conjunctivitis, possibly idiopathic epidemic flaccid paralysis</td>
<td>As in poliomyelitis</td>
<td>As in poliomyelitis</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>West Nile virus</td>
<td>Meningitis encephalitis</td>
<td>As in poliomyelitis</td>
<td>As in poliomyelitis</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>OTHER NEUROTROPIC VIRUSES</td>
<td></td>
<td></td>
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<tr>
<td>Rabies virus</td>
<td>Exanthematous vesicular eruptions</td>
<td>Month–year</td>
<td>Acute, symmetric, ascending</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>±</td>
</tr>
<tr>
<td>Varicella-zoster virus</td>
<td></td>
<td>Incubation period 10-21 days</td>
<td>Acute, symmetric, ascending</td>
<td>Yes</td>
<td>±</td>
<td>±</td>
<td>Yes</td>
</tr>
<tr>
<td>Japanese encephalitis virus</td>
<td></td>
<td>Incubation period 5-15 days</td>
<td>Acute, proximal, asymmetric</td>
<td>±</td>
<td>±</td>
<td>±</td>
<td>Yes</td>
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<tr>
<td>GUILLAIN-BARRÉ SYNDROME</td>
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<tr>
<td>Acute inflammatory polyradiculoneuropathy</td>
<td>Preceding infection, bilateral facial weakness</td>
<td>Hours to 10 days</td>
<td>Acute, symmetric, ascending (days to 4 wk)</td>
<td>Yes</td>
<td>Yes</td>
<td>±</td>
<td>No</td>
</tr>
<tr>
<td>Acute motor axonal neuropathy</td>
<td>Fulminant, widespread paralysis, bilateral facial weakness, tongue involvement</td>
<td>Hours to 10 days</td>
<td>1-6 days</td>
<td>No</td>
<td>Yes</td>
<td>±</td>
<td>No</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Condition</th>
<th>Onset of Paralysis</th>
<th>Progression</th>
<th>Sensory Signs and Symptoms</th>
<th>Reduction or Absence of Deep Tendon Reflexes</th>
<th>Residual Paralysis</th>
<th>Pleocytosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poliomyelitis (wild and vaccine-associated paralytic poliomyelitis)</td>
<td>24-48 hr to onset of full paralysis; proximal → distal, asymmetric</td>
<td>Yes, early</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>Incubation period 7-14 days (range: 4-35 days)</td>
<td></td>
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<tr>
<td>West Nile virus</td>
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<tr>
<td>Meningitis encephalitis</td>
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<tr>
<td>Other neurotropic viruses</td>
<td></td>
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<tr>
<td>Rabies virus</td>
<td></td>
<td></td>
<td></td>
<td>±</td>
<td>No</td>
<td></td>
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<tr>
<td>Varicella-zoster virus</td>
<td></td>
<td></td>
<td>±</td>
<td>±</td>
<td>Yes</td>
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<tr>
<td>Japanese encephalitis virus</td>
<td></td>
<td></td>
<td>±</td>
<td>±</td>
<td>Yes</td>
<td></td>
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<tr>
<td>Guillain-Barré syndrome</td>
<td></td>
<td></td>
<td>±</td>
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<td>Yes</td>
<td></td>
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<tr>
<td>Acute motor axonal neuropathy</td>
<td></td>
<td></td>
<td>±</td>
<td>±</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Acute inflammatory polyradiculoneuropathy</td>
<td>Acute, symmetric, ascending</td>
<td>Yes, early</td>
<td>Yes</td>
<td>±</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>ACUTE TRAUMATIC SCIATIC NEURITIS</td>
<td>Hours to 4 days</td>
<td>Complete, affected limb</td>
<td>Yes</td>
<td>±</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Intramuscular gluteal injection</td>
<td>Acute, asymmetric</td>
<td>Acute, symmetric hypotonia of lower limbs</td>
<td>Yes</td>
<td>Yes, early</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Epidural abscess</td>
<td>Complete</td>
<td>Yes, early</td>
<td>Yes</td>
<td>±</td>
<td>Yes</td>
<td></td>
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<tr>
<td>Spinal cord compression; trauma</td>
<td>Complete</td>
<td>Yes, early</td>
<td>±</td>
<td>±</td>
<td>No</td>
<td></td>
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<tr>
<td>NEUROPATHIES</td>
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<td></td>
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<tr>
<td>Exotoxin of Corynebacterium diphtheriae</td>
<td>Incubation period 1-8 wk (paralysis 8-12 wk after onset of illness)</td>
<td>Yes</td>
<td>Yes</td>
<td>±</td>
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<tr>
<td>Toxin of Clostridium botulinum</td>
<td>Incubation period 18-36 hr</td>
<td>Rapid, descending, symmetric</td>
<td>±</td>
<td>No</td>
<td>No</td>
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<td>Tick bite paralysis</td>
<td>Incubation period 5-10 days</td>
<td>Acute, symmetric, ascending</td>
<td>±</td>
<td>No</td>
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<td>Neuropathies</td>
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<td>DISEASES OF THE NEUROMUSCULAR JUNCTION</td>
<td>Incubation period 1-8 wk (paralysis 8-12 wk after onset of illness)</td>
<td>Yes</td>
<td>Yes</td>
<td>±</td>
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<td>Myasthenia gravis</td>
<td>Incubation period 1-8 wk (paralysis 8-12 wk after onset of illness)</td>
<td>Yes</td>
<td>Yes</td>
<td>±</td>
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<td>DISORDERS OF MUSCLE</td>
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<td>Polymyositis</td>
<td>Neoplasm, autoimmune disease</td>
<td>Subacute, proximal → distal</td>
<td>Weeks to months</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
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<tr>
<td>Viral myositis</td>
<td></td>
<td>Pseudoparalysis</td>
<td></td>
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<td>Viral myositis</td>
<td></td>
<td>Hours to days</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td></td>
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<td>METABOLIC DISORDERS</td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Hypokalemic periodic paralysis</td>
<td>Proximal limb, respiratory muscles</td>
<td>Sudden postprandial</td>
<td>No</td>
<td>Yes</td>
<td>±</td>
<td>No</td>
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<tr>
<td>INTENSIVE CARE UNIT WEAKNESS</td>
<td>Flaccid limbs and respiratory weakness</td>
<td>Acute, following systemic inflammatory response syndrome/sepsis</td>
<td>±</td>
<td>Yes</td>
<td>±</td>
<td>No</td>
</tr>
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</table>

Conditions causing pseudoparalysis do not present with nuchal-spiral rigidity or plecysosis. These causes include unrecognized trauma, transient (toxic) synovitis, acute osteomyelitis, acute rheumatic fever, scurry, and congenital syphilis (pseudoparalysis of Parrot).

**TREATMENT**

There is no specific antiviral treatment for poliomyelitis. The management is supportive and aimed at limiting progression of disease, preventing ensuing skeletal deformities, and preparing the child and family for the prolonged treatment required and for permanent disability if this seems likely. Patients with the nonparalytic and mildly paralytic forms of poliomyelitis may be treated at home. All intramuscular injections and surgical procedures are contraindicated during the acute phase of the illness, especially in the 1st wk of illness, because they might result in progression of disease.

**Abortive Poliomyelitis**

Supportive treatment with analgesics, sedatives, an attractive diet, and bed rest until the child's temperature is normal for several days is usually sufficient. Avoidance of exertion for the ensuing 2 wk is desirable, and careful neurologic and musculoskeletal examinations should be performed 2 mo later to detect any minor involvement.

**Nonparalytic Poliomyelitis**

Treatment for the nonparalytic form is similar to that for the abortive form; in particular, relief is indicated for the discomfort of muscle tightness and spasm of the neck, trunk, and extremities. Analgesics are more effective when they are combined with the application of hot packs for 15-30 min every 2-4 hr. Hot tub baths are sometimes useful. A firm bed is desirable and can be improvised at home by placing table leaves or a sheet of plywood beneath the mattress. A footboard or splint should be used to keep the feet at a right angle to the legs. Because muscular discomfort and spasm may continue for some weeks, even in the nonparalytic form, hot packs and gentle physical therapy may be necessary. Patients with nonparalytic poliomyelitis should also be carefully examined 2 mo after apparent recovery to detect minor residual effects that might cause postural problems in later years.

**Paralytic Poliomyelitis**

Most patients with the paralytic form of poliomyelitis require hospitalization with complete physical rest in a calm atmosphere for the 1st 2-3 wk. Suitable body alignment is necessary for comfort and to avoid excessive skeletal deformity. A neutral position with the feet at right angles to the legs, the knees slightly flexed, and the hips and spine straight is achieved by use of boards, sandbags, and, occasionally, light splint shells. The position should be changed every 3-6 hr. Active and passive movements are indicated as soon as the pain has disappeared. Moist hot packs may relieve muscle pain and spasm. Opiates and sedatives are permissible only if no impairment of ventilation is present or impending. Constipation is common, and fecal impaction should be prevented. When bladder paralysis occurs, a parasympathetic stimulant such as bethanechol may induce voiding in 15-30 min; some patients show no response to this agent, and others respond with nausea, vomiting, and palpitations. Bladder paresis rarely lasts more than a few days. If bethanechol fails, manual compression of the bladder and the psychologic effect of running water should be tried. If catheterization must be performed, care must be taken to prevent urinary tract infections. An appealing diet and a relatively high fluid intake should be started at once unless the patient is vomiting. Additional salt should be provided if the environmental temperature is high or if the application of hot packs induces sweating. Anorexia is common initially. Adequate dietary and fluid intake can be maintained by placement of a central venous catheter. An orthopedist and a physiatrist should see patients as early in the course of the illness as possible and should assume responsibility for their care before fixed deformities develop.

The management of pure bulbar poliomyelitis consists of maintaining the airway and avoiding all risk of inhalation of saliva, food, and vomitus. Gravity drainage of accumulated secretions is favored by using the head-low (foot of bed elevated 20-25 degrees) prone position with the face to one side. Patients with weakness of the muscles of respiration or swallowing should be nursed in a lateral or semiprone position. Aspirators with rigid or semirigid tips are preferred for direct oral and pharyngeal aspiration, and soft, flexible catheters may be used for nasopharyngeal aspiration. Fluid and electrolyte equilibrium is best maintained by intravenous infusion because tube or oral feeding in the 1st few days may incite vomiting. In addition to close observation for respiratory insufficiency, the blood pressure should be measured at least twice daily because hypertension is not uncommon and occasionally leads to hypertensive encephalopathy. Patients with pure bulbar poliomyelitis may require tracheostomy because of vocal cord paralysis or constriction of the hypopharynx; most patients who recover have little residual impairment, although some exhibit mild dysphagia and occasional vocal fatigue with slurring of speech.

Impaired ventilation must be recognized early; mounting anxiety, restlessness, and fatigue are early indications for preemptive intervention. Tracheostomy is indicated for some patients with pure bulbar poliomyelitis, spinal respiratory muscle paralysis, or bulbospinal paralysis because such patients are generally unable to cough, sometimes for many months. Mechanical respirators are often needed.

**COMPLICATIONS**

Paralytic poliomyelitis may be associated with numerous complications. Acute gastric dilation may occur abruptly during the acute or convalescent stage, causing further respiratory embarrassment; immediate gastric aspiration and external application of ice bags are indicated. Melena severe enough to require transfusion may result from single or multiple superficial intestinal erosions; perforation is rare. Mild hypertension for days or weeks is common in the acute stage and probably related to lesions of the vasoregulatory centers in the medulla and especially to underventilation. In the later stages, because of immobilization, hypertension may occur along with hypercalcemia, nephrocalcinosis, and vascular lesions. Dimness of vision, headache, and a lightheaded feeling associated with hypertension should be regarded as premonitory of a frank convulsion. Cardiac irregularities are uncommon, but electrocardiographic abnormalities suggesting myocarditis occur with some frequency. Acute pulmonary edema occurs occasionally, particularly in patients with arterial hypertension. Hypercalcemia occurs because of skeletal decalcification that begins soon after immobilization and results in hypercalcuria, which in turn predisposes the patient to urinary calculi, especially when urinary stasis and infection are present. High fluid intake is the only effective prophylactic measure.

**PROGNOSIS**

The outcome of inapparent, abortive poliomyelitis and aseptic meningitis syndromes is uniformly good, with death being exceedingly rare and with no long-term sequelae. The outcome of paralytic disease is determined primarily by degree and severity of CNS involvement. ln severe bulbar poliomyelitis, the mortality rate may be as high as 60%, whereas in less-severe bulbar involvement and/or spinal poliomyelitis, the mortality rate varies from 5-10%, death generally occurring from causes other than the poliovirus infection.

Maximum paralysis usually occurs 2-3 days after the onset of the paralytic phase of the illness, with stabilization followed by gradual return of muscle function. The recovery phase lasts usually about 6 mo, beyond which persisting paralysis is permanent. Generally, paralysis is more likely to develop in male children and female adults. Mortality and the degree of disability are greater after the age of puberty. Pregnancy is associated with an increased risk for paralytic disease. Tonsillectomy and intramuscular injections may enhance the risk for acquisition of bulbar and localized disease, respectively. Increased physical activity, exercise, and fatigue during the early phase of illness have been cited as factors leading to a higher risk for paralytic disease. Finally, it has been clearly demonstrated that type 1 poliovirus has the greatest propensity for natural poliomyelitis, and type 3 poliovirus has a predilection for producing VAPP.

**Postpolio Syndrome**

After an interval of 30-40 yr, as many as 30-40% of persons who survived paralytic poliomyelitis in childhood may experience muscle pain
and exacerbation of existing weakness or development of new weakness or paralysis. This entity, referred to as postpolio syndrome, has been reported only in persons who were infected in the era of wild-type poliovirus circulation. Risk factors for postpolio syndrome include increasing length of time since acute poliovirus infection, presence of permanent residual impairment after recovery from acute illness, and female sex.

**PREVENTION**

Vaccination is the only effective method of preventing poliomyelitis. Hygienic measures help limit the spread of the infection among young children, but immunization is necessary to control transmission among all age groups. Both the inactivated polio vaccine (IPV), which is currently produced using better methods than those for the original vaccine and is sometimes referred to as enhanced IPV, and the live-attenuated OPV have established efficacy in preventing poliovirus infection and paralytic poliomyelitis. Both vaccines induce production of antibodies against the 3 strains of poliovirus. IPV elicits higher serum IgG antibody titer, but the OPV also induces significantly greater mucosal IgA immunity in the oropharynx and gastrointestinal tract, which limits replication of the wild poliovirus at these sites. Transmission of wild poliovirus by fecal spread is limited in OPV recipients. The immunogenicity of IPV is not affected by the presence of maternal antibodies, and IPV has no adverse effects. Live vaccine may undergo reversion to neurovirulence as it multiplies in the human intestinal tract and may cause VAPP in vaccinees or in their contacts. The overall risk for recipients varies from 1 case per 750,000 immunized infants in the United States to 1 in 143,800 immunized infants in India. The risk for paralysis in the B-cell–immunodeficient recipient may be as much as 6,800 times that in normal subjects. HIV infection has not been found to result in long-term excretion of virus. As of January 2000, the IPV-only schedule is recommended for routine polio vaccination in the United States. All children should receive 4 doses of IPV, at 2 mo, 4 mo, 6-18 mo, and 4-6 yr of age.

In 1988, the World Health Assembly resolved to eradicate poliomyelitis globally by 2000, and remarkable progress had been made toward reaching this target. To achieve this goal, the WHO used 4 basic strategies: routine immunization, National Immunization Days, acute flaccid paralysis surveillance, and “mop-up” immunization. This strategy has resulted in a >99% decline in poliomyelitis cases; in early 2002, there were only 10 countries in the world endemic for poliomyelitis. In 2012, there were the fewest cases of poliomyelitis ever, and the virus was endemic in only 3 countries (Afghanistan, Pakistan, and Nigeria). India has not had a child paralyzed with wild poliovirus type 2 since February 2011. The last case of wild poliovirus type 3 infection occurred in Nigeria in 2012, and the last case of wild poliovirus type 2 infection occurred in India in 1999. This progress prompted the WHO assembly, in May 2013, to recommend the development of a Polio Eradication and Endgame Strategic Plan 2013-2018. This plan includes the withdrawal of trivalent OPV with bivalent OPV (bOPV) in all countries by 2016 and the introduction of initially one dose of IPV followed by the replacement of bivalent IPV with IPV in all countries of the world by 2019. As long as the OPV is being used, there is the potential that vaccine-derived poliovirus will acquire the neurovirulent phenotype and transmission characteristics of the wild-type polioviruses. Vaccine-derived poliovirus emerges from the OPV because of continuous replication in immunodeficient persons or by circulation in populations with low vaccine coverage (cVDPVs). The risk appears to be highest with the type 2 strain. Currently, 90% of all cVDPV outbreaks are caused by type 2 strains (Fig. 249-2). Outbreaks of cVDPV2 occurred in Hispaniola, the Philippines, and Madagascar in 2001, and endemic cVDPV2 circulation occurred in Egypt from 1983-1993. As of 2012, 5 outbreaks of cVDPV2 were detected in the 3 polio endemic countries and in Chad, Democratic Republic of Congo, Kenya, Somalia, and China. Several countries are global priorities because they face challenges in eradication of the disease (see Fig. 249-1). Polioviruses are endemic in Pakistan, Afghanistan, and Nigeria. Twenty previously polio-free countries were infected by importations of wild poliovirus type 1 originating from Nigeria, and 3 polio-free African countries experienced infections with wild poliovirus type 1 imported from India. For the 3 countries with uninterrupted outbreaks, there are 2 main reasons for the failure to eradicate polio. The suboptimal campaign quality in Nigeria, parts of Pakistan and southern Afghanistan, and the countries with prolonged transmission of imported virus as well as security-compromised areas in parts of Afghanistan and Pakistan are still the main difficulties faced in 2014. Of the 416 wild poliovirus cases in 2012, 160 cases were in the 3 endemic countries and 256 were in nonendemic countries. There have been importations from Nigeria into the horn of Africa and the Middle East (Cameroon, Ethiopia, Kenya, Somalia, and Syrian Arab Republic). However, since December 2014 this ratio has changed, and the number of cases in endemic countries (especially Nigeria and Afghanistan) has increased to 306, mostly in Pakistan (276). Equally worrisome to the strategy of switching completely to IPV is the detection of a Pakistani strain of wild poliovirus type 1 in Israel and the West Bank, first in sewage, and now found in up to 4% of children and adults. Israel has used IPV exclusively for the past 10 yr and has introduced bOPV as a single continuous supplementary immunization activity (SIA). bOPV is included in routine immunization, following at least 1 dose of IPV. This follows the experience in the United States that reported no VAPP following a sequential use of IPV followed by OPV. Global synchronous cessation of OPV will need to be coordinated by the WHO, but the recent experiences in the horn of Africa and Israel/West Bank suggest that stopping transmission of wild poliovirus type 1 in the 3 endemic countries is of the utmost urgency, if we are ever going to be able to stop using OPV.

**Bibliography is available at Expert Consult.**
Bibliography

The genus *Enterovirus* contains a large number of agents that produce a broad range of illnesses. The genus name reflects the importance of the gastrointestinal tract as the primary site of invasion and replication and the source for transmission. Viremic spread to distant sites accounts for the majority of clinical manifestations.
Large enterovirus outbreaks have included echovirus meningitis epidemics in numerous countries (echoviruses 4, 6, 9, 13, and 30 commonly); epidemics of hand-foot-and-mouth disease with severe central nervous system (CNS) and/or cardiopulmonary disease caused by enterovirus 71 in Asia and Australia; outbreaks of atypical hand-foot-and-mouth disease caused by coxsackievirus A6 in the United States and United Kingdom; outbreaks of human enterovirus 68 producing respiratory illness and possibly acute flaccid paralysis in the United States, Europe, and Asia; outbreaks of acute hemorrhagic conjunctivitis caused by enterovirus 70, coxsackievirus A24, and coxsackievirus A24 variant in tropical and temperate regions; and community outbreaks of uveitis. Reverse transcription polymerase chain reaction (RT-PCR), restriction fragment length polymorphism analysis, single-strand conformation polymorphism analysis, heteroduplex mobility analysis, and genomic sequencing help identify outbreaks and allow phylogenetic analyses that demonstrate, depending on the outbreak, commonality of outbreak strains, differences among epidemic strains and older prototype strains, changes in circulating viral subgroups over time, cocirculation of multiple genetic lineages, coinfections with different enterovirus serotypes, and associations between specific genotypes and/or substitutions at specific genetic loci and epidemiologic and clinical characteristics. Genetic analyses have demonstrated recombination and genetic drift that lead to evolutionary changes in genomic sequence and antigenicity and extensive genetic diversity. Rapid genetic evolution and recombination events associated with emergence of new subgenotypes and genetic lineages of enterovirus 71 may contribute to sequential outbreaks and increases in viral circulation.

The incubation period is typically 3-6 days, except for a 1-3 day incubation period for acute hemorrhagic conjunctivitis. Infected children, both symptomatic and asymptomatic, frequently shed cultivable enteroviruses from the respiratory tract for <1-3 wk, whereas fecal shedding continues for as long as 7-11 wk. Enterovirus RNA can be shed from mucosal sites for comparable, and, possibly, longer periods.

**PATHOGENESIS**

Following oral or respiratory acquisition, initial replication occurs in the pharynx and intestine, possibly within mucosal M cells. The absence of an envelope favors survival in the gastrointestinal tract. Cell surface macromolecules, including poliovirus receptor, integrin very late-activation antigen (VLA)-2, decay-accelerating factor/complement regulatory protein (DAF/CD55), intercellular adhesion molecule-1 (ICAM-1), and coxsackievirus-adenovirus receptor, serve as receptors, as do sialic acid for enterovirus 68, enterovirus 70, and coxsackievirus A24 variants and human scavenger receptor class B2 (SCARB2), human P-selectin glycoprotein ligand-1, and DC-SIGN for enterovirus 71. Two or more enteroviruses may invade and replicate in the gastro-intestinal tract simultaneously, but replication of 1 type often hinders growth of the heterologous type (interference).

After the virus attaches to a cell surface receptor, a conformational change in surface capsid proteins facilitates penetration and uncoating with release of viral RNA in the cytoplasm. Translation of the positive-sense RNA produces a polyprotein that undergoes cleavage by proteases encoded in the polyprotein. Several proteins produced guide synthesis of negative-sense RNA that serves as a template for
replication of new positive-sense RNA. The genome is approximately 7,500 nucleotides long and includes a highly conserved 5′ noncoding region important for replication efficiency and a highly conserved 3′ polyA region, which flank a continuous region encoding viral proteins. The 5′ end is covalently linked to a small viral protein (VPg) necessary for initiation of RNA synthesis. There is significant variation within genomic regions encoding the structural proteins (with corresponding variability in antigenicity). Replication is followed by further cleavage of proteins and assembly into 30 nm icosahedral virions. Of the 4 structural proteins (VP1-VP4) in the capsid (additional regulatory proteins such as an RNA-dependent RNA polymerase and proteases are also present in the virion), VP1 is the most important determinant of serotype specificity. Approximately 10^4-10^5 virions are released from an infected cell by lysis within 5-10 hr of infection.

Initial replication in the pharynx and intestine is followed within days by multiplication in lymphoid tissue such as tonsils, Peyer patches, and regional lymph nodes. A primary, transient viremia (minor viremia) results in spread to distant parts of the reticuloendothelial system, including the liver, spleen, bone marrow, and distant lymph nodes. Host immune responses may limit replication and progression beyond the reticuloendothelial system, resulting in subclinical infection. Clinical infection occurs if replication proceeds in the reticuloendothelial system and virus spreads via a secondary, sustained viremia (major viremia) to target organs such as the CNS, heart, and skin. Tropism to target organs is determined in part by the infecting serotype.

Enteroviruses can damage a wide variety of organs and systems, including the CNS, heart, liver, lungs, pancreas, kidneys, muscle, and skin. Damage is mediated by necrosis and the inflammatory response. CNS infections are often associated with mononuclear pleocytosis of the cerebrospinal fluid (CSF), composed of macrophages and activated T lymphocytes, and a mixed meningeal inflammatory response. Parenchymal involvement may affect the cerebral white and gray matter, cerebellum, basal ganglia, brainstem, and spinal cord with perivascular and parenchymal mixed or lymphocytic inflammation, gliosis, cellular degeneration, and neuronophagocytosis. Encephalitis during enterovirus 71 epidemics has been characterized by severe involvement of the brainstem, spinal cord gray matter, hypothalamus, and subthalamic and dentate nuclei, and frequently complicated by pulmonary edema, hemorrhage and/or interstitial pneumonitis and cardiopulmonary failure, presumed secondary to brainstem damage, sympathetic hyperactivity, autonomic dysfunction, and CNS and systemic inflammatory responses (including cytokine and chemokine overexpression), and, only occasionally, myocarditis. Immunologic cross-reactivity with brain tissue has been postulated as one mechanism responsible for neurologic damage and sequelae following enterovirus 71 infection. Enterovirus myocarditis is characterized by perivascular and interstitial mixed inflammatory infiltrates and myocardite damage, possibly mediated by viral cytolytic (e.g., cleavage of dystrophin or serum response factor) and innate and adaptive immune-mediated mechanisms. Chronic inflammation may persist after viral clearance.

The potential for enteroviruses to cause persistent infection is controversial. Persistent infection has been implicated in dilated cardiomyopathy and in myocardial infarction, with enteroviral RNA sequences and/or antigens demonstrated in cardiac tissues in some, but not other, series. Infections with enteroviruses such as coxsackievirus B4, during gestation or subsequently, have been implicated as a trigger for development of β-cell autoantibodies and/or type 1 diabetes in genetically susceptible hosts. Persistent infection in the pancreas, intestine, or peripheral blood mononuclear cells, with downstream immunomodulatory effects, has also been suggested, but data are inconsistent. Similarly, persistent infection is implicated in amyotrophic lateral sclerosis, Sjögren syndrome, and gastrointestinal tract tumors, and evidence of chronic infection has been described in some studies of chronic fatigue syndrome but not in others.

Severe neonatal infections can manifest as hepatic necrosis, hemorrhage, inflammation, endocarditis, and venoocclusive disease; myocardial mixed inflammatory infiltrates, edema, and necrosis; meningeval and brain inflammation, hemorrhage, gliosis, necrosis, and white matter damage; inflammation, hemorrhage, thrombosis, and necrosis in the lungs, pancreas, and adrenal glands; and disseminated intravascular coagulation. In utero infections are characterized by placentalitis and infection of multiple fetal organs such as heart, lung, and brain.

Development of type-specific neutralizing antibodies appears to be the most important immune defense, mediating prevention against and recovery from infection. Immunoglobulin (Ig) M antibodies, followed by long-lasting IgA and IgG antibodies, and secretory IgA, mediating mucosal immunity, are produced. Although local reinfec tion of the gastrointestinal tract can occur, replication is usually limited and not associated with disease. In vitro and animal experiments suggest that heterotypic antibodies may enhance disease caused by a different serotype. Evidence also suggests that subneutralizing concentrations of serotype-specific antibody may lead to antibody-dependent enhancement of enterovirus 71 infection. Innate and cellular defenses (macrophages and cytotoxic T lymphocytes) may play important roles in recovery from infection. Altered cellular responses to enterovirus 71, including T lymphocyte and natural killer cell depletion, were associated with severe meningoencephalitis ≥ pulmonary edema.

Hypogammaglobulinemia and agammaglobulinemia predispose to severe, often chronic enterovirus infections. Similarly, perinatally infected neonates lacking maternal type-specific antibody to the infecting virus are at risk for severe disease. Enterovirus 71 disease increases after 6 mo of age, when maternal serotype-specific antibody levels have declined. Other risk factors for significant illness include young age, immune suppression (posttransplantation and lymphoid malignancy), and, according to animal models and/or epidemiologic observations, exercise, cold exposure, malnutrition, and pregnancy. Specific human leukocyte antigen genes, immune response gene (e.g., interleukin-10 and interferon-γ) polymorphisms, and low vitamin A levels have been linked to enterovirus 71 susceptibility and severe disease.

**CLINICAL MANIFESTATIONS**

Manifestations are protean, ranging from asymptomatic infection or undifferentiated febrile or respiratory illnesses in the majority, to, less frequently, severe diseases such as meningoencephalitis, myocardiitis, and neonatal sepsis. A majority of individuals are asymptomatic or have very mild illness, yet may serve as significant sources for spread of infection. Symptomatic disease is generally more common in young children.

**Nonspecific Febrile Illness**

Nonspecific febrile illnesses are the most common symptomatic manifestations, especially in infants and young children. These are difficult to clinically differentiate from serious infections such as bacteremia and bacterial meningitis, necessitating diagnostic testing, presumptive therapy, and hospitalizations for suspected bacterial infection in young infants.

Illness usually begins abruptly with fever of 38.5-40°C (101-104°F), malaise, and irritability. Other symptoms are lethargy, anorexia, diarrhea, nausea, vomiting, abdominal discomfort, rash, sore throat, and respiratory symptoms, and, in older children, headache and myalgia. Findings are generally nonspecific and may include mild conjunctivitis, pharyngeal infection, and cervical lymphadenopathy. Meningitis may be present, but, in infants, specific clinical features distinguishing those with meningitis are often lacking. Fever lasts a mean of 3 days and, occasionally, is biphasic. Duration of illness is usually 4-7 days but can range from 1 day to >1 wk. White blood cell (WBC) count and results of routine laboratory tests are generally normal, although transient neutropenia can be seen. Concomitant enterovirus and bacterial infection has been observed in a small number of infants.

Enterovirus illnesses may be associated with a wide variety of skin manifestations, including macular, maculopapular, urticarial, vesicular, and petechial eruptions. Rare cases of idiopathic thrombocytopenic purpura have been reported. Enteroviruses have also been implicated in pityriasis rosea. In general, the frequency of cutaneous manifestations is inversely related to age. Serotypes commonly associated with rashes are echoviruses 9, 11, 16, and 25; coxsackie A viruses 2, 4, 6, 9, and 16; coxsackie B viruses 3-5; and enterovirus 71. Virus can occasionally be recovered from vesicular skin lesions.

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Nonspecific febrile illnesses are the most common symptomatic manifestations, especially in infants and young children. These are difficult to clinically differentiate from serious infections such as bacteremia and bacterial meningitis, necessitating diagnostic testing, presumptive therapy, and hospitalizations for suspected bacterial infection in young infants.

**Noninvasive Systemic Infections**

**Central Nervous System (CNS) Infections**

Infections of the CNS are often associated with long-lasting sequelae. CNS infections are often associated with mononuclear pleocytosis of the cerebrospinal fluid (CSF), composed of macrophages and activated T lymphocytes, and a mixed meningeal inflammatory response. Parenchymal involvement may affect the cerebral white and gray matter, cerebellum, basal ganglia, brainstem, and spinal cord with perivascular and parenchymal mixed or lymphocytic inflammation, gliosis, cellular degeneration, and neuronophagocytosis. Encephalitis during enterovirus 71 epidemics has been characterized by severe involvement of the brainstem, spinal cord gray matter, hypothalamus, and subthalamic and dentate nuclei, and frequently complicated by pulmonary edema, hemorrhage and/or interstitial pneumonitis and cardiopulmonary failure, presumed secondary to brainstem damage, sympathetic hyperactivity, autonomic dysfunction, and CNS and systemic inflammatory responses (including cytokine and chemokine overexpression), and, only occasionally, myocarditis. Immunologic cross-reactivity with brain tissue has been postulated as one mechanism responsible for neurologic damage and sequelae following enterovirus 71 infection. Enterovirus myocarditis is characterized by perivascular and interstitial mixed inflammatory infiltrates and myocardite damage, possibly mediated by viral cytolytic (e.g., cleavage of dystrophin or serum response factor) and innate and adaptive immune-mediated mechanisms. Chronic inflammation may persist after viral clearance.

**Esophageal Infections**

Esophageal infections may result in ulcerative or inflammatory changes that can lead to stricture formation. The majority of esophageal infections are asymptomatic, but some may present with symptoms such as dysphagia, odynophagia, or abdominal pain. Rare cases of Ludwig’s angina have been reported in association with enteroviral esophageal infection.

**Other Systemic Infections**

Other systemic infections associated with enteroviruses include pneumonia, hepatitis, pancreatitis, and myositis. Pneumonia can manifest as either community-acquired or nosocomial pneumonia. Enteroviral pneumonia is more common in young children and can be severe, with a mortality rate of approximately 2%. Hepatitis can range from asymptomatic to severe, with fulminant cases occurring in immunocompromised individuals. Pancreatitis and myositis are rare but potentially severe complications.

**Diagnosis**

The diagnosis of enterovirus infections is typically made through the identification of viral RNA or antigen in clinical specimens such as throat swabs, cerebrospinal fluid, or tissue samples. Viral culture, polymerase chain reaction (PCR), and serological testing are commonly used diagnostic methods. Serological testing can be used to confirm a past infection but is not useful for diagnosing active infection.

**Treatment**

There is no specific antiviral treatment for enterovirus infections. Treatment is primarily supportive, focusing on managing symptoms and complications. Antibiotics are not indicated for enterovirus infections. Immunosuppressive agents may be considered for patients with severe immune deficiencies or those at high risk for life-threatening complications.

**Prevention**

Prevention of enterovirus infections includes hand hygiene and respiratory etiquette to prevent transmission. Vaccination with enterovirus 71 vaccines is recommended for high-risk groups, such as individuals with primary or secondary immunodeficiencies. Good general hygiene practices, such as frequent hand washing, are also important for preventing the spread of enterovirus infections.
Hand-Foot-and-Mouth Disease

Hand-foot-and-mouth disease, one of the more distinctive rash syndromes, is most frequently caused by coxsackievirus A16, sometimes in large outbreaks, and can also be caused by enterovirus 71; coxsackie A viruses 5, 6, 7, 9, and 10; coxsackie B viruses 2 and 5; and some echoviruses. It is usually a mild illness, with or without low-grade fever. The oropharynx is inflamed and contains scattered vesicles on the tongue, buccal mucosa, posterior pharynx, palate, gingiva, and/or lips (Fig. 250-1). These may ulcerate, leaving 4-8 mm shallow lesions with surrounding erythema. Maculopapular, vesicular, and/or pustular lesions may occur on the hands and fingers, feet, and buttocks and groin; the hands are more commonly involved than the feet (see Fig. 250-1). Lesions on the hands and feet are usually tender, 3-7 mm vesicles that occur more commonly on dorsal surfaces but frequently also on palms and soles. Vesicles resolve in about 1 wk. Buttock lesions do not usually progress to vesiculation. Disseminated vesicular rashes may complicate preexisting eczema. Hand-foot-and-mouth disease caused by enterovirus 71 is frequently more severe than coxsackievirus A16 disease, with high rates of neurologic and cardiopulmonary involvement, especially in young children (see “Neurologic Manifestations” below). Coxsackievirus A16 also can occasionally be associated with complications such as encephalitis, acute flaccid paralysis, myocarditis, pericarditis, and shock. Coxsackievirus A6 is also responsible for atypical hand-foot-and-mouth disease (and herpangina), notable for affecting adults and children and causing relatively severe disease, including fever, generalized rash (face, proximal extremities, and trunk, in addition to hands, feet, and buttocks), pain, dehydration, and desquamation of palms and soles. Onychomadesis (nail shedding) has been observed following coxsackievirus A6 and other coxsackievirus infections.

Respiratory Manifestations

Symptoms such as sore throat and coryza frequently accompany and sometimes dominate enterovirus illnesses. Other respiratory findings may include wheezing, exacerbation of asthma, apnea, respiratory distress, pneumonia, otitis media, bronchiolitis, croup, parotitis, and pharyngotonsillitis, which may occasionally be exudative. Lower respiratory tract infection may be significant in immunocompromised patients. Clusters and outbreaks of cases of severe respiratory disease, including pneumonia and wheezing (both in children with a history of asthma and those unaffected by asthma), have been observed in association with multiple lineages of enterovirus 68.

Pleurodynia (Bornholm disease), caused most frequently by coxsackie B viruses 3, 5, 1, and 2 and echoviruses 1 and 6, is an epidemic or sporadic illness characterized by paroxysmal thoracic pain, due to myositis involving chest and abdominal wall muscles and, possibly, pleural inflammation. In epidemics, children and adults are affected, but most cases occur in persons younger than age 30 yr. Malaise, myalgias, and headache are followed by sudden onset of fever and spasmodic, pleuritic pain in the chest or upper abdomen aggravated by coughing, sneezing, deep breathing, or other movement. During spasms, which last from a few minutes to several hours, pain may be severe and respirations are usually rapid, shallow, and grunting, suggesting pneumonia or pleural inflammation. A pleural friction rub may be noted during pain episodes. Chest radiographs are generally normal but can demonstrate pulmonary infiltrates or pleural effusions. Pain localized to the abdomen may suggest colic, intestinal obstruction, appendicitis, or peritonitis. Illness usually lasts 3-6 days, and, occasionally, up to 2 wk. It is frequently biphasic and is rarely associated with recurrent episodes over a few weeks, with less prominent fever during recurrences. Pleurodynia may be associated with meningitis, orchitis, myocarditis, or pericarditis. Life-threatening pulmonary edema, hemorrhage, and/or interstitial pneumonitis may occur in patients with enterovirus 71 encephalitis.

Ocular Manifestations

Epidemics of acute hemorrhagic conjunctivitis, primarily caused by enterovirus 70 and coxsackievirus A24/A24 variant, are explosive, spreading mainly via eye-hand-fomite-eye transmission. School-age children, teenagers, and adults 20-50 yr of age have the highest attack rates. Sudden onset of severe eye pain is associated with photophobia, blurred vision, lacrimation, conjunctival erythema and congestion, lid edema, preauricular lymphadenopathy, and, in some cases, subconjunctival hemorrhages and superficial punctate keratitis. Eye discharge is initially serous but becomes mucopurulent with secondary bacterial infection. Systemic symptoms including fever are rare, although manifestations suggestive of pharyngoconjunctival fever occasionally occur. Recovery is usually complete within 1-2 wk.

Herpangina

Herpangina is characterized by sudden onset of fever, sore throat, dysphagia, and lesions in the posterior pharynx. Temperatures range from normal to 41°C (106°F); fever tends to be greater in younger patients. Headache and backache may occur in older children, and vomiting and abdominal pain occur in 25% of cases. Characteristic lesions, present on the anterior tonsillar pillars, soft palate, uvula, tonsils, posterior pharyngeal wall, and, occasionally, the posterior buccal surfaces, are discrete 1-2 mm vesicles and ulcers that enlarge over 2-3 days to 3-4 mm and are surrounded by erythematous rings that vary in size up to 10 mm. Typically, approximately 5 lesions are present, with a range of 1 to >15. The remainder of the pharynx appears normal or minimally erythematous. Most cases are mild and have no complications; however, some are associated with meningitis or more severe illness. Fever generally lasts 1-4 days, and resolution of symptoms occurs in 3-7 days. A variety of enteroviruses cause herpangina, including enterovirus 71, although coxsackie A viruses are implicated most often.
Occasionally. Other enteroviruses have occasionally been implicated as causes of keratoconjunctivitis.

Epidemic and sporadic uveitis in infants caused by subtypes of enteroviruses 11 and 19 can be associated with severe complications, including destruction of the iris, cataracts, and glaucoma. Enteroviruses have been implicated in cases of chorioretinitis, uveoretinitis, optic neuritis, and unilateral acute idiopathic maculopathy.

**Myocarditis and Pericarditis**

Enteroviruses account for approximately 25-35% of cases of myocarditis and pericarditis with proven cause (see Chapters 440 and 441). Coxsackie B viruses are most commonly implicated, although coxsackie A viruses and echoviruses also may be causative. Adolescents and young adults, especially males, are disproportionately affected. Myopericarditis may be the dominant feature or it may be part of disseminated disease, as in neonates. Disease ranges from relatively mild to severe. Upper respiratory symptoms frequently precede fatigue, dyspnea, chest pain, congestive heart failure, and dysrhythmias. Presentations may mimic myocardial infarction; sudden death may also occur (including apparent sudden infant death syndrome). A pericardial friction rub indicates pericardial involvement. Chest radiography often demonstrates cardiac enlargement. Electrocardiography frequently reveals ST segment, T wave, and/or rhythm abnormalities, and echocardiography may confirm cardiac dilation, reduced contractility, and/or pericardial effusion. Myocardial enzyme serum concentrations may be elevated. The acute mortality of enterovirus myocarditis is 0-4%. Recovery is complete without residual disability in the majority. Occasionally, chronic cardiomyopathy, inflammatory ventricular microaneurysms, or constrictive pericarditis may result. The role of persistent infection in chronic dilated cardiomyopathy is controversial. Enteroviruses have also been implicated in late adverse cardiac events following heart transplantation and in acute coronary events, including myocardial infarction, endocarditis, and peripartum cardiomyopathy. Myocardial dysfunction observed in enterovirus 71 epidemics most commonly has occurred without evidence of myocarditis and may be of neurogenic origin; however, true myocarditis has also been described.

**Gastrointestinal and Genitourinary Manifestations**

Symptoms such as emesis (especially with meningitis), diarrhea (rarely severe), and abdominal pain are frequent but generally not dominant. Diarrhea, hematochezia, pneumatosis intestinalis, and necrotizing enterocolitis have occurred in premature infants during nursery outbreaks. Enterovirus infection has been implicated in acute and chronic gastritis, intussusception, chronic intestinal inflammation in hypogammaglobulinemic patients, sporadic hepatitis in normal children, severe hepatitis in neonates, and pancreatitis, which may result in transient exocrine pancreatic insufficiency.

Coxsackie B viruses are second only to mumps as causes of orchitis. The illness is frequently biphasic; fever and pleurodynia or meningitis are followed, in approximately 2 wk, by orchitis, often with epididymitis. Enteroviruses have also been implicated in cases of nephritis and IgA nephropathy.

**Neurologic Manifestations**

Enteroviruses are the most common cause of viral meningoencephalitis in mumps-immunized populations, accounting for up to 90% or more of cases in which a cause is identified. Meningitis is particularly common in infants, especially in those younger than 3 mo of age, often in community epidemics. Frequently implicated serotypes include coxsackie B viruses 2-5; echoviruses 4, 6, 7, 9, 11, 13, 16, and 30; and enteroviruses 70 and 71. Most cases in infants and young children are mild and lack specific signs and symptoms. Fever is present in 50-100%, accompanied by irritability, malaise, headache, photophobia, nausea, emesis, anorexia, lethargy, hypotonia, rash, cough, rhinorrhea, pharyngitis, diarrhea, and/or myalgia. Nuchal rigidity is apparent in more than half of children older than 1-2 yr of age. Some cases are biphasic, with fever and nonspecific symptoms for a few days followed by return of fever with meningeal signs several days later. Fever usually resolves in 3-5 days, and other symptoms in infants and young children usually resolve within 1 wk. Symptoms tend to be more severe and longer lasting in adults. CSF findings include pleocytosis (generally \( <500 \) but occasionally as high as \( 1,000-8,000 \) WBCs/\( \mu L \); often predominantly polymorphonuclear cells in the 1st 48 hr before becoming mostly mononuclear); normal or slightly low glucose content (10% \( <40 \) mg/dL); and normal or mildly increased protein content (generally \( <100 \) mg/dL). CSF can have normal parameters despite positive viral culture or polymerase chain reaction (PCR) results, particularly in the 1st few months of life and early after illness onset. Complications occur in approximately 10% of young children, including simple and complex seizures, obtundation, increased intracranial pressure, syndrome of inappropriate antidiuretic hormone secretion, ventriculitis, transient cerebral arteriopathy, and coma. The prognosis for most children is good.

Enteroviruses are also responsible for \( \geq 10-20\% \) of cases of encephalitis with an identified cause. Frequently implicated serotypes include echoviruses 3, 4, 6, 9, and 11; coxsackie B viruses 2, 4, and 5; coxsackie A virus 9; and enterovirus 71. After initial nonspecific symptoms, there is progression to confusion, weakness, lethargy, and/or irritability. Depression is usually generalized, although focal findings, including focal motor seizures, hemichorea, acute cerebellar ataxia, aphasia, extrapyramidal symptoms, and/or focal imaging abnormalities, may occur. Manifestations range from altered mental status to coma to decerebrate status. Long-term sequelae, including epilepsy, weakness, cranial nerve palsies, spasticity, psychomotor retardation, and hearing loss, or death may follow severe disease. Persistent or recurrent cases have been observed rarely.

Neurologic disorders have been prominent in recent epidemics in Asia and Australia of enterovirus 71, and, to a lesser extent, coxsackievirus A16 disease. The majority of affected children had hand-foot-and-mouth disease, some had herpangina, and others had no mucocutaneous manifestations. Neurologic syndromes in a fraction of children included meningitis, meningoencephalomyelitis, poliomylitis-like acute flaccid paralysis, Guillain-Barré syndrome, transverse myelitis, cerebellar ataxia, opsoclonus-myoclonus syndrome, benign intracranial hypertension, and brainstem encephalitis (rhabdencephalitis involving the midbrain, pons, and medulla). The last is characterized by altered consciousness, myoclonus, vomiting, ataxia, nystagmus, tremor, cranial nerve abnormalities, autonomic dysfunction, and MRI demonstrating lesions in the brainstem, thalamus, and cerebellum. Although the disease was mild and reversible in some children, others had rapid progression to neurogenic pulmonary edema and hemorrhage, cardiopulmonary failure, shock, and coma. High mortality rates have been reported in children younger than 5 yr of age, especially in those younger than 1 yr of age. Deficits such as central hypventilation, bulbar dysfunction, neurodevelopmental delay, cerebellar defects, attention deficit/hyperactivity-related symptoms, and limb weakness, atrophy have been observed among survivors, especially those who experienced cardiopulmonary failure during their acute illness. Although the most severe cases have been associated with enterovirus 71, similar clinical pictures have been produced by other enterovirus serotypes (e.g., coxsackieviruses A16 and B5, echovirus 7).

Patients with antibody or combined immunodeficiencies (including human immunodeficiency virus infection, acute lymphocytic leukemia, and transplantation) and patients receiving anti-CD20 antibody therapy are at risk for acute or, more commonly, chronic meningoencephalitis. The latter is characterized by persistent CSF abnormalities, viral detection by culture or PCR for years, and recurrent encephalitis and/or progressive neurologic deterioration, including insidious intellectual or personality deterioration, altered mental status, seizures, motor weakness, and increased intracranial pressure. Although disease may wax and wane, deficits generally become progressive and ultimately are frequently fatal or lead to long-term sequelae. A dermatomyositis-like syndrome, hepatitis, arthritis, myocarditis, or disseminated infection may also occur. Chronic enterovirus meningoencephalitis has become less common with high-dose intravenous immunoglobulin replacement.

A variety of nonpoliovirus enteroviruses, including enteroviruses 70 and 71, coxsackie A viruses 7 and 24, coxsackie B viruses, several
echoviruses, and possibly enterovirus 68, can cause poliomyelitis-like acute flaccid paralysis with motor weakness because of spinal cord anterior horn cell involvement. Disease tends to be milder than that caused by poliovirus, with less bulbar involvement and less persistent weakness. Other neurologic syndromes include cerebellar ataxia; transverse myelitis; Guillain-Barré syndrome, axonal polynuropathy, and Miller-Fisher syndrome; acute disseminated encephalomyelitis; peripheral neuritis; optic neuritis; sudden hearing loss, tinnitus, and inner ear disorders such as vestibular neuritis; and other cranial neuropathies.

Myositis and Arthritis

Although myalgia is common, direct evidence of muscle involvement, including rhabdomyolysis, muscle swelling, focal myositis, and poly-myositis, has uncommonly been reported. A dermatomyositis-like syndrome and arthritis can be seen in enterovirus-infected hypogammaglobulinemic patients. Enteroviruses are a rare cause of arthritis in normal hosts.

Neonatal Infections

Neonatal infections are relatively common, with a disease incidence comparable to or greater than that of neonatal herpes simplex virus, cytomegalovirus, and group B streptococcus disease. Infection frequently is caused by coxsackie B viruses 2-5 and echoviruses 6, 9, 11, and 19, although many serotypes have been implicated, including, in more recent years, coxsackie B virus 1 and echovirus 30. Enteroviruses may be acquired vertically before, during, or after delivery, including possible transmission via breast milk; horizontally from family members; or by sporadic or epidemic transmission in nurseries. In utero infection can lead to fetal demise, nonimmune hydrops fetalis, or neonatal illness. Additionally, maternal and intrauterine infections have been speculatively linked to congenital anomalies; prematurity, low birthweight, and intrauterine growth retardation; neurodevelopmental sequelae; unexplained neonatal illness and death; and increased risk of type 1 diabetes.

Neonatal infection may range from asymptomatic (the majority) to benign febrile illness to severe multisystem disease. Most affected newborns are full term and previously well; maternal history often reveals a recent viral illness, including fever and, frequently, abdominal pain. Neonatal symptoms may occur as early as day 1 of life, with onset of severe disease generally within the 1st 2 wk of life. Frequent findings include fever or hypothermia, irritability, lethargy, anorexia, rash (usually maculopapular, occasionally petechial or papulovesicular), jaundice, respiratory symptoms, apnea, hepatomegaly, abdominal distention, emesis, diarrhea, and decreased perfusion. Most patients have benign courses, with resolution of fever in an average of 3 days and of other symptoms in about 1 wk. A biphasic course may occur occasionally. A minority have severe disease dominated by any combination of sepsis, meningoencephalitis, myocarditis, hepatitis, coagulopathy, and/or pneumonitis. Meningoencephalitis may be manifested by focal or complex seizures, bulging fontanelle, nuchal rigidity, or reduced level of consciousness. Myocarditis, most often associated with coxsackie B virus infection, may be suggested by tachycardia, dyspnea, cyanosis, and cardiomegaly. Hepatitis and pneumonitis are associated with echovirus infection, although they may occur with coxsackie B viruses. Gastrointestinal manifestations may predominate in premature neonates. Laboratory and radiographic evaluation may reveal leukocytosis, thrombocytopenia, CSF pleocytosis, CNS white matter damage, elevations of serum transaminases and bilirubin, coagulopathy, pulmonary infiltrates, and electrocardiographic changes.

Complications of severe neonatal illness include CNS necrosis and generalized or focal neurologic compromise; arrhythmias, congestive heart failure, myocardial infarction, and pericarditis; hepatic necrosis and failure; intracranial or other bleeding; adrenal necrosis and hemorrhage; and rapidly progressive pneumonitis and pulmonary hypertension. Myositis, arthritis, necrotizing enterocolitis, inappropriate antidiuretic hormone secretion, hemophagocytic lymphohistiocytosis-like presentation, bone marrow failure, and sudden death are rare events. Mortality with severe disease is significant and most often associated with hepatitis and bleeding complications, myocarditis, or pneumonitis.

Survivors of severe neonatal disease may have gradual resolution of hepatic and cardiac dysfunction, although persistent hepatic dysfunction and residual cardiac impairment, chronic calcific myocarditis, and ventricular aneurysm can occur. Meningoencephalitis may be associated with speech and language impairment; cognitive deficits; spasticity, hypotonicity, or weakness; seizure disorders; microcephaly or hydrocephaly; and ocular abnormalities. However, many survivors appear not to have long-term sequelae. Risk factors for severe disease include illness onset in the 1st few days of life, maternal illness just prior to or at delivery, prematurity, male sex, infection by echovirus 11 or a coxsackie B virus, positive serum viral culture, absence of neutralizing antibody to the infecting virus, and evidence of severe hepatitis and/or multisystem disease.

Transplant Recipients and Patients with Malignancies

Enterovirus infections in stem cell and solid organ transplant recipients may be severe and/or prolonged, causing progressive pneumonia, severe diarrhea, pericarditis, heart failure, meningoencephalitis, and disseminated disease. Enterovirus-associated hemophagocytic lymphohistiocytosis, meningitis, encephalitis, and myocarditis have been reported in children with malignancies and patients treated with anti-CD20 monoclonal antibody. Infections in these groups are associated with high fatality rates.

Diagnosis

Clues to enterovirus infection include characteristic findings such as hand-foot-and-mouth disease or herpangina lesions, consistent seasonality, known community outbreak, and exposure to enterovirus-compatible disease. In the neonate, history of maternal fever, malaise, and/or abdominal pain near delivery during enterovirus season is suggestive.

Enterovirus infection can be confirmed with viral culture using a combination of cell lines. Sensitivity ranges from 50-75% and can be increased by sampling of multiple sites (e.g., CSF plus throat and rectum in children with meningitis). In neonates, yields of 30-70% are achieved when blood, urine, CSF, and mucosal swabs are cultured. A major limitation is the inability of most coxsackie A viruses to grow in culture. Yield may also be limited by neutralizing antibody in patient specimens, improper specimen handling, or insensitivity of the cell lines used. Culture is relatively slow, with 3-8 days usually required to detect growth. Centrifugation-enhanced antigen detection coupled with culture (shell vial techniques) can shorten the time to detection, but the sensitivity of this method has been limited. Although cultivation of an enterovirus from any site can generally be considered evidence of recent infection, isolation from the rectum or stool can reflect more remote shedding. Similarly, recovery from a mucosal site may suggest an association with an illness, whereas recovery from a normally sterile site (e.g., CSF, blood, or tissue) is more conclusive evidence of causation. Serotype identification by type-specific antibody staining or neutralization of a viral isolate is generally required only for investigation of an outbreak or an unusual disease manifestation, surveillance, or to distinguish nonpoliovirus enteroviruses from vaccine or wild-type polioviruses.

Direct testing for nucleic acid overcomes the imperfect sensitivity and delayed results of culture. RT-PCR detection of highly conserved areas of the enterovirus genome can detect the majority of enteroviruses, including coxsackie A viruses (but generally not the parechoviruses) in CSF; serum; urine; conjunctival, nasopharyngeal, throat, tracheal, rectal, and stool specimens; dried blood spots; and tissues such as myocardium, liver, and brain. Sensitivity and specificity of RT-PCR are high, with results in as short as 2-3 hr. Real-time, quantitative PCR assays and nested PCR assays with enhanced sensitivity have been developed, as have enterovirus-containing multiplex PCR assays, nucleic acid sequence–based amplification assays, reverse transcription-loop-mediated isothermal amplification, culture-enhanced PCR assays, and PCR-based microarray assays. PCR testing of CSF from children with meningitis and from hypogammaglobulinemic patients with chronic meningoencephalitis is frequently positive despite negative cultures. Routine application of CSF PCR for infants and young children with
suspected meningitis decreases the number of diagnostic tests, duration of hospital stay, antibiotic use, and overall costs. PCR testing of tracheal aspirates of children with myocarditis has good concordance with testing of myocardial specimens. In ill neonates and young infants, PCR testing of serum and urine has higher yields than culture. Viral load in blood of neonates is correlated with disease severity, and viral nucleic acid may persist in blood of severely ill newborns for up to 2 mo.

Sequence analysis of amplified nucleic acid can be used for serotype identification and phylogenetic analysis and to establish a transmission link among cases. Serotype-specific (e.g., enterovirus 71 and coxsackie A virus 16) PCR assays have been developed, including assays that can be used in resource-poor regions. For enterovirus 71, the yield of specimens other than CSF and blood (throat, nasopharyngeal, rectal, and vesicle swabs and CNS tissue) is greater (by PCR or culture) than the yield of CSF and blood, which are infrequently positive. Antigen detection assays that target specific serotypes such as enterovirus 71 with monoclonal antibodies have also been developed.

Enterovirus infections can be detected serologically by a rise, in serum or CSF, of neutralizing, complement fixation, enzyme-linked immunosorbent assay, or other type-specific antibody or by detection of serotype-specific IgM antibody. However, serologic testing requires presumptive knowledge of the infecting serotype or an assay with sufficiently broad cross-reactivity. Sensitivity and specificity may be limiting, and cross-reactivity among serotypes may occur. Except for epidemiologic studies or cases characteristic of specific serotypes (e.g., enterovirus 71), serology is generally less useful than culture or nucleic acid detection.

**Differential Diagnosis**

The differential diagnosis of enterovirus infections varies with the clinical presentation (Table 250-2).

**Human parechoviruses**, members of the *Picornaviridae* family, produce many manifestations similar to the nonpolio enteroviruses. Human parechoviruses are small RNA viruses that were once mistakenly classified as echoviruses. Infections in older children are often unrecognized or cause nonspecific acute and benign febrile illnesses with very few specific findings. Neonates and young infants are often more severely affected, demonstrating aseptic meningitis, encephalitis, a sepsis-like picture, and hepatitis. The viral sepsis and the encephalitic presentations are the most common serious manifestations, often requiring intensive care treatment for shock, seizures, and other signs of encephalitis. Epidemics occur in the same season as enterovirus infections; in contrast to the enteroviruses there is a higher incidence of MRI abnormalities in those with encephalitis.

More frequently than with enteroviruses, those affected by parechovirus may have no CSF pleocytosis despite the presence of CNS infection. The diagnosis is confirmed by human parechovirus-specific PCR on CSF, stool, and nasopharyngeal secretions. Infants suspected of having an enteroviral infection should also be considered as possibly having a parechovirus infection because the two may be indistinguishable; nonetheless, parechovirus infections appear to be less common.

**TREATMENT**

In the absence of a proven antiviral agent for enterovirus infections, supportive care is the mainstay of treatment. Newborns and young infants with nonspecific febrile illnesses and children with meningitis frequently require diagnostic evaluations for bacterial and herpesvirus infections and hospitalization for presumptive treatment until tests rule out these diagnoses. Neonates with severe disease and infants and children with myocarditis or concerning neurologic diseases (e.g., enterovirus 71 neurologic and/or cardiopulmonary disease) may require intensive supportive care, including cardiorespiratory and blood product support. Milrinone has been suggested as a useful agent in severe enterovirus 71 cardiopulmonary disease. Liver and cardiac transplantation have been performed for neonates with progressive end-organ failure.

Immunoglobulin has been utilized to treat enterovirus infections based on the importance of the humoral immune response to enterovirus infection and the observation that absence of neutralizing antibody is a risk factor for symptomatic infection. Immunoglobulin products contain neutralizing antibodies to many commonly circulating serotypes, although titers vary with serotype and among products and lots. Ancrodotal and retrospective, uncontrolled use of intravenous immunoglobulin or infusion of maternal convalescent plasma to treat newborns with severe disease has been associated with varying outcomes. The one randomized, controlled trial was too small to demonstrate significant clinical benefits, although neonates who received immunoglobulin containing high neutralizing titers to their own isolates had shorter periods of viremia and viruria. Immunoglobulin has been administered intravenously and intrathecally to treat hypogammaglobulinemic patients with chronic enterovirus meningoencephalitis and intravenously in transplant and oncology patients with severe infections, with variable success. Intravenous immunoglobulin and corticosteroids have been used for patients with neurologic disease caused by enterovirus 71 and other enteroviruses; modulation of cytokine profiles after administration of intravenous immunoglobulin for enterovirus 71–associated brainstem encephalitis has been demonstrated. High-titer enterovirus 71 immunoglobulin appeared promising in animal models, and clinical trials in regions with epidemic enterovirus 71 disease are underway. Development of anti–enterovirus 71 monoclonal antibodies is also being pursued. A retrospective study suggested that treatment of presumed viral myocarditis with immunoglobulin was associated with improved outcome; however, virologic diagnoses were not made. Evaluation of corticosteroids and

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### Table 250-2  Differential Diagnosis of Enterovirus Infections

<table>
<thead>
<tr>
<th>CLINICAL MANIFESTATION</th>
<th>BACTERIAL PATHOGENS</th>
<th>VIRAL PATHOGENS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonspecific febrile illness</td>
<td><em>Streptococcus pneumoniae</em>, <em>Haemophilus influenzae</em> type b, <em>Neisseria meningitidis</em></td>
<td>Influenza viruses, human herpesviruses 6 and 7, human parechoviruses</td>
</tr>
<tr>
<td>Respiratory illness/conjunctivitis</td>
<td><em>S. pneumoniae</em>, <em>H. influenzae</em> (nontypeable and type b), <em>N. meningitidis</em>, <em>Mycoplasma pneumoniae</em>, <em>Chlamydia pneumoniae</em></td>
<td><em>Adenoviruses</em>, <em>influenza</em> viruses, <em>respiratory syncytial virus</em>, parainfluenza viruses, <em>rhinoviruses</em>, human <em>metapneumovirus</em>, <em>coronaviruses</em></td>
</tr>
<tr>
<td>Myocarditis/pericarditis</td>
<td><em>S. aureus</em>, <em>H. influenzae</em> type b, <em>M. pneumoniae</em></td>
<td><em>Adenoviruses</em>, <em>influenza</em> virus, parvovirus, <em>cytomegalovirus</em></td>
</tr>
<tr>
<td>Neonatal infections</td>
<td>Group B streptococcus, Gram-negative enteric bacilli, <em>L. monocytogenes</em>, <em>Enterococcus</em></td>
<td><em>Herpes simplex</em> virus, adenoviruses, <em>cytomegalovirus</em>, rubella virus, human parechoviruses</td>
</tr>
</tbody>
</table>
cyclosporine and other immunosuppressive therapy for myocarditis has been inconclusive. Successful treatment of enterovirus myocarditis with interferon-α has been reported anecdotally, and interferon-β treatment was associated with viral clearance, improved cardiac function, and survival in chronic cardiomyopathy associated with persistence of enterovirus (or adenovirus) genome. Activity of interferon-α against enterovirus 71 has been demonstrated in in vitro and in animal models, but potency varies with interferon-α type.

Antiviral agents that act at various steps in the enterovirus life cycle—attachment, penetration, uncoating, translation, polyprotein processing, protease activity, replication, and assembly—are being evaluated. Candidates include pharmacologically active chemical compounds, small interfering RNAs and DNA-like antisense agents, purine nucleoside analogs, synthetic peptides, enzyme inhibitors of signal transduction pathways, interferon-inducers, and herbal compounds. Pleconaril, an inhibitor of attachment and uncoating, was associated with benefit in some controlled studies of enterovirus meningitis and picornavirus upper respiratory tract infections, and uncontrolled experience suggested possible benefits in high-risk infections; however, application for licensure was denied because of concern about potential medication interactions. A randomized, controlled trial of pleconaril in neonates with severe hepatitis, coagulopathy, and/or myocarditis suggested possible virologic and clinical benefits of treatment.

Design and evaluation of candidate agents active against enterovirus 71 is a priority. Of currently available agents, lactoferrin and ribavirin have demonstrated activity in vitro and/or in animal models. Challenges to development of antivirals for enterovirus 71 include limited cross-genotypic activity of candidate compounds and high viral mutagenicity that favors emergence of resistance.

COMPLICATIONS AND PROGNOSIS
The prognosis in the majority of enterovirus infections is excellent. Morbidity and mortality are associated primarily with myocarditis, neurologic disease, severe neonatal infections, and infections in immune compromised hosts.

PREVENTION
The first line of defense is hygiene, such as handwashing, to prevent fecal-oral and respiratory spread within families, schools, and institutional settings; avoidance of sharing utensils and drinking containers and other potential fomites; disinfection of contaminated surfaces; and avoiding community settings where exposures are likely to occur. Chlorination of drinking water and swimming pools may be important. Infection control techniques such as cohorting have proven effective in limiting nursery outbreaks. Prophylactic administration of immunoglobulin or convalescent plasma has been used in nursery epidemics; simultaneous use of infection control interventions makes it difficult to determine efficacy.

Pregnant women near term should avoid contact with individuals ill with possible enterovirus infections. If a pregnant woman experiences a suggestive illness, it is advisable not to proceed with emergency delivery unless there is concern for fetal compromise or obstetric emergencies cannot be excluded. Rather, it may be advantageous to extend pregnancy, allowing the fetus to passively acquire protective antibodies. A strategy of prophylactically administering immunoglobulin to neonates born to mothers with enterovirus infections is untested.

Maintenance antibody replacement with high-dose intravenous immunoglobulin for patients with hypogammaglobulinemia has reduced the incidence of chronic enterovirus meningoencephalitis, although breakthrough infections occur. Vaccines for nonpoliovirus enteroviruses are not available, but candidates for virulent serotypes such as enterovirus 71 are being investigated. Approaches include inactivated vaccines; VP1 capsid protein-based subunit, DNA, and vector vaccines; combined peptide vaccines; live-attenuated vaccines; virus-like particles; breast milk enriched with VP1 capsid protein or lactoferrin; and interferon-γ-expressing recombinant viral vectors. Several enterovirus 71 candidate vaccines have demonstrated protection in animal models and human clinical trials. Circulation of multiple enterovirus 71 types, antigenic drift, viral recombination, and potential immunologic cross-reactivity with brain tissue may pose challenges to vaccine development.

Bibliography is available at Expert Consult.
Bibliography


The parvoviruses are small, single-stranded DNA viruses. They are common infectious agents of a variety of animal species, including mammals, birds, and insects. Parvoviruses as a group include a number of important animal pathogens. There are now 4 different types of parvoviruses known to infect humans: the dependoviruses also called adeno-associated viruses (AAVs), parvovirus B19 (B19), human bocaviruses (HBoV), and parvovirus 4. B19 and HBoV are the only 2 parvoviruses known to be pathogenic in humans. B19 is the most well studied and clinically important of the human parvoviruses and the cause of *erythema infectiosum* or *fifth disease*. The more recently described human bocavirus is an emerging human pathogen.

**ETIOLOGY**

The 4 human parvoviruses are distinct enough from each other to represent 4 different genera within the Paroviridae family. B19 is a member of the genus *Erythrovirus*. The virus is composed of an icosahedral protein capsid without an envelope and contains a single-stranded DNA genome of approximately 5.5 kb. It is relatively heat and solvent resistant. It is antigenically distinct from other mammalian parvoviruses and has only 1 known serotype. The relatively short parvovirus genome does not encode a DNA polymerase, so all parvoviruses require either host cell factors present in late S phase or coinfection with another virus to replicate their DNA. B19 can be propagated effectively in vitro only in CD36+ erythroid progenitor cells derived from human bone marrow, umbilical cord blood, or peripheral blood.

HBoV is a member of the genus *Bocavirus*. HBoV was first isolated from nasopharyngeal specimens from children with respiratory tract infection in 2005. It was identified using random polymerase chain reaction (PCR) amplification and sequencing methods specifically designed to detect previously unknown viral sequences. Analysis of the gene sequences showed similarities to both bovine and canine parvoviruses, and thus the virus was named human bocavirus. Later, 3 other HBoVs were identified in stool samples and named HBoV types 2, 3, and 4, with the initial respiratory isolate called HBoV1. The HBoV capsid structure and genome size are similar to those of B19, but the genomic organization and replication are different (though not fully characterized to date). HBoVs cannot be propagated in conventional cell culture but have been grown in a pseudostratified human airway epithelial cell culture system.

The AAVs are members of the genus *Dependovirus* and were the first parvoviruses to be found in humans. They were originally identified as contaminants in adenovirus preparations, resulting in the designation “adeno-associated viruses.” They were later isolated directly from human tissue samples, and now several AAV serotypes are known to commonly infect humans. AAVs have a unique life cycle that can take 1 of 2 paths: (1) a lytic infection with replication of viral DNA and production of new virus, or (2) viral integration into the host cell DNA. In the presence of a “helper” virus, usually an adenovirus or a herpesvirus, AAV can replicate its DNA, produce capsids, and release new virions by cell lysis. In the absence of a helper virus infection, the AAV genome becomes integrated into the host cell DNA. This feature has drawn interest in AAVs as potential vectors for gene therapy. Although
human infection with AAVs is common, there is no known disease association and no evidence of pathogenicity, so this virus will not be discussed further in this chapter.

Parvovirus 4 was initially identified in 2005 from the blood of an adult patient with “acute viral syndrome,” who was also an intravenous drug user coinfected with hepatitis C. Subsequently, this virus has been found in blood donors and donated plasma pools in many different countries. It appears to be present in approximately 3% of blood donors in the United States and 4% of plasma pools. There is, as of this writing, no known disease association or clinical symptoms associated with infection. The virus has not yet been assigned to a parvovirus genus and may represent a new genus once its virology is better characterized. The full epidemiology and clinical relevance of this virus await further study, and the reader is referred to the bibliography for further information.

**Epidemiology**

**Parvovirus B19**

Infections with B19 are common and occur worldwide. Clinically apparent infections, such as the rash illness of erythema infectiosum and transient aplastic crisis, are most prevalent in school-age children (70% of cases occur in patients between 5 and 15 yr of age). Seasonal peaks occur in the late winter and spring, with sporadic infections throughout the year. Seroprevalence increases with age, 40-60% of adults having evidence of prior infection.

Transmission of B19 is by the respiratory route, presumably via large-droplet spread from nasopharyngeal viral shedding. The transmission rate is 15-30% among susceptible household contacts, and mothers are more commonly infected than fathers. In outbreaks of erythema infectiosum in elementary schools, the secondary attack rates range from 10-60%. Nosocomial outbreaks also occur, with secondary attack rates of 30% among susceptible healthcare workers.

Although respiratory spread is the primary mode of transmission, B19 is also transmissible in blood and blood products, as documented among children with hemophilia receiving pooled-donor clotting factor. Given the resistance of the virus to solvents, fomite transmission could be important in childcare centers and other group settings, but this mode of transmission has not been established.

**Human Bocaviruses**

The majority of studies published have used molecular methods to detect HBoV DNA in respiratory secretions, fecal samples, blood, and other tissues. HBoV DNA (HBoV1) can be found commonly in respiratory secretions from children hospitalized with acute lower respiratory tract infections (LRTIs). It is more prevalent in children younger than 2 yr of age and seems to be associated with wheezing respiratory illness. However, it can be isolated from respiratory secretions from asymptomatic children and can often be found as a coinfection with other common respiratory pathogens of children this age, including respiratory syncytial virus, human metapneumovirus, and rhinoviruses. This has caused some confusion as to the pathogenic role of HBoV in acute LRTI, including whether it can persist in secretions long after a subclinical infection or requires a helper virus. A limited number of seroepidemiologic studies have been performed, and these suggest that infection is common in children younger than 5 yr of age. The most recent studies provide evidence that the virus is in fact pathogenic, especially in children younger than 2 with wheezing and LRTI, as HBoV1 is more likely to be the only virus isolated in these patients and more likely to have an acute antibody response when coupled with antibody testing. When quantitative PCR is used, the virus is found to be much higher in titer in these symptomatic cases. HBoV DNA (HBoV2, HBoV3, and HBoV4) has also been found in fecal samples in studies from various countries, but its role as a cause of viral gastroenteritis is still undetermined.

**Pathogenesis**

**Parvovirus B19**

The primary target of B19 infection is the erythroid cell line, specifically erythroid precursors near the pronormoblast stage. Viral infection produces cell lysis, leading to a progressive depletion of erythroid precursors and a transient arrest of erythropoiesis. The virus has no apparent effect on the myeloid cell line. The tropism for erythroid cells is related to the erythrocyte P blood group antigen, which is the primary cell receptor for the virus and is also found on endothelial cells, placental cells, and fetal myocardial cells. Thrombocytopenia and neutropenia are often observed clinically, but the pathogenesis of these abnormalities is unexplained.

Experimental infection of normal volunteers with B19 revealed a biphasic illness. From 7-11 days after inoculation, subjects had viremia and nasopharyngeal viral shedding with fever, malaise, and rhinorrhea. Reticulocyte counts dropped to undetectable levels but resulted in only a mild, clinically insignificant fall in serum hemoglobin. With the appearance of specific antibodies, symptoms resolved and serum hemoglobin returned to normal. Several subjects experienced a rash associated with arthralgia 17-18 days after inoculation. Some manifestations of B19 infection, such as transient aplastic crisis, appear to be a direct result of viral infection, whereas others, including the exanthem and arthritis, appear to be postinfectious phenomena related to the immune response. Skin biopsy of patients with erythema infectiosum reveals edema in the epidermis and a perivascular mononuclear infiltrate compatible with an immune-mediated process.

Individuals with chronic hemolytic anemia and increased red blood cell (RBC) turnover are very sensitive to minor perturbations in erythropoiesis. Infection with B19 leads to a transient arrest in RBC production and a precipitous fall in serum hemoglobin, often requiring transfusion. The reticulocyte count drops to undetectable levels, reflecting the lysis of infected erythroid precursors. Humoral immunity is crucial in controlling infection. Specific immunoglobulin (Ig) M appears within 1-2 days of infection and is followed by anti-B19 IgG, which leads to control of the infection, restoration of reticulocytosis, and a rise in serum hemoglobin.

Individuals with impaired humoral immunity are at increased risk for more serious or persistent infection with B19, which usually manifests as chronic RBC aplasia, although neutropenia, thrombocytopenia, and marrow failure are also described. Children undergoing chemotherapy for leukemia or other forms of cancer, transplant recipients, and patients with congenital or acquired immunodeficiency states (including AIDS) are at risk for chronic B19 infections.

Infections in the fetus and neonate are somewhat analogous to infections in immunocompromised persons. B19 is associated with nonimmune fetal hydrops and stillbirth in women experiencing a primary infection but does not appear to be teratogenic. Like most mammalian parvoviruses, B19 can cross the placenta and cause fetal infection during primary maternal infection. Parvovirus cytopathic effects are seen primarily in erythroblasts of the bone marrow and sites of extramedullary hematopoiesis in the liver and spleen. Fetal infection can presumably occur as early as 6 wk of gestation, when erythroblasts are first found in the fetal liver; after the 4th mo of gestation, hematopoiesis switches to the bone marrow. In some cases, fetal infection leads to profound fetal anemia and subsequent high-output cardiac failure (see Chapter 103). Fetal hydrops ensues and is often associated with fetal death. There may also be a direct effect of the virus on myocardial tissue that contributes to the cardiac failure. However, most infections during pregnancy result in normal deliveries at term. Some of the asymptomatic infants from these deliveries have been reported to have chronic postnatal infection with B19 that is of unknown significance.

**Human Bocaviruses**

Mechanisms of HBoV replication and pathogenesis are poorly characterized to date. Growth of HBoV1 in tissue culture is difficult, though the virus has been cultured in primary respiratory epithelial cells as noted above. The primary site of viral replication appears to be the respiratory tract, as the virus has been detected most frequently and in highest copy numbers here. HBoV1 has also been found occasionally in the serum, suggesting the potential for systemic spread. HBoV1 has also been detected in stool, but copy numbers are very low. In contrast, HBoV types 2-4 are found predominantly in the stool, but host cell types are not known.
CLINICAL MANIFESTATIONS

Parvovirus B19

Many infections are clinically inapparent. Infected children characteristically demonstrate the rash illness of erythema infectiosum. Adults, especially women, frequently experience acute polyarthropathy with or without a rash.

Erythema Infectiosum (Fifth Disease)

The most common manifestation of parvovirus B19 is erythema infectiosum, also known as fifth disease, which is a benign, self-limited exanthematous illness of childhood.

The incubation period for erythema infectiosum is 4-28 days (average: 16-17 days). The prodromal phase is mild and consists of low-grade fever in 15-30% of cases, headache, and symptoms of mild upper respiratory tract infection. The hallmark of erythema infectiosum is the characteristic rash, which occurs in 3 stages that are not always distinguishable. The initial stage is an erythematous facial flushing, often described as a “slapped-cheek” appearance (Fig. 251-1). The rash tends to be more prominent on extensor surfaces, sparing the palms and soles. Affected children are afebrile and do not appear ill. Some have petechiae. Older children and adults often complain of mild pruritus. The rash resolves spontaneously without desquamation, but tends to wax and wane over 1-3 wk. It can recur with exposure to sunlight, heat, exercise, and stress. Lymphadenopathy and atypical papular, purpuric, vesicular rashes are also described.

Arthropathy

Arthritis and arthralgia may occur in isolation or with other symptoms. Joint symptoms are much more common among adults and older adolescents with B19 infection. Females are affected more frequently than males. In 1 large outbreak of fifth disease, 60% of adults and 80% of adult women reported joint symptoms. Joint symptoms range from diffuse polyarthralgia with morning stiffness to frank arthritis. The joints most often affected are the hands, wrists, knees, and ankles, but practically any joint may be affected. The joint symptoms are self-limited and, in the majority of patients, resolve within 2-4 wk. Some patients may have a prolonged course of many months, suggesting rheumatoid arthritis. Transient rheumatoid factor positivity is reported in some of these patients but with no joint destruction.

Transient Aplastic Crisis

The transient arrest of erythropoiesis and absolute reticulocytopenia induced by B19 infection leads to a sudden fall in serum hemoglobin in individuals with chronic hemolytic conditions. This B19-induced RBC aplasia or transient aplastic crisis occurs in patients with all types of chronic hemolysis and/or rapid RBC turnover, including sickle cell disease, thalassemia, hereditary spherocytosis, and pyruvate kinase deficiency. In contrast to children with erythema infectiosum only, patients with aplastic crisis are ill with fever, malaise, and lethargy and have signs and symptoms of profound anemia, including pallor, tachycardia, and tachypnea. Rash is rarely present. The incubation period for transient aplastic crisis is shorter than that for erythema infectiosum because the crisis occurs coincident with the viremia.

Persons with sickle cell hemoglobinopathies may also have a concurrent vaso-occlusive pain crisis, further confusing the clinical presentation.

Immunocompromised Persons

Persons with impaired humoral immunity are at risk for chronic parvovirus B19 infection. Chronic anemia is the most common manifestation, sometimes accompanied by neutropenia, thrombocytopenia, or complete marrow suppression. Chronic infections occur in persons receiving cancer chemotherapy or immunosuppressive therapy for transplantation and persons with congenital immunodeficiencies, AIDS, and functional defects in IgG production who are thereby unable to generate neutralizing antibodies.

Fetal Infection

Primary maternal infection is associated with nonimmune fetal hydrops and intrauterine fetal demise, with the risk for fetal loss after infection estimated at <3%. The mechanism of fetal disease appears to be a viral-induced RBC aplasia at a time when the fetal erythroid fraction is rapidly expanding, leading to profound anemia, high-output cardiac failure, and fetal hydrops. Viral DNA has been detected in infected abortuses. The 2nd trimester seems to be the most sensitive period, but fetal losses are reported at every stage of gestation. If maternal B19 infection is suspected, fetal ultrasonography and measurement of the peak systolic flow velocity of the middle cerebral artery are sensitive,
noninvasive procedures to diagnose fetal anemia and hydrops. Most infants infected in utero are born normally at term, including some who have had ultrasonographic evidence of hydrops. A small subset of infants infected in utero may acquire a chronic or persistent postnatal infection with B19 that is of unknown significance. Congenital anemia associated with intrauterine B19 infection has been reported in a few cases, sometimes following intrauterine hydrops. This process may mimic other forms of congenital hypoplastic anemia (e.g., Diamond-Blackfan syndrome). Fetal infection with B19 has been associated with bone lesions but has not been associated with other birth defects. B19 is only 1 of many causes of hydrops fetalis (see Chapter 103.2).

Myocarditis
B19 infection has been associated with myocarditis in fetuses, infants, children, and a few adults. Diagnosis has often been based on serologic findings suggestive of a concurrent B19 infection, but in many cases B19 DNA has been demonstrated in cardiac tissue. B19-related myocarditis is plausible because fetal myocardial cells are known to express P antigen, the cell receptor for the virus. In the few cases in which histology is reported, a predominantly lymphocytic infiltrate is described. Outcomes have varied from complete recovery to chronic cardiomyopathy to fatal cardiac arrest. Although B19-associated myocarditis seems to be a rare occurrence, there appears to be enough evidence to consider B19 as a potential cause of lymphocytic myocarditis, especially in infants and immunocompromised persons.

Other Cutaneous Manifestations
A variety of atypical skin eruptions have been reported with B19 infection. Most of these are petechial or purpuric in nature, often with evidence of vasculitis on biopsy. Among these rashes, the papular-purpuric "gloves-and-socks" syndrome (PPGSS) is well established in the dermatologic literature as distinctively associated with B19 infection (Fig. 251-3). PPGSS is characterized by fever, pruritus, and painful edema and erythema localized to the distal extremities in a distinct "gloves-and-socks" distribution, followed by acral petechiae and oral lesions. The syndrome is self-limited and resolves within a few weeks. Although PPGSS was initially described in young adults, a number of reports of the disease in children have since been published. In those cases linked to B19 infection, the eruption is accompanied by serologic evidence of acute infection.

Human Bocaviruses
Many studies have reported an association between respiratory tract infection and HBoV1 infection as detected by PCR of respiratory secretions, primarily nasopharyngeal secretions. Clinical manifestations in these studies have ranged from mild upper respiratory symptoms to pneumonia. However, the role of HBoV1 as a pathogen has been challenged by the detection of the virus in asymptomatic children and by the frequent detection of other respiratory viruses in the same samples. Nonetheless, studies that have included some combination of quantitative PCR, serum PCR, and serology have been more convincing about HBoV1 as a human pathogen. The use of a quantitative PCR method also seems to differentiate between HBoV1 infection (and wheezing) and prolonged viral shedding, as patients with higher viral titers were more likely to be symptomatic, to be viremic, and to have HBoV1 isolated without other viruses.

HBoV type 2 DNA has been found in the stool of 3-25% of children with gastroenteritis, but often with another enteric virus. DNA of HBoV types 2, 3, and 4 has also been found in the stool of healthy, asymptomatic individuals. At present, there are few data linking HBoV2, HBoV3, or HBoV4 to gastroenteritis or any clinical illness. Further studies are required to determine if any of the HBoVs are associated with some cases of childhood gastroenteritis.

DIAGNOSIS
Parvovirus B19 Infection
The diagnosis of erythema infectiosum is usually based on clinical presentation of the typical rash and rarely requires virologic confirmation. Similarly, the diagnosis of a typical transient aplastic crisis in a child with sickle cell disease is generally made on clinical grounds without specific virologic testing. Serologic tests for the diagnosis of B19 infection are available. B19-specific IgM develops rapidly after infection and persists for 6-8 wk. Anti-B19 IgG serves as a marker of past infection or immunity. Determination of anti-B19 IgM is the best marker of recent/acute infection on a single serum sample; seroconversion of anti-B19 IgG antibodies in paired sera can also be used to confirm recent infection. Demonstration of anti-B19 IgG in the absence of IgM, even in high titer, is not diagnostic of recent infection.

Serologic diagnosis is unreliable in immunocompromised persons; diagnosis in these patients requires methods to detect viral DNA. Because the virus cannot be isolated by standard cell culture, methods to detect viral particles or viral DNA, such as PCR and nucleic acid hybridization, are necessary to establish the diagnosis. These tests are not widely available outside of research centers or reference laboratories. Prenatal diagnosis of B19-induced fetal hydrops can be accomplished by detection of viral DNA in fetal blood or amniotic fluid by these methods.

Human Bocavirus Infections
HBoV1 infections cannot be differentiated from other viral respiratory infections on clinical grounds. HBoV DNA can be readily detected by PCR methods and is now included in several commercially available multiplex respiratory virus PCR assays. As noted above, quantitative
PCR is useful to differentiate acute infection from persistent viral shedding, as higher viral copy numbers (>10^4 HBoV1 genomes/mL) correlate with acute illness, but this test is not widely available. Likewise, serologic methods to detect specific IgM and IgG antibodies have been developed, but these too are not routinely available and there are problems with cross-reactivity among antibodies to the various HBoV types. The most reliable method to diagnose HBoV1 infection would include detection of viral DNA in serum by PCR, and in respiratory tract samples by quantitative PCR, with concurrent detection of IgM or a diagnostic IgG response in paired samples.

**DIFFERENTIAL DIAGNOSIS**

**Parvovirus B19**
The rash of erythema infectiosum must be differentiated from rubella, measles, enteroviral infections, and drug reactions. Rash and arthritis in older children should prompt consideration of juvenile rheumatoid arthritis, systemic lupus erythematosus, serum sickness, and other connective tissue disorders.

**Human Bocavirus**
Respiratory illness and wheezing caused by HBoV1 cannot clinically be differentiated from other common viral respiratory infections, especially respiratory syncytial virus, human metapneumovirus, rhinoviruses, enterovirus 68, and parainfluenza viruses. HBoV1 infection in young children seems to most closely resemble that of respiratory syncytial virus and human metapneumovirus, as the clinical symptoms and age ranges will overlap.

**TREATMENT**

**Parvovirus B19**
There is no specific antiviral therapy for B19 infection. Commercial lots of intravenous immunoglobulin (IVIG) have been used with some success to treat B19-related episodes of anemia and bone marrow failure in immunocompromised children. Specific antibody may facilitate clearance of the virus; it is not always necessary, however, because cessation of cytotoxic chemotherapy with subsequent restoration of immune function often suffices. In patients whose immune status is not likely to improve, such as patients with AIDS, administration of IVIG may give only a temporary remission, and periodic reinfusions may be required. In patients with AIDS, clearance of B19 infection has been reported after initiation of highly active antiretroviral therapy without the use of IVIG.

No controlled studies have been published regarding dosing of IVIG for B19-induced RBC aplasia. Doses reported with good results in a limited number of cases include 200 mg/kg/day for 5-10 days and 1 g/kg/day for 3 days. IVIG should not be used for treatment of B19-induced arthropathy.

B19-infected fetuses with anemia and hydrops have been managed successfully with intrauterine RBC transfusions, but this procedure has significant attendant risks. Once fetal hydrops is diagnosed, regardless of the suspected cause, the mother should be referred to a fetal therapy center for further evaluation because of the high risk for serious complications (see Chapter 103.2).

**Human Bocavirus**
There is no specific antiviral therapy available. Appropriate supportive treatment for viral LRTI and pneumonia is recommended, as directed by clinical severity. For children with wheezing illness specifically caused by HBoV1 infection, there are no data examining their response to bronchodilator therapy.

**COMPLICATIONS**

**Parvovirus B19**
Erythema infectiosum is often accompanied by arthralgias or arthritis in adolescents and adults that may persist after resolution of the rash. B19 may rarely cause thrombocytopenic purpura. Neurologic conditions, including aseptic meningitis, encephalitis, and peripheral neuropathy, have been reported in both immunocompromised and healthy individuals in association with B19 infection. The incidence of stroke may be increased in children with sickle cell disease following B19-induced transient aplastic crisis. B19 is also a cause of infection-associated hemophagocytic syndrome, usually in immunocompromised persons.

**Human Bocavirus**
There are no studies reporting on complications of HBoV1 infection. Complications of wheezing and viral pneumonia would be possible, including hypoxemia and secondary bacterial infection, among others.

**PREVENTION**

**Parvovirus B19**
Children with erythema infectiosum are not likely to be infectious at presentation because the rash and arthropathy represent immune-mediated, postinfectious phenomena. Isolation and exclusion from school or child care are unnecessary and ineffective after diagnosis.

Children with B19-induced RBC aplasia, including the transient aplastic crisis, are infectious upon presentation and demonstrate a more intense viremia. Most of these children require transfusions and supportive care until their hematologic status stabilizes. They should be isolated in the hospital to prevent spread to susceptible patients and staff. Isolation should continue for at least 1 wk and until after resolution of fever. Pregnant caregivers should not be assigned to these patients. Exclusion of pregnant women from workplaces where children with erythema infectiosum may be present (e.g., primary and secondary schools) is not recommended as a general policy because it is unlikely to reduce their risk. There are no data to support the use of IVIG for postexposure prophylaxis in pregnant caregivers or immunocompromised children. No vaccine is currently available, though this is a topic of ongoing research.

**Human Bocavirus**
There are no studies that have addressed the prevention of transmission of this infection. In the hospital setting, standard precautions should be observed to limit spread of the virus. Since HBoV1 causes respiratory infection and can be detected in respiratory secretions sometimes in very high titer, measures to limit contact with respiratory secretions should be considered, including contact and droplet isolation for severely symptomatic young children. No vaccine is available, and no other preventive measures have been reported.

Bibliography is available at Expert Consult.
Bibliography


The 2 closely related herpes simplex viruses (HSV), HSV type 1 (HSV-1) and HSV type 2 (HSV-2), cause a variety of illnesses, depending on the anatomic site where the infection is initiated, the immune state of the host, and whether the symptoms reflect primary or recurrent infection. Common infections involve the skin, eye, oral cavity, and genital tract. Infections tend to be mild and self-limiting, except in the immunocompromised patient and newborn infant, in whom they may be severe and life-threatening.

**Primary infection** occurs in individuals who have not been infected previously with either HSV-1 or HSV-2. Because these individuals are HSV seronegative and have no preexisting immunity to HSV, primary infections can be severe. **Nonprimary 1st infection** occurs in individuals previously infected with 1 type of HSV (e.g., HSV-1) who have become infected for the 1st time with the other type of HSV (in this case, HSV-2). Because immunity to 1 HSV type provides some cross-protection against disease caused by the other HSV type, nonprimary 1st infections tend to be less severe than true primary infections.
During primary and nonprimary initial infections, HSV establishes latent infection in regional sensory ganglion neurons. Virus is maintained in this latent state for the life of the host but periodically can reactivate and cause recurrent infection. Symptomatic recurrent infections tend to be less severe and of shorter duration than 1st infections. Asymptomatic recurrent infections are extremely common. They cause no physical distress, although patients with recurrent infections are contagious and can transmit the virus to susceptible individuals. Reinfection with a new strain of either HSV-1 or HSV-2 at a previously infected anatomic site (e.g., the genital tract) can occur but is relatively uncommon, suggesting that host immunity, perhaps site-specific local immunity, resulting from the initial infection affords protection against exogenous reinfection. This observation suggests that it might be feasible to develop effective HSV vaccines.

**ETIOLOGY**

HSVs contain a double-stranded DNA genome of approximately 152 kb that encodes at least 84 proteins. The DNA is contained within an icosahedral capsid, which is surrounded by an outer envelope composed of a lipid bilayer containing at least 12 viral glycoproteins. These glycoproteins are the major targets for humoral immunity, whereas other nonstructural proteins are important targets for cellular immunity. Two encoded proteins, viral DNA polymerase and thymidine kinase, are targets for antiviral drugs. HSV-1 and HSV-2 have a similar genetic composition with extensive DNA and protein homology. One important difference in the 2 viruses is their glycoprotein G genes, which have been exploited to develop a new generation of commercially available, accurate, type-specific serologic tests that can be used to discriminate whether a patient has been infected with HSV-1 or HSV-2, or both.

**EPIDEMIOLOGY**

HSV infections are ubiquitous, and there are no seasonal variations in risk for infection. The only natural host is humans, and the mode of transmission is direct contact between mucocutaneous surfaces. There are no documented incidental transmissions from inanimate objects such as toilet seats.

All infected individuals harbor latent infection and experience recurrent infections, which may be symptomatic or may go unrecognized, and thus are periodically contagious. This information helps explain the widespread prevalence of HSV.

HSV-1 and HSV-2 are equally capable of causing initial infection at any anatomic site but differ in their capacity to cause recurrent infections. HSV-1 has a greater propensity to cause recurrent oral infections, whereas HSV-2 has a greater proclivity to cause recurrent genital infections. For this reason, HSV-1 infection typically results from contact with contaminated oral secretions, whereas HSV-2 infection most commonly results from anogenital contact.

HSV seroprevalence rates are highest in developing countries and among lower socioeconomic groups, although high rates of HSV-1 and HSV-2 infections are found in developed nations and among persons of the highest socioeconomic strata. Incident HSV-1 infections are more common during childhood and adolescence but are also found throughout later life. Data from the U.S. population–based National Health and Nutrition Examination Survey conducted between 1999 and 2004 showed a consistent increase of HSV-1 prevalence with age, which rose from 39% in adolescents 14-19 yr of age to 65% among those 40-49 yr of age. HSV-1 seroprevalence was not influenced by gender but rates were highest in Mexican-Americans (80.8%), intermediate in non-Hispanic blacks (68.3%), and lowest in non-Hispanic whites (50.1%). The National Health and Nutrition Examination Survey study conducted between 2005 and 2008 found an overall HSV-2 prevalence of 16.2% with a steady increase with age from 1.4% in the 14-19 yr old age group to 26.1% in the 40-49 yr old group. The rate was higher among females than males (20.9% and 11.5%, respectively) and varied by race and ethnic group, with an overall seroprevalence of 39.2% in blacks, 10.1% in Mexican-Americans, and 12.3% in whites. Modifiable factors that predict HSV-2 seropositivity include less education, poverty, cocaine use, and a greater lifetime number of sexual partners. Studies show that only approximately 10-20% of HSV-2–seropositive subjects report a history of genit herpes, emphasizing the asymptomatic nature of most HSV infections.

A 3 yr longitudinal study of Midwestern adolescent girls 12-15 yr of age found that 44% were seropositive for HSV-1 and 7% for HSV-2 at enrollment. At the end of the study, 49% were seropositive for HSV-1 and 14% for HSV-2. The attack rates, based on the number of cases per 100 person-years, were 3.2 for HSV-1 infection among all girls and 4.4 for HSV-2 infection among girls who reported being sexually experienced. Findings of this study indicate that sexually active young women have a high attack rate for genital herpes and suggest that genital herpes should be considered in the differential diagnosis of any young woman who reports recurrent genital complaints. In this study, participants with preexisting HSV-1 antibodies had a significantly lower attack rate for HSV-2 infection, and those who became infected were less likely to have symptomatic disease than girls who were HSV seronegative when they entered the study. Prior HSV-1 infection appears to afford adolescent girls some protection against becoming infected with HSV-2; in adolescent girls infected with HSV-2, the preexisting HSV-1 immunity appears to protect against development of symptomatic genital herpes.

**Neonatal herpes** is an uncommon but potentially fatal infection of the fetus or more likely the newborn. It is not a reportable disease in most states, and therefore there are no solid epidemiologic data regarding its frequency in the general population. In King County, Washington, the estimated incidence of neonatal herpes was 2.6 cases per 100,000 live births in the late 1960s, 11.9 cases per 100,000 live births from 1978-1981, and 31 cases per 1,000,000 live births from 1982-1999. This increase in neonatal herpes cases parallels the increase in cases of genital herpes. The estimated rate of neonatal herpes is 1 per 3,000-5,000 live births, which is higher than reported for the reportable perinatally acquired sexually transmitted infections such as congenital syphilis and gonococcal ophthalmia neonatorum. More than 90% of the cases are the result of maternal-fetal transmission. The risk for transmission is greatest during a primary or nonprimary 1st infection (30-50%) and much lower when the exposure is during a recurrent infection (<2%). HSV viral suppression therapy in mothers does not consistently eliminate the possibility of neonatal infection. Infants born to mothers dually infected with HIV and HSV-2 are also at higher risk for acquiring HIV than infants born to HIV-positive mothers who are not HSV-2 infected. It is estimated that approximately 25% of pregnant women are HSV-2 infected and that approximately 2% of pregnant women acquire HSV-2 infection during pregnancy. HSV is a leading cause of sporadic, fatal encephalitis in children and adults. In the United States it is estimated that there are 1,250 cases annually of HSV encephalitis.

**PATHOGENESIS**

In the immunocompetent host the pathogenesis of HSV infection involves viral replication in skin and mucous membranes followed by replication and spread in neural tissue. Viral infection typically begins at a cutaneous portal of entry such as the oral cavity, genital mucosa, ocular conjunctiva, or breaks in keratinized epithelia. Virus replicates locally, resulting in the death of the cell, and sometimes produces clinically apparent inflammatory responses that facilitate the development of characteristic herpetic vesicles and ulcers. Virus also enters nerve endings and spreads beyond the portal of entry to sensory ganglia by intraneuronal transport. Virus replicates in some sensory neurons, and the progeny virions are sent via intraneuronal transport mechanisms back to the periphery, where they are released from nerve endings and replicate further in skin or mucosal surfaces. It is virus moving through this neural arc that is primarily responsible for the development of characteristic herpetic lesions, although most HSV infections do not reach a threshold necessary to cause clinically recognizable disease. Although many sensory neurons become productively infected during the initial infection, some infected neurons do not initially support viral replication. It is in these neurons that the virus establishes a latent infection, a condition in which the viral genome persists within the neuronal nucleus in a largely metabolically inactive state. Intermittently throughout the life of the host, undefined changes can occur in latently infected neurons that trigger the virus to begin to replicate.
This replication occurs despite the host’s having established a variety of humoral and cellular immune responses that successfully controlled the initial infection. With reactivation of the latent neuron, progeny virions are produced and transported within nerve fibers back to cutaneous sites somewhere in the vicinity of the initial infection, where further replication occurs and causes recurrent infections. Recurrent infections may be symptomatic (with typical or atypical herpetic lesions) or asymptomatic. In either case, virus is shed at the site where cutaneous replication occurs and can be transmitted to susceptible individuals who come in contact with the site or with contaminated secretions. Latency and reactivation are the mechanisms by which the virus is successfully maintained in the human population.

Viremia, or hematogenous spread of the virus, does not appear to play an important role in HSV infections in the immunocompetent host but can occur in neonates, infants with eczema, and severely malnourished children. It is also seen in patients with depressed or defective cell-mediated immunity, such as occurs with HIV infection or some immunosuppressive therapies. Viremia can result in dissemination of the virus to visceral organs, including the liver and adrenals. Hematogenous dissemination of virus to the central nervous system appears to only occur in neonates.

The pathogenesis of HSV infection in newborns is complicated by their relative immunologic immaturity. The source of virus in neonatal infections is typically not but exclusively the mother. Transmission generally occurs during delivery, although it is well documented to occur even with cesarean delivery with intact fetal membranes. The most common portals of entry are the conjunctiva, mucosal epithelium of the nose and mouth, and breaks or abrasions in the skin that occur with scalp electrode use or forceps delivery. With prompt antiviral therapy, virus replication may be restricted to the site of inoculation (the skin, eye, or mouth). However, virus may also extend from the nose to the respiratory tract to cause pneumonia, move via intraneuronal transport to the central nervous system to cause encephalitis, or spread by hematogenous dissemination to visceral organs and the brain. Factors that may influence neonatal HSV infection include the virus type, portal of entry, inoculum of virus to which the infant is exposed, gestational age of the infant, and presence of maternally derived antibodies specific to the virus causing infection. Latent infection is established during neonatal infection, and survivors may experience recurrent cutaneous and neural infections. Persistent central nervous system infection may impact the neurodevelopment of the infant.

**CLINICAL MANIFESTATIONS**

The hallmarks of common HSV infections are skin vesicles and shallow ulcers. Classic infections manifest as small, 2-4 mm vesicles that may be surrounded by an erythematous base. These may persist for a few days before evolving into shallow, minimally erythematous ulcers. The vesicular phase tends to persist longer when keratinized epithelia is involved and is generally brief and sometimes just fleeting when moist mucous membranes are the site of infection. Because HSV infections are common and their natural history is influenced by many factors, including portal of entry, immune status of the host, and whether it is an initial or recurrent infection, the typical manifestations are seldom classic. Most infections are asymptomatic or unrecognized, and nonclassic presentations, such as small skin fissures and small erythematous nonvesicular lesions, are common.

**Acute Oropharyngeal Infections**

Herpes gingivostomatitis most often affects children 6 mo to 5 yr of age but is seen across the age spectrum. It is an extremely painful condition with sudden onset, pain in the mouth, drooling, refusal to eat or drink, and fever of up to 40.0-40.6°C (104-105.1°F). The gums become markedly swollen, and vesicles may develop throughout the oral cavity, including the gums, lips, tongue, palate, tonsils, pharynx, and perioral skin (Fig. 252-1). The vesicles may be more extensively distributed than typically seen with enteroxiral herpangina. During the initial phase of the illness there may be tonsillar exudates suggestive of bacterial pharyngitis. The vesicles are generally present only a few days before progressing to form shallow indurated ulcers that may be covered with a yellow-gray membrane. Tender submandibular, submaxillary, and cervical lymphadenopathy is common. The breath may be foul as a result of overgrowth of anaerobic oral bacteria. Untreated, the illness resolves in 7-14 days, although the lymphadenopathy may persist for several weeks.

In older children, adolescents, and college students, the initial HSV oral infection may manifest as pharyngitis and tonsillitis rather than gingivostomatitis. The vesicular phase is often over by the time the patient presents to a healthcare provider, and signs and symptoms may be indistinguishable from those of streptococcal pharyngitis, consisting of fever, malaise, headache, sore throat, and white plaques on the tonsils. The course of illness is typically longer than for untreated streptococcal pharyngitis.

**Herpes Labialis**

Fever blisters (cold sores) are the most common manifestation of recurrent HSV-1 infections. The most common site of herpes labialis is the vermilion border of the lip, although lesions sometimes occur on the nose, chin, cheek, or oral mucosa. Older patients report experiencing burning, tingling, itching, or pain 3-6 hr (rarely as long as 24-48 hr) before the development of the herpes lesion. The lesion generally begins as a small grouping of erythematous papules that over a few hours progress to create a small, thin-walled vesicle. The vesicles may form shallow ulcers or become pustular. The short-lived ulcer dries and develops a crusted scab. Complete healing without scarring occurs with reepithelialization of the ulcerated skin, usually within 6-10 days. Some patients experience local lymphadenopathy but no constitutional symptoms.

**Cutaneous Infections**

In the healthy child or adolescent, cutaneous HSV infections are generally the result of skin trauma with macro or micro abrasions and

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**Figure 252-1** Clustered perioral vesicles and erosions in an infant with primary herpetic gingivostomatitis. (From Schachner LA, Hansen RC, editors: Pediatric dermatology, ed 3. Philadelphia, 1988, Mosby, p. 1078.)
exposure to infectious secretions. This situation most often occurs in play or contact sports such as wrestling (herpes gladiatorum) and rugby (scrum pox). As with other HSV infections, an initial cutaneous infection establishes a latent infection that can subsequently result in recurrent infections at or near the site of the initial infection. Pain, burning, itching, or tingling often precedes the herpetic eruption by a few hours to a few days. Like herpes labialis, lesions begin as grouped, erythematous papules that progress to vesicles, pustules, ulcers, and crusts and then heal without scarring in 6-10 days. Although herpes labialis typically results in a single lesion, a cutaneous HSV infection results in multiple discrete lesions and involves a larger surface area. Regional lymphadenopathy may occur but systemic symptoms are uncommon. Recurrences are sometimes associated with local edema and lymphangitis or local neuralgia.

Herpes whitlow is a term generally applied to HSV infection of fingers or toes, although strictly speaking it refers to HSV infection of the paronychia. Among children, this condition is most commonly seen in infants and toddlers who suck the thumb or fingers and who are experiencing either a symptomatic or a subclinical oral HSV-1 infection (Fig. 252-2). An HSV-2 herpes whitlow occasionally develops in an adolescent as a result of exposure to infectious genital secretions. The onset of the infection is heralded by itching, pain, and erythema 2-7 days after exposure. The cuticle becomes erythematous and tender and may appear to contain pus, although if it is incised, little fluid is present. Incising the lesion is discouraged, as this maneuver typically prolongs recovery and increases the risk for secondary bacterial infection. Lesions and associated pain typically persist for about 10 days, followed by rapid improvement and complete recovery in 18-20 days. Regional lymphadenopathy is common, and lymphangitis and neuralgia may occur. Unlike other recurrent herpes infections, recurrent herpetic whitlows are often as painful as the primary infection but are generally shorter in duration.

Cutaneous HSV infections can be severe or life-threatening in patients with disorders of the skin such as eczema (eczema herpeticum), pemphigus, burns, and Darier disease, and following laser skin resurfacing. The lesions are frequently ulcerative and nonspecific in appearance, although typical vesicles may be seen in adjacent normal skin (Fig. 252-3). If untreated, these lesions can progress to disseminated infection and death. Recurrent infections are common but generally less severe than the initial infection.

Genital Herpes

Genital HSV infection is common in sexually experienced adolescents and young adults, but up to 90% of infected individuals are unaware they are infected. Infection may result from genital-genital transmission (usually HSV-2) or oral-genital transmission (usually HSV-1). Symptomatic and asymptomatic individuals periodically shed virus from anogenital sites. Most sexual transmissions and maternal-infant transmissions of virus result from asymptomatic shedding from anogenital sites. Most sexual transmissions and maternal-infant transmissions of virus result from asymptomatic shedding from anogenital sites. Most sexual transmissions and maternal-infant transmissions of virus result from asymptomatic shedding from anogenital sites. Most sexual transmissions and maternal-infant transmissions of virus result from asymptomatic shedding from anogenital sites. Most sexual transmissions and maternal-infant transmissions of virus result from asymptomatic shedding from anogenital sites.
Genital infections caused by HSV-1 and HSV-2 are indistinguishable, but HSV-1 causes significantly fewer subsequent episodes of recurrent infection; hence, knowing which virus is causing the infection has important prognostic value. Genital HSV infection increases the risk for acquiring HIV infection.

Rarely, genital HSV infections are identified in young children and preadolescents. Although genital disease in children should raise concerns about possible sexual abuse, there are documented cases of autoinoculation, in which a child has inadvertently transmitted virus from contaminated oral secretions to his or her own genitalia.

**Ocular Infections**

HSV ocular infections may involve the conjunctiva, cornea, or retina and may be primary or recurrent. Conjunctivitis or keratoconjunctivitis is usually unilateral and is often associated with blepharitis and tender preauricular lymphadenopathy. The conjunctiva appears edematous but there is rarely purulent discharge. Vesicular lesions may be seen on the lid margins and periorbital skin. Patients typically have fever. Untreated infection generally resolves in 2-3 wk. Obvious corneal involvement is rare, but when it occurs it can produce ulcers that are described as appearing dendritic or geographic. Extension to the stroma is uncommon although more likely to occur in patients inadvertently treated with corticosteroids. When it occurs, it may be associated with corneal edema, scarring, and corneal perforation. Recurrent infections tend to involve the underlying stroma and can cause progressive corneal scarring and injury that can lead to blindness.

Retinal infections are rare and are more likely among infants with neonatal herpes and immunocompromised persons with disseminated HSV infections.

**Central Nervous System Infections**

HSV encephalitis is the leading cause of sporadic, nonepidemic encephalitis in children and adults in the United States. It is an acute necrotizing infection generally involving the frontal and/or temporal cortex and the limbic system and, beyond the neonatal period, is almost always caused by HSV-1. The infection may manifest as nonspecific findings, including fever, headache, nuchal rigidity, nausea, vomiting, generalized seizures, and alteration of consciousness. Injury to the frontal or temporal cortex or limbic system may produce findings more indicative of HSV encephalitis, including anosmia, memory loss, peculiar behavior, expressive aphasia and other changes in speech, hallucinations, and focal seizures. The untreated infection progresses to coma and death in 75% of cases. Examination of the cerebrospinal fluid (CSF) typically shows a moderate number of mononuclear cells and polymorphonuclear leukocytes, a mildly elevated protein concentration, a normal or slightly decreased glucose concentration, and often a moderate number of erythrocytes.

HSV is also a cause of aseptic meningitis and is the most common cause of recurrent aseptic meningitis (Mollaret meningitis).

**Infections in Immunocompromised Persons**

Severe, life-threatening HSV infections can occur in patients with compromised immune functions, including neoplasms, the severely malnourished, those with primary or secondary immunodeficiency diseases, including AIDS, and those receiving some immunosuppressive regimens, particularly for cancer and organ transplantation. Mucocutaneous infections, including mucositis and esophagitis, are most common, although their presentations may be atypical and can result in lesions that slowly enlarge, ulcerate, become necrotic, and extend to deeper tissues. Other HSV infections include tracheobronchitis, pneumonitis, and anogenital infections. Disseminated infection can result in a sepsis-like presentation, with liver and adrenal involvement, disseminated intravascular coagulopathy, and shock.

**Perinatal Infections**

HSV infection may be acquired in utero, during the birth process, or during the neonatal period. Intrauterine and postpartum infections are well described but occur infrequently. Postpartum transmission may be from the mother or another adult with a nongenital (typically HSV-1) infection such as herpes labialis. Most cases of neonatal herpes result from maternal infection and transmission, usually during passage through an infected birth canal of a mother with asymptomatic genital herpes. Transmission is well documented in infants delivered by cesarean section. Fewer than 30% of mothers of an infant with neonatal herpes have a history of genital herpes. The risk for infection is higher in infants born to mothers with primary genital infection (>30%) than with recurrent genital infection (<2%). Use of scalp electrodes may also increase risk. There also have been rare cases of neonatal herpes associated with Jewish ritual circumcisions, but only with ritual oral contact with the circumcision site.

Neonatal HSV infection is thought to never be asymptomatic. Its clinical presentation reflects timing of infection, portal of entry, and extent of spread. Infants with intrauterine infection typically have skin vesicles or scarring, eye findings including chorioretinitis and keratoconjunctivitis, and microcephaly or hydranencephaly that are present at delivery. Few infants survive without therapy, and those who do generally have severe sequelae. Infants infected during delivery or the postpartum period present with 1 of the following 3 patterns of disease: (1) disease localized to the skin, eyes, or mouth; (2) encephalitis with or without skin, eye, and mouth disease; and (3) disseminated infection involving multiple organs, including the brain, lungs, liver, heart, adrenals, and skin.

Infants with **skin, eye, and mouth disease** generally present at 5-11 days of life and typically demonstrate a few small vesicles, particularly on the presenting part or at sites of trauma such as sites of scalp electrode placement. If untreated, skin, eye, and mouth disease in infants may progress to encephalitis or disseminated disease.

Infants with encephalitis typically present at 8-17 days of life with clinical findings suggestive of bacterial meningitis, including irritability, lethargy, poor feeding, poor tone, and seizures. Fever is relatively uncommon, and skin vesicles occur in only approximately 60% of cases (Fig. 252-4). If untreated, 50% of infants with HSV encephalitis die and most survivors have severe neurologic sequelae.

Infants with disseminated HSV infections generally become ill at 5-11 days of life. Their clinical picture is similar to that of infants with bacterial sepsis, consisting of hyperthermia or hypothermia, irritability, poor feeding, and vomiting. They may also exhibit respiratory distress, cyanosis, apneic spells, jaundice, purpuric rash, and evidence of central nervous system infection; seizures are common. Skin vesicles
are seen in approximately 75% of cases. If untreated, the infection causes shock and disseminated intravascular coagulation; approximately 90% of these infants die, and most survivors have severe neurologic sequelae.

Infants with neonatal herpes whose mothers received antivirals antiviral drugs in the weeks prior to delivery may present later than their untreated counterparts; whether the natural history of the infection in these infants is different is an unanswered question.

**DIAGNOSIS**
The clinical diagnosis of HSV infections, particularly life-threatening infections and genital herpes, should be confirmed by laboratory test, preferably isolation of virus or viral DNA detection by polymerase chain reaction (PCR). Histologic findings or imaging studies may support the diagnosis but should not substitute for virus-specific tests. HSV immunoglobulin M tests are notoriously unreliable, and the demonstration of a 4-fold or greater rise in HSV-specific immunoglobulin G titers between acute and convalescent serum samples is useful only in retrospect.

Virus culture remains the gold standard for diagnosing HSV infections. The highest yield comes from rupturing a suspected herpetic vesicle and vigorously rubbing the base of the lesion to collect fluid and cells. Culturing dried, crusted lesions is generally of low yield. Although not as sensitive as viral culture, direct detection of HSV antigens in clinical specimens can be done rapidly and has very good specificity. The use of PCR for detection of HSV DNA is highly sensitive and specific and in some instances can be performed rapidly. It is the test of choice in examining CSF in cases of suspected HSV encephalitis.

Evaluation of the neonate with suspected HSV infection should include cultures of suspicious lesions as well as eye and mouth swabs and PCR of CSF and blood. In neonates testing for elevation of liver enzymes may provide indirect evidence of HSV dissemination to visceral organs. Culture or antigen detection should be used in evaluating lesions associated with suspected acute genital herpes. HSV-2 typespecific antibody tests are useful for evaluating sexually experienced adolescents or young adults who have a history of unexplained recurrent nonspecific urogenital signs and symptoms, but these tests are less useful for general screening in populations in which HSV-2 infections are of low prevalence.

Because most HSV diagnostic tests take at least a few days to complete, treatment should not be withheld but rather initiated promptly so as to ensure the maximum therapeutic benefit.

**LABORATORY FINDINGS**
Most self-limited HSV infections cause few changes in routine laboratory parameters. Mucocutaneous infections may cause a moderate polymorphonuclear leukocytosis. In HSV meningoencephalitis there can be an increase in mononuclear cells and protein in CSF, the glucose content may be normal or reduced, and red blood cells may be present. The electroencephalogram and MRI of the brain may show temporal lobe abnormalities in HSV encephalitis beyond the neonatal period. Encephalitis in the neonatal period tends to be more global and not limited to the temporal lobe (Fig. 252-5). Disseminated infection may cause elevated liver enzymes, thrombocytopenia, and abnormal coagulation.

**TREATMENT**
See Chapter 245 for more information about principles of antiviral therapy.

Three antiviral drugs are available in the United States for the management of HSV infections, namely acyclovir, valacyclovir, and

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**Figure 252-5 Involvement of corticospinal tract and thalamus in a 2 wk old infant. A, MRI with axial T1-weighted image demonstrating subtle loss of T1 hyperintensity corresponding to myelination in the posterior limb of the right internal capsule (white arrow). T1 hyperintensity in the left posterior limb of the internal capsule is maintained (black arrow). B, T2-weighted image showing findings similar to those seen on T1-weighted imaging. C, Axial T1- and (D) T2-weighted images through the vertex demonstrating subtle indistinct margins of the cortex around the right central sulcus (white arrow) compared with the normal appearance on the left side (black arrow). E and F, Diffusion-weighted images with more extensive diffusion restriction in the posterior limb of the right internal capsule and lateral thalamus (arrows), and in the right pre- and postcentral gyrus (arrow). (From Bajaj M, Mody S, Natarajan G: Clinical and neuroimaging findings in neonatal herpes simplex virus infection. J Pediatr 165:404–407, 2014, Fig. 1.)**
Acute Mucocutaneous Infections
For gingivostomatitis, oral acyclovir (15 mg/kg/dose 5 times a day PO for 7 days; maximum: 1 g/day) started within 72 hr of onset reduces the severity and duration of the illness. Pain associated with swallowing may limit oral intake of infants and children, putting them at risk for dehydration. Intake should be encouraged through the use of cold beverages, ice cream, and yogurt.

For herpes labialis, oral treatment is superior to topical antiviral therapy. For treatment of a recurrence in adolescents, oral valacyclovir (2,000 mg bid PO for 1 day), acyclovir (200–400 mg 5 times daily PO for 5 days), or famciclovir (1,500 mg once daily PO for 1 day) shortens the duration of the episode. Long-term daily use of oral acyclovir (400 mg bid PO) or valacyclovir (500 mg once daily PO) has been used to prevent recurrences in individuals with frequent or severe recurrences.

Anecdotal reports suggest that treatment of adolescents with herpes gladiatorum with oral acyclovir (200 mg 5 times daily PO for 7–10 days) or valacyclovir (500 mg bid PO for 7–10 days) at the first signs of the outbreak can shorten the course of the recurrence. For patients with a history of recurrent herpes gladiatorum, chronic daily prophylaxis with valacyclovir (500–1,000 mg daily) has been reported to prevent recurrences.

There are no clinical trials assessing the benefit of antiviral treatment for herpetic whitlow. High-dose oral acyclovir (1,600–2,000 mg/day divided in 2–3 doses PO for 10 days) started at the first signs of illness has been reported to abort some recurrences and reduce the duration of others in adults.

A clinical trial in adults has established the effectiveness of oral acyclovir (200 mg 5 times a day PO for 5 days) in the treatment of eczema herpeticum; however, serious infections should be treated with intravenous acyclovir. Oral-facial HSV infections can reactivate after cosmetic facial laser resurfacing, causing extensive disease and scarring. Treatment of adults beginning the day before the procedure with either valacyclovir (500 mg twice daily PO for 10–14 days) or famciclovir (250–500 mg bid PO for 10 days) has been reported to be effective in preventing the infections. HSV infections in burn patients can be severe or life-threatening and have been treated with intravenous acyclovir (10–20 mg/kg/day divided every 8 hr IV).

Antiviral drugs are not effective in the treatment of HSV-associated erythema multiforme, but their daily use as for herpes labialis prophylaxis prevents recurrences of erythema multiforme.

Genital Herpes
Pediatric patients, usually adolescents or young adults, with suspected 1st-episode genital herpes should be treated with antiviral therapy. Treatment of the initial infection reduces the severity and duration of the illness but has no effect on the frequency of subsequent recurrent infections. Treatment options for adolescents include acyclovir (400 mg tid PO for 7–10 days), famciclovir (250 mg tid PO for 7–10 days), or valacyclovir (1,000 mg bid PO for 7–10 days). The twice-daily valacyclovir option avoids treatment during school hours. For smaller children, acyclovir suspension can be used at a dose of 10–20 mg/kg/dose 4 times daily not to exceed the adult dose. The 1st episode of genital herpes can be extremely painful, and use of analgesics is generally indicated. All patients with genital herpes should be offered counseling to help them deal with psychosocial issues and understand the chronic nature of the illness.

There are 3 strategic options regarding the management of recurrent infections. The choice should be guided by several factors, including the frequency and severity of the recurrent infections, the psychologic impact of the illness on the patient, and concerns regarding transmission to a susceptible sexual partner. Option 1 is no therapy; option 2 is episodic therapy; and option 3 is long-term suppressive therapy. For episodic therapy, treatment should be initiated at the first signs of an outbreak. Recommended choices for episodic therapy in adolescents include famciclovir (1,000 mg bid PO for 1 day), acyclovir (800 mg tid PO for 2 days), or valacyclovir (500 mg bid PO for 3 days or 1,000 mg once daily for 5 days). Long-term suppressive therapy offers the advantage that it prevents most outbreaks, improves patient quality of life in terms of the psychosocial impact of genital herpes, and, with daily valacyclovir therapy, also reduces (but does not eliminate) the risk for sexual transmission to a susceptible sexual partner. Options for long-term suppressive therapy are acyclovir (400 mg bid PO), famciclovir (250 mg bid PO), and valacyclovir (500 or 1,000 mg qd PO).

Ocular Infections
HSV ocular infections can result in blindness. Management should involve consultation with an ophthalmologist.

Central Nervous System Infections
Patients older than neonates who have herpes encephalitis should be promptly treated with intravenous acyclovir (10 mg/kg every 8 hr given as a 1 hr infusion for 14–21 days). Treatment for increased intracranial pressure, management of seizures, and respiratory compromise may be required.

Infections in Immunocompromised Persons
Severe mucocutaneous and disseminated HSV infections in immunocompromised patients should be treated with intravenous acyclovir (5–10 mg/kg or 250 mg/m² every 8 hr) until there is evidence of resolution of the infection. Oral antiviral therapy with acyclovir, famciclovir, or valacyclovir has been used for treatment of less-severe HSV infections and for suppression of recurrences during periods of significant immunosuppression. Drug resistance does occur occasionally in immunocompromised patients, and in individuals whose HSV infection does not respond to antiviral drug therapy, viral isolates should be tested to determine sensitivity. Acyclovir-resistant viruses are often also resistant to famciclovir but may be sensitive to foscarnet or cidofovir.

Perinatal Infections
All infants with proven or suspected neonatal HSV infection should be treated immediately with high-dose intravenous acyclovir (60 mg/kg/day divided every 8 hr IV). Treatment may be discontinued in infants shown by laboratory testing not to be infected. Infants with HSV disease limited to skin, eyes, and mouth should be treated for 14 days, whereas those with disseminated or central nervous system disease should receive 21 days of therapy. Patients receiving high-dose therapy should be monitored for neutropenia.

Suppressive oral acyclovir therapy for 6 mo after completion of the intravenous therapy has been shown to improve the neurodevelopment of infants with central nervous system infection and to prevent cutaneous recurrences in infants regardless of disease pattern. Infants should receive 300 mg/m² per dose 3 times daily for 6 mo. The absolute
neutrophil count should be measured at weeks 2 and 4 after initiation treatment and then monthly.

**PROGNOSIS**
Most HSV infections are self-limiting, last from a few days (for recurrent infections) to 2-3 wk (for primary infections), and heal without scarring. Recurrent oral-facial herpetic shows in a patient who has undergone dermabrasion or laser resurfacing can be severe and lead to scarring. Because genital herpes is a sexually transmitted infection, it can be stigmatizing, and its psychologic consequences may be much greater than its physiologic effects. Some HSV infections can be severe and may have grave consequences without prompt antiviral therapy. Life-threatening conditions include neonatal herpes, herpes encephalitis, and HSV infections in immunocompromised patients, burn patients, and severely malnourished infants and children. Recurrent ocular herpes can lead to corneal scarring and blindness.

**PREVENTION**
Transmission of infection occurs through exposure to virus either as the result of skin-to-skin contact or from contact with contaminated secretions. Good handwashing and, when appropriate, the use of gloves provide healthcare workers with excellent protection against HSV infection in the workplace. Healthcare workers with active oral-facial herpes or herpes whitlow should take precautions, particularly when caring for high-risk patients such as newborns, immunocompromised individuals, and patients with chronic skin conditions. Patients and parents should be advised about good hygienic practices, including handwashing and avoiding contact with lesions and secretions, during active herpes outbreaks. Schools and daycare centers should clean shared toys and athletic equipment such as wrestling mats at least daily after use. Athletes with active herpes infections who participate in contact sports such as wrestling and rugby should be excluded from practice or games until the lesions are completely healed. Genital herpes can be prevented by avoiding genital-genital and oral-genital contact. The risk for acquiring genital herpes can be reduced but not eliminated through the correct and consistent use of condoms. Male circumcision is associated with a reduced risk of acquiring genital HSV infection. The risk for transmitting genital HSV-2 infection to a susceptible sexual partner can be reduced but not eliminated by the daily use of oral valacyclovir by the infected partner.

For **pregnant women** with **active genital herpes** at the time of delivery, the risk for mother-to-baby transmission can be reduced but not eliminated by delivering the baby via a cesarean section (within 4-6 hr of rupture of membranes). The risk for recurrent genital herpes, and therefore the need for cesarean delivery, can be reduced but not eliminated in pregnant women with a history of genital herpes by the daily use of oral acyclovir, valacyclovir, or famciclovir during the last 4 wk of gestation, which is recommended by the American College of Obstetrics and Gynecology. There are documented cases of neonatal herpes occurring in infants delivered by cesarean section, as well as in infants born to mothers who have been appropriately treated with antiviral drugs for the last month of gestation. Hence a history of cesarean delivery or antiviral treatment at term does not rule out consideration of neonatal herpes.

Infants delivered vaginally to women with 1st-episode genital herpes are at very high risk for acquiring HSV infection. The nasopharynx, mouth, conjunctivae, rectum, and umbilicus should be cultured (some add PCR surface testing) at delivery and on day 1-2 of life. Some also recommend HSV-PCR on blood. Some authorities recommend that these infants receive acyclovir therapy for at least 2 wk, and others treat such infants if signs develop or if the 48 hr cultures have positive results. Infants delivered to women with a history of recurrent genital herpes are at low risk for development of neonatal herpes. In this setting, parents should be educated about the signs and symptoms of neonatal HSV infection and should be instructed to seek care without delay at the first suggestion of infection. When the situation is in doubt, infants should be evaluated and tested with surface culture (and PCR) for neonatal herpes as well as with PCR on blood and CSF; intravenous acyclovir is begun until culture results are negative or until another explanation can be found for the signs and symptoms.

Recurrent genital HSV infections can be prevented by the daily use of oral acyclovir, valacyclovir, or famciclovir, and these drugs have been used to prevent recurrences of oral-facial (labialis) and cutaneous (gladiatorum) herpes. Oral and intravenous acyclovir has also been used to prevent recurrent HSV infections in immunocompromised patients. Use of sun blockers is reported to be effective in preventing recurrent oral-facial herpes in patients with a history of sun-induced recurrent disease.

*Bibliography is available at Expert Consult.*
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Varicella-zoster virus (VZV) causes primary, latent, and recurrent infections. The primary infection is manifested as varicella (chickenpox) and results in establishment of a lifelong latent infection of sensory ganglion neurons. Reactivation of the latent infection causes herpes zoster (shingles). Although often a mild illness of childhood, varicella can cause substantial morbidity and mortality in otherwise healthy children. Morbidity and mortality are higher in immunocompetent infants, adolescents, and adults as well as in immunocompromised persons. Varicella predisposes to severe group A Streptococcus and Staphylococcus aureus infections. A clinically modified disease can occur among vaccinated persons (breakthrough varicella), usually with milder presentation. Varicella and herpes zoster can be treated with antiviral drugs. Primary clinical disease can be prevented by immunization with live-attenuated VZV vaccine (varicella vaccine). Herpes zoster vaccine (zoster vaccine), which contains the same VZV strain used in the varicella vaccine but with a higher potency, is available for persons 50 yr of age and older to boost their immunity to VZV and prevent herpes zoster and its major complication, painful postherpetic neuralgia.

ETIOLOGY
VZV is a neurotropic human herpesvirus with similarities to herpes simplex virus. These enveloped viruses contain double-stranded DNA genomes that encode more than 70 proteins, including proteins that are targets of cellular and humoral immunity.

EPIDEMIOLOGY
Before the introduction of varicella vaccine in 1996, varicella was an almost universal communicable infection of childhood in the United States. Most children were infected by 15 yr of age, with fewer than 5% of adults remaining susceptible. This pattern of infection at younger ages remains characteristic in all countries in temperate climates. In contrast, in tropical areas, children acquire varicella at older ages and a higher proportion of young adults remain susceptible leading to a higher proportion of cases occurring among adults. In the United States, prior to introduction of varicella vaccination, annual varicella epidemics occurred in winter and spring, and there were about 4 million cases of varicella, 11,000-15,000 hospitalizations, and 100-150 deaths every year. Varicella is a more serious disease in young infants, adults, and immunocompromised persons, in whom there are higher rates of complications and deaths than in healthy children. Within households, transmission of VZV to susceptible individuals occurs at a rate of 65-86%; more casual contact, such as occurs in a
school classroom, is associated with lower attack rates among susceptible children. Persons with varicella are contagious 24-48 hr before the rash is evident and until vesicles are crusted, usually 3-7 days after onset of rash. Susceptible persons may also acquire varicella after close, direct contact with adults or children who have herpes zoster.

Since implementation of the varicella vaccination program in 1996, there have been substantial declines in varicella morbidity and mortality in the United States. By 2006, prior to implementation of the 2 dose program, 1 dose vaccination coverage had reached 90% and varicella incidence had declined 96-91% since 1995 in sites where active surveillance was being conducted; varicella-related hospitalizations had declined 84% from prevaccine years. Varicella-related deaths decreased by 88% from 1990-1994 to 2005-2007; in persons younger than 20 yr of age there was a 97% decline in deaths. Declines in morbidity and mortality were seen in all age groups, including infants younger than 12 mo of age who were not eligible for vaccination, indicating protection from exposure by indirect vaccination effects. Although the age-specific incidence has declined in all age groups, the median age at infection has increased, and cases occur predominantly in children in upper elementary school rather than in the preschool years. This change in varicella epidemiology highlights the importance of offering vaccine to every susceptible child, adolescent, and adult. The continued occurrence of breakthrough infections and of outbreaks in settings with high 1-dose varicella vaccine coverage, together with the evidence that 1 dose is only approximately 85% effective against all varicella, prompted adoption in 2006 of a routine 2 dose childhood varicella vaccination program with catch-up vaccination of all individuals without evidence of immunity. Between 2006 and 2010, varicella incidence declined further by approximately 70% and fewer outbreaks were reported.

Herpes zoster is caused by the reactivation of latent VZV. It is not common in childhood and shows no seasonal variation in incidence. Zoster is not caused by exposure to a patient with varicella; in fact, exposures to varicella boost the cell-mediated immune response to VZV in individuals with prior infection, decreasing the likelihood of reactivation of latent virus. The lifetime risk for herpes zoster for individuals with a history of varicella is 20-30%, with 75% of cases occurring after 45 yr of age. Herpes zoster is very rare in healthy children younger than 10 yr of age, with the exception of those infected with VZV in utero or in the 1st yr of life, who have an increased risk for development of zoster in the 1st few yr of life. Herpes zoster in children tends to be milder than herpes zoster in adults, is less frequently associated with acute pain, and postherpetic neuralgia generally does not occur in healthy children. In children receiving immunosuppressive therapy for malignancy or other diseases and in those who have HIV infection, herpes zoster occurs more frequently, occasionally multiple times, and may be severe. The attenuated VZV in the varicella vaccine can establish latent infection and reactivate as herpes zoster. However, the evidence to date indicates that the risk for development of subsequent herpes zoster is lower after vaccination than after natural VZV infection among both healthy and immunocompromised children. Vaccinated children who do develop zoster may have disease resulting from vaccine or wild-type VZV.

**PATHOGENESIS**

VZV is transmitted by contact with oropharyngeal secretions and the fluid of skin lesions of infected individuals, either by airborne spread or through direct contact. Primary infection (varicella) results from inoculation of the virus onto the mucosa of the upper respiratory tract and tonsillar lymphoid tissue. During the early part of the 10-21 day incubation period, virus replicates in the local lymphoid tissue, and then a brief subclinical viremia spreads the virus to the reticuloendothelial system. Widespread cutaneous lesions occur during a 2nd viremic phase that lasts 3-7 days. Peripheral blood mononuclear cells carry infectious virus, generating new crops of vesicles during this period of viremia. VZV is also transported back to the mucosa of the upper respiratory tract and oropharynx during the late incubation period, permitting spread to susceptible contacts 1-2 days before the appearance of rash. Host immune responses limit viral replication and facilitate recovery from infection. In the immunocompromised child, the failure of immune responses, especially cell-mediated immune responses, results in continued viral replication that may lead to prolonged and/or disseminated infection with resultant complications in the lungs, liver, brain, and other organs. Virus is transported in a retrograde manner through sensory axons to the dorsal root ganglia throughout the spinal cord, where the virus establishes latent infection in the neurons and satellite cells associated with these axons. Virus may also reach the ganglia by the hematogenous route. Subsequent reactivation of latent virus causes herpes zoster, a vesicular rash that usually is dermatomal in distribution. During herpes zoster, necrotic changes may be produced in the neurons and surrounding satellite cells in associated ganglia. The skin lesions of varicella and herpes zoster have identical histopathology, and infectious VZV is present in both. Varicella elicits humoral and cell-mediated immunity that is highly protective against symptomatic reinfection. Suppression of cell-mediated immunity to VZV correlates with an increased risk for VZV reactivation as herpes zoster.

**CLINICAL MANIFESTATIONS**

Varicella is an acute febrile rash illness that was common in children in the United States before the universal childhood vaccination program. It has variable severity but is usually self-limited. It may be associated with severe complications, including staphylococcal and streptococcal superinfection, pneumonia, encephalitis, bleeding disorders, congenital infection, and life-threatening perinatal infection. Herpes zoster, not common in children, causes localized cutaneous symptoms, but may disseminate in immunocompromised patients.

**Varicella in Unvaccinated Individuals**

The illness usually begins 14-16 days after exposure, although the incubation period can range from 10-21 days. Subclinical varicella is rare; almost all exposed, susceptible persons experience a rash, albeit so mild in some cases that it may go unnoticed. Prodromal symptoms may be present, particularly in older children and adults. Fever, malaise, anorexia, headache, and occasionally mild abdominal pain may occur 24-48 hr before the rash appears. Temperature elevation is usually 37.8-38.9°C (100-102°F) but may be as high as 41.1°C (106°F); fever and other systemic symptoms usually resolve within 2-4 days after the onset of the rash.

Varicella lesions often appear first on the scalp, face, or trunk. The initial exanthem consists of intensely pruritic erythematous macules that evolve through the papular stage to form clear, fluid-filled vesicles. Clouding and umbilication of the lesions begin in 24-48 hr. While the initial lesions are crusting, new crops form on the trunk and then the extremities; the simultaneous presence of lesions in various stages of evolution is characteristic of varicella (Fig. 253-1). The distribution of the rash is predominantly central or centripetal with the greatest concentration on the trunk and proximally on the extremities. Ulcerative lesions involving the mucosa of the oropharynx and vagina are also common; many children have vesicular lesions on the eyelids and conjunctivae, but corneal involvement and serious ocular disease are rare. The average number of varicella lesions is about 300, but healthy children may have fewer than 10 to more than 1,500 lesions. In cases resulting from secondary household spread and in older children, more lesions usually occur, and new crops of lesions may continue to develop for more than 7 days. The exanthem may be much more extensive in children with skin disorders, such as eczema or recent sunburn. Hypopigmentation or hyperpigmentation of lesion sites persists for days to weeks in some children, but severe scarring is unusual unless the lesions were secondarily infected.

The differential diagnosis of varicella includes vesicular rashes caused by other infectious agents, such as herpes simplex virus, enterovirus, monkey pox, rickettsial pox, and S. aureus; drug reactions; disseminated herpes zoster; contact dermatitis; and insect bites (especially for breakthrough varicella). Severe varicella was the most common illness confused with smallpox before the eradication of smallpox.

**Varicelliform Rashes in Vaccinated Individuals**

Varicelliform rashes that occur after vaccination could be a result of wild-type VZV, vaccine strain VZV, or other etiologies (e.g., insect bites, coxsackievirus). During days 0-42 after vaccination, the
Figure 253-1  A, Varicella lesions in unvaccinated persons display the characteristic "cropping" distribution, or manifest themselves in clusters; the simultaneous presence of lesions in various stages of evolution is characteristic.  B, Breakthrough varicella lesions are predominantly maculopapular, and vesicles are less common; the illness is most commonly mild with <50 lesions. (A courtesy of the Centers for Disease Control and Prevention [CDC]; B courtesy of the CDC and Dr. John Noble, Jr.)

likelihood of rash from wild-type or vaccine strain VZV varies depending on the stage of a country’s vaccination program. In the early stages of a vaccine program, rash within 1-2 wk is still most commonly caused by wild-type VZV, reflecting exposure to varicella before vaccination could provide protection. Rash occurring 14-42 days after vaccination is a result of either wild-type or vaccine strains, reflecting exposure and infection before protection from vaccination or an adverse event of vaccination (vaccine-associated rash), respectively. As wild-type varicella continues to decline as a consequence of the vaccination program, VZV circulation will also decline and rashes in the interval 0-42 days after vaccination will be less commonly caused by wild-type VZV.

Breakthrough varicella is disease that occurs in a person vaccinated more than 42 days before rash onset and is caused by wild-type virus. One dose of varicella vaccine is >97% effective in preventing moderate and severe varicella and is 85% (median; range: 44-100%) effective in preventing all disease at exposure to wild-type VZV. This means that after close exposure to VZV, as may occur in a household or an outbreak setting in a school or daycare center, about 1 of every 5 children who received one dose of vaccine may experience breakthrough varicella. Exposure to VZV may also result in asymptomatic infection in the previously immunized child. The rash in breakthrough disease is frequently atypical and predominantly maculopapular, vesicles are seen less commonly. The illness is most commonly mild with <50 lesions, shorter duration of rash, fewer complications, and little or no fever. However, approximately 25-30% of breakthrough cases in vaccinees who received one dose are not mild, with clinical features more similar to those of wild-type infection. Breakthrough cases are overall less contagious than wild-type infections within household settings, but contagiousness varies proportionally with the number of lesions; typical breakthrough cases (<50 lesions) is about one third as contagious as disease in unvaccinated cases, whereas breakthrough cases with ≥50 lesions are as contagious as wild-type cases. Consequently, children with breakthrough disease should be considered potentially infectious and excluded from school until lesions have crusted or, if there are no vesicles present, until no new lesions are occurring. Transmission has been documented to occur from breakthrough cases in household, childcare, and school settings. Fewer studies have evaluated the performance of the 2 dose varicella vaccine regimen. One clinical trial estimated the 2 dose vaccine effectiveness for preventing all disease at 98%; the estimate is 95% (median; range: 88-98%) in conditions of everyday clinical practice. Breakthrough cases have been reported among 2 dose vaccinees, although recipients of 2 doses of varicella vaccine are less likely to have breakthrough disease than those who received 1 dose. Additionally, data suggest that disease may be further attenuated among 2 dose vaccine recipients.

Neonatal Varicella
Mortality is particularly high in neonates born to susceptible mothers who contracted varicella around the time of delivery. Infants whose mothers demonstrate varicella in the period from 5 days prior to delivery to 2 days afterward are at high risk for severe varicella. These infants acquire the infection transplacentally as a result of maternal viremia, which may occur up to 48 hr prior to onset of maternal rash. The infant's rash usually occurs toward the end of the 1st wk to the early part of the 2nd wk of life (although it may be as soon as 2 days). Because the mother has not yet developed a significant antibody response, the infant receives a large dose of virus without the moderating effect of maternal anti-VZV antibody. If the mother demonstrates varicella more than 5 days prior to delivery, she still may pass virus to the soon-to-be-born child, but infection is attenuated because of transmission of maternal VZV-specific antibody across the placenta. This moderating effect of maternal antibody is present if delivery occurs after about 30 wk of gestation, when maternal immunoglobulin (Ig) G is able to cross the placenta in significant amounts. The recommendations for use of human varicella-zoster immunoglobulin (VZIG) differ based on when the infant is exposed to varicella. Newborns whose mothers develop varicella during the period of 5 days before to 2 days after delivery should receive VZIG as soon as possible. Although neonatal varicella may occur in about half of these infants despite administration of VZIG, it is usually milder than in the absence of VZIG administration. All premature infants born >28 wk of gestation to a mother with active varicella at delivery (even if the maternal rash has been present for >1 wk) should receive VZIG. If VZIG is not available, intravenous immunoglobulin (IVIG) may provide some protection, although varicella-specific antibody titers may vary from lot to lot. Because perinatally acquired varicella may be life threatening, the infant should be treated with acyclovir (10 mg/kg every 8 hr IV) when lesions develop. Some experts might initiate treatment with oral acyclovir in infants who received VZIG. Neonatal varicella can also follow a postpartum exposure of an infant delivered to a mother who was susceptible to VZV, although the frequency of complications declines rapidly in the weeks after birth. Recommendations for VZIG administration for these infants are presented in the postexposure prophylaxis section. Neonates with community-acquired varicella who experience severe varicella, especially those who have a complication such as pneumonia, hepatitis, or encephalitis, should also receive treatment with intravenous acyclovir (10 mg/kg every 8 hr). Infants with neonatal varicella who receive prompt antiviral therapy have an excellent prognosis.

Congenital Varicella Syndrome
In utero transmission of VZV can occur; however, because most adults in temperate climates are immune, pregnancy complicated by varicella is unusual in these settings. When pregnant women do contract
The congenital varicella syndrome occurs in approximately 0.4% of infants born to women who have varicella during pregnancy before 13 wk of gestation and in approximately 2% of infants born to women with varicella between 13 and 20 wk of gestation. Rarely, cases of congenital varicella syndrome have been reported in infants of women infected after 20 wk of pregnancy, the latest occurring at 28 wk of gestation. Before availability of varicella vaccine in the United States, 44 cases of congenital varicella syndrome were estimated to occur each year. The congenital varicella syndrome is characterized by cicatrical skin scarring in a zoster-like distribution; limb hypoplasia; and abnormalities of the neurologic system (e.g., microcephaly, cortical atrophy, seizures, and mental retardation), eye (e.g., chorioretinitis, microphthalmia, and cataracts), renal system (e.g., hydronephrosis and hydroureter), and autonomic nervous system (neurogenic bladder, swallowing dysfunction, and aspiration pneumonia). Low birthweight is common among infants with congenital varicella syndrome. Most of the stigmata can be attributed to virus-induced injury to the nervous system, although there is no obvious explanation why certain regions of the body are preferentially infected during fetal VZV infection. The characteristic cutaneous lesion has been called a cicatrix, a zigzag scarring, in a dermatomal distribution, often associated with atrophy of the affected limb (Fig. 253-2). Many infants with severe manifestations of congenital varicella syndrome (atrophy and scarring of a limb) have significant neurologic deficiencies. Alternatively, there may be neither skin nor limb abnormalities but the infant may show cataracts or even extensive aplasia of the entire brain.

There are rare case reports of fetal abnormalities following the development of herpes zoster in the mother; whether or not these cases truly represent the congenital varicella syndrome is unclear. If it does occur, the congenital syndrome acquired as a result of maternal herpes zoster is exceedingly rare. Maternal herpes zoster was associated with typical congenital varicella syndrome in 1 case, but the mother had disseminated herpes zoster (at 12 wk of gestation).

The diagnosis of VZV fetopathy is based mainly on the history of gestational varicella combined with the presence of characteristic abnormalities in the newborn infant. Virus cannot be cultured from the affected newborn, but viral DNA may be detected in tissue samples by polymerase chain reaction (PCR). VZV-specific IgM antibody is detectable in the cord blood sample in some infants, although the IgM titer drops quickly in the postpartum period and can be nonspecifically positive. Chorionic villus sampling and fetal blood collection for the detection of viral DNA, virus, or antibody have been used in an attempt to diagnose fetal infection and embryopathy. The usefulness of these tests for patient management and counseling has not been defined. Because these tests may not distinguish between infection and disease, their utility may primarily be that of reassurance when the result is negative. A persistently positive VZV IgG antibody titer at 12-18 mo of age is a reliable indicator of prenatal infection in the asymptomatic child, as is the development of zoster in the 1st yr of life without evidence of postnatal infection.

VZIG has often been administered to the susceptible mother exposed to varicella to modify maternal disease severity; it is uncertain whether this step modifies infection in the fetus, although some evidence suggests that it may be beneficial for the fetus too. Similarly, acyclovir treatment may be given to the mother with severe varicella. A prospective registry of acyclovir use in the 1st trimester demonstrated that the occurrence of birth defects approximates that found in the general population. Acyclovir is a class B drug for pregnancy and should be considered when the benefit to the mother outweighs the potential risk to the fetus. The efficacy of acyclovir treatment of the pregnant woman in preventing or modifying the severity of congenital varicella is not known, but its use should be considered to protect the mother from severe disease. Because the damage caused by fetal VZV infection does not progress in the postpartum period, antiviral treatment of infants with congenital VZV syndrome is not indicated.

### Complications

The complications of VZV infection occur with varicella or with reactivation of infection, more commonly in immunocompromised patients. In the otherwise healthy child, mild varicella hepatitis is relatively common but rarely clinically symptomatic. Mild thrombocytopenia occurs in 1-2% of children with varicella and may be associated with transient petechiae. Purpura, hemorrhagic vesicles, hematuria, and gastrointestinal bleeding are rare complications that may have serious consequences. Other complications of varicella, some of them rare, include acute cerebellar ataxia, encephalitis, pneumonia, nephritis, nephrotic syndrome, hemolytic-uremic syndrome, arthritis, myocarditis, pericarditis, pancreatitis, orchitis, and acute retinal necrosis. A reduction in the number and rates of varicella-related complications is seen with the use of the vaccine. Reports of serious varicella-related complications in vaccinated persons (breakthrough) have been rare (meningitis, 1 case of acute transverse myelitis, 1 fatal case of VZV encephalitis in an apparently immunocompetent child, and 4 fatal cases of breakthrough disease, 3 of which involved high-dose steroids or an underlying immunocompromising condition).

Declines in varicella-related hospitalizations and deaths in the United States since implementation of the varicella vaccination program provide supporting evidence that varicella vaccine reduces severe complications from varicella. Approximately 100 deaths (with varicella listed as the underlying cause of death) occurred in the United States annually before the introduction of the varicella vaccine; during 2005-2007 the annual average number of varicella deaths was 15. In both the pre- and postvaccine era, the majority of deaths (>80%) have been among persons without high-risk preexisting conditions.

### Bacterial Infections

Secondary bacterial infections of the skin, usually caused by group A Streptococcus and S. aureus, may occur in up to 5% of children with varicella. These range from impetigo to cellulitis, lymphadenitis, and subcutaneous abscesses. An early manifestation of secondary bacterial infection is erythema of the base of a new vesicle. Recrudescence of fever 3-4 days after the initial exanthem may also herald a secondary bacterial infection. Varicella is a well-described risk factor for serious invasive infections caused by group A Streptococcus, which can have a fatal outcome. The more invasive infections, such as varicella gangrenosa, bacterial sepsis, pneumonia, arthritis, osteomyelitis, cellulitis, and necrotizing fasciitis, account for much of the morbidity and
mortality of varicella in otherwise healthy children. Bacterial toxin-mediated diseases (e.g., toxic shock syndrome) also may complicate varicella. A substantial decline in varicella-related invasive bacterial infections is associated with the use of the varicella vaccine.

**Encephalitis and Cerebellar Ataxia**
Encephalitis (1 per 50,000 cases of varicella in unvaccinated children) and acute cerebellar ataxia (1 per 4,000 cases of varicella in unvaccinated children) are well-described neurologic complications of varicella; morbidity from central nervous system complications is highest among patients younger than 5 yr and older than 20 yr. Nuchal rigidity, altered consciousness, and seizures characterize meningoencephalitis. Patients with cerebellar ataxia have a gradual onset of gait disturbance, nystagmus, and slurred speech. Neurologic symptoms usually begin 2-6 days after the onset of the rash but may occur during the incubation period or after resolution of the rash. Clinical recovery is typically rapid, occurring within 24-72 hr, and is usually complete. Although severe hemorrhagic encephalitis, analogous to that caused by herpes simplex virus, is very rare in children with varicella, the consequences are similar to those of herpes encephalitis. Reye syndrome (hepatic dysfunction with hypoglycemia and encephalopathy) associated with varicella and other viral illnesses such as influenza is rare now that salicylates are no longer used as antipyretics in these situations (see Chapter 361).

**Pneumonia**
Varicella pneumonia is a severe complication that accounts for most of the increased morbidity and mortality from varicella in adults and other high-risk populations, but pneumonia may also complicate varicella in young children. Respiratory symptoms, which may include cough, dyspnea, cyanosis, pleuritic chest pain, and hemoptysis, usually begin within 1-6 days after the onset of the rash. Smoking has been described as a risk factor for severe pneumonia complicating varicella. The frequency of varicella pneumonia may be greater in the parturient.

**Progressive Varicella**
Progressive varicella, with visceral organ involvement, coagulopathy, severe hemorrhage, and continued vesicular lesion development after 7 days, is a severe complication of primary VZV infection. Severe abdominal pain, which may reflect involvement of mesenteric lymph nodes or the liver, or the appearance of hemorrhagic vesicles in otherwise healthy adolescents and adults, immunocompromised children, pregnant women, and newborns, may herald severe, and potentially fatal, disease. Although rare in healthy children, the risk for progressive varicella is highest in children with congenital cellular immune deficiency disorders and those with malignancy, particularly if chemotherapy, and especially corticosteroids, had been given during the incubation period and the absolute lymphocyte count is <500 cells/µL. The mortality rate for children who acquired varicella while undergoing treatment for malignancy and who were not treated with antiviral therapy approached 7%; varicella-related deaths usually occurred within 3 days after the diagnosis of varicella pneumonia. Children who acquire varicella after organ transplantation are also at risk for progressive VZV infection. Children undergoing long-term, low-dose systemic or inhaled corticosteroid therapy are not considered to be at higher risk for severe varicella, but progressive varicella does occur in patients receiving high-dose corticosteroids. There are case reports in patients receiving inhaled corticosteroids as well as in asthmatic patients receiving multiple short courses of systemic corticosteroid therapy. Unusual clinical findings of varicella, including lesions that develop a hyperkertotic appearance and continued new lesion formation for weeks or months, have been described in children with untreated, late-stage HIV infection. Immunization of HIV-infected children who have a CD4+ T-lymphocyte percent ≥15%, as well as children with leukemia and solid organ tumors who are in remission and whose chemotherapy can be interrupted for 2 wk around the time of immunization or has been terminated, have reduced frequency of severe disease. Moreover, since the advent of the universal immunization program in the United States, many children who would become immunocompromised later in life because of disease or treatment are protected before the immunosuppression occurs; also, as a result of reductions in varicella incidence, immunocompromised children are less likely to be exposed to varicella.

**Herpes Zoster**
Herpes zoster manifests as vesicular lesions clustered within 1 or, less commonly, 2 adjacent dermatomes (Fig. 253-3). In the elderly, herpes zoster typically begins with burning pain followed by clusters of skin lesions in a dermatomal pattern. Almost half of the elderly with herpes zoster experience complications; the most frequent complication is postherpetic neuralgia, a painful condition that affects the nerves despite resolution of the skin lesions. Approximately 4% of patients suffer a 2nd episode of herpes zoster; 3 or more episodes are rare. Unlike herpes zoster in adults, zoster in children is infrequently associated with localized pain, hyperesthesia, pruritus, low-grade fever, or complications. In children, the rash is mild, with new lesions appearing for a few days (Fig. 253-4); symptoms of acute neuritis are minimal; and complete resolution usually occurs within 1-2 wk. Unlike in adults, postherpetic neuralgia is unusual in children. An increased risk for herpes zoster early in childhood has been described in children who acquire infection with VZV in utero or in the 1st yr of life.

Immunocompromised children may have more severe herpes zoster, similar to the situation in adults, including postherpetic neuralgia. Immunocompromised patients may also experience disseminated cutaneous disease that mimics varicella, with or without initial dermatomal rash, as well as visceral dissemination with pneumonia, hepatitis, encephalitis, and disseminated intravascular coagulopathy. Severely immunocompromised children, particularly those with advanced HIV infection, may have unusual, chronic, or relapsing cutaneous disease,
retinitis, or central nervous system disease without rash. The finding of a lower risk for herpetic zoster among vaccinated children with leukemia than in those who have had varicella suggested that the vaccine virus reactivates less commonly than wild-type VZV. Studies to date indicate that the risk for herpetic zoster in healthy children who have received one dose of vaccine is lower than in children who had wild-type varicella. Many more years of follow-up are needed to determine whether this lower risk is maintained among older persons who are at greatest risk for herpetic zoster. The risk for herpetic zoster in healthy children following 2 doses of varicella vaccine has not been evaluated.

**DIAGNOSIS**

Varicella and herpetic zoster have been diagnosed primarily by their clinical appearance. Laboratory evaluation has not been considered necessary for diagnosis or management. However, as varicella disease has declined to low levels, laboratory confirmation has become increasingly useful. The atypical nature of breakthrough varicella, with a higher proportion of papular rather than vesicular rash, poses both clinical and laboratory diagnostic challenges.

Leukopenia is typical during the 1st 72 hr after onset of rash; it is followed by a relative and absolute lymphocytosis. Results of liver function tests are also usually (75%) mildly elevated. Patients with neurologic complications of varicella or uncomplicated herpetic zoster have a mild lymphocytic pleocytosis and a slight to moderate increase in protein content of the cerebrospinal fluid; the cerebrospinal fluid glucose concentration is usually normal.

Rapid laboratory diagnosis of VZV is often important in high-risk patients and can be important for infection control, especially for breakthrough cases that have mild or atypical presentations. Confirmation of VZV infections can be accomplished by many referral hospital laboratories and all state health laboratories. VZV can be identified quickly by direct fluorescence assay of cells from cutaneous lesions (vesicular fluid) in 15–20 min, by PCR amplification testing (vesicular fluid, crusts) in hours to days, depending on availability, and by rapid culture with specific immunofluorescence staining (shell vial technique) in 48–72 hr. In the absence of vesicles or scabs, scrapings of maculopapular lesions can be collected for PCR or direct fluorescence assay testing. Infectious virus may be recovered by means of tissue culture methods; such methods require specific expertise, and virus may take days to weeks to grow. Of available tests, PCR is the most sensitive and allows for differentiation of wild-type and vaccine strains. Direct fluorescence assay is specific and less sensitive than PCR but when available allows for rapid diagnosis. Although multinucleated giant cells can be detected with nonspecific stains (Tzanck smear), they have poor sensitivity and do not differentiate VZV from herpes simplex virus infections. Strain identification (genotyping) can distinguish wild-type VZV from the vaccine strain in a vaccinated child; however, genotyping is available only at specialized reference laboratories. Laboratory tests of lesions cannot be used to distinguish between varicella and disseminated herpetic zoster. VZV IgG antibodies can be detected by several methods, and a 4-fold or greater rise in IgG antibodies is confirmatory of acute infection (although this requires a 2-3 wk delay to collect a convalescent specimen); in vaccinated persons, commercially available tests are not sufficiently sensitive to always detect antibody following vaccination and a 4-fold rise in IgG antibody may not occur. VZV IgG antibody tests can also be valuable to determine the immune status of individuals whose clinical history of varicella is unknown or equivocal. Testing for VZV IgM antibodies is not useful for routine confirmation or ruling out of varicella because commercially available methods are unreliable and the kinetics of the IgM response have not been well defined. Reliable VZV-specific IgM assays are available in certain reference laboratories, including a capture-IgM assay available at the national VZV laboratory at the Centers for Disease Control and Prevention. Serologic tests are not useful for the initial diagnosis of herpetic zoster, but a large rise in IgG titer in convalescent titer in the presence of an atypical zoster rash is confirmatory. As with any laboratory tests, a negative varicella test should be considered in the context of the clinical presentation. Clinicians should use clinical judgment to decide on the best course of therapy.

**TREATMENT**

Antiviral treatment modifies the course of both varicella and herpes zoster. Antiviral drug resistance is rare but has occurred, primarily in children with HIV infection and other immunocompromising conditions where frequent relapse of VZV infections has resulted in multiple courses of antiviral therapy. Foscarnet and cidovanlovir may be useful for the treatment of acyclovir-resistant VZV infections, but consultation of an infectious disease specialist is recommended.

**Varicella**

The only antiviral drug available in liquid formulation that is licensed for treatment of varicella for pediatric use is acyclovir. Given the safety profile of acyclovir and its demonstrated efficacy in the treatment of varicella, treatment of all children, adolescents, and adults with varicella is acceptable. However, acyclovir therapy is not recommended routinely by the American Academy of Pediatrics for treatment of uncomplicated varicella in the otherwise healthy child because of the marginal benefit, the cost of the drug, and the low risk for complications of varicella. Oral therapy with acyclovir (20 mg/kg/dose; maximum: 800 mg/dose) given as 4 doses/day for 5 days can be used to treat uncomplicated varicella in individuals at increased risk for moderate to severe varicella: nonpregnant individuals older than 12 yr of age and individuals older than 12 mo of age with chronic cutaneous or pulmonary disorders; individuals receiving short-term, intermittent, or aerosolized corticosteroid therapy; individuals receiving long-term salicylate therapy; and possibly secondary cases among household contacts. To be most effective, treatment should be initiated as early as possible, preferably within 24 hr of the onset of the exanthem. There is less clinical benefit if treatment is initiated more than 72 hr after onset of the exanthem. Acyclovir therapy does not interfere with the induction of VZV immunity. Acyclovir has been used to treat varicella in pregnant women; its safety for the fetus has not been established (see congenital varicella syndrome section). Some experts recommend the use of famciclovir or valacyclovir in older children who can swallow tablets. These drugs are highly active against VZV by the same mechanism as acyclovir and are better absorbed by the oral route than acyclovir. Valacyclovir (20 mg/kg/dose; maximum: 1,000 mg/dose, administered 3 times daily for 5 days) is licensed for treatment of varicella in children 2 to <18 yr of age, and both valacyclovir and famciclovir are approved for treatment of herpes zoster in adults.

**Intravenous therapy** is indicated for severe disease and for varicella in immunocompromised patients (even if begun more than 72 hr after onset of rash). Any patient who has signs of disseminated VZV, including pneumonia, severe hepatitis, thrombocytopenia, or encephalitis, should receive immediate treatment. IV acyclovir therapy (500 mg/m² every 8 hr) initiated within 72 hr of development of initial symptoms decreases the likelihood of progressive varicella and visceral dissemination in high-risk patients. Treatment is continued for 7–10 days or until no new lesions have appeared for 48 hr. Delaying antiviral treatment in high-risk individuals until it is obvious that prolonged new lesion formation is occurring is not advisable because visceral dissemination occurs during the same period.

Acyclovir-resistant VZV has been identified primarily in children infected with HIV. These children may be treated with intravenous foscarnet (120 mg/kg/day divided every 8 hr for up to 3 wk). The dose should be modified in the presence of renal insufficiency. Resistance to foscarnet has been reported with prolonged use. Cidofovir is also useful in this situation. Because of the increased toxicity profile of foscarnet and cidofovir, these 2 drugs should be initiated in collaboration with an infectious disease specialist.

**Herpes Zoster**

Antiviral drugs are effective for treatment of herpes zoster. In healthy adults, acyclovir (800 mg 5 times a day PO for 5–7 days), famciclovir (500 mg tid PO for 7 days), and valacyclovir (1,000 mg tid PO for 7 days) reduce the duration of the illness and the risk for development of postherpetic neuralgia. In otherwise healthy children, herpes zoster is a less-severe disease, and postherpetic neuralgia usually does not occur. Therefore, treatment of uncomplicated herpes zoster in the child
with an antiviral agent may not always be necessary, although some experts would treat with oral acyclovir (20 mg/kg/dose; maximum: 800 mg/dose) to shorten the duration of the illness. It is important to start antiviral therapy as soon as possible. Delay beyond 72 hr from onset of rash limits its effectiveness.

In contrast, herpes zoster in immunocompromised children can be severe, and disseminated disease may be life-threatening. Patients at high risk for disseminated disease should receive IV acyclovir (500 mg/m² or 10 mg/kg every 8 hr). Oral acyclovir, famciclovir, and valacyclovir are options for immunocompromised patients with uncontrolled herpes zoster, who are considered at low risk for visceral dissemination. Neuritis with herpes zoster should be managed with appropriate analgesics.

Use of corticosteroids in the treatment of herpes zoster in children is not recommended.

PROGNOSIS

Primary varicella has a mortality rate of 2-3 per 100,000 cases, with the lowest case fatality rates among children 1-9 yr of age (<1 death per 100,000 cases). Compared with these age groups, infants have a 4 times greater risk of dying and adults have a 25 times greater risk of dying. The most common complications among people who died from varicella were pneumonia, central nervous system complications, secondary infections, and hemorrhagic conditions. The mortality rate of untreated primary infection is 7-14% in immunocompromised children and may approach 50% in untreated adults with pneumonia. Herpes zoster among healthy children has an excellent prognosis and is usually self-limited. Severe presentation with complications and sometimes fatalities can occur in immunocompromised children.

PREVENTION

VZV transmission is difficult to prevent, especially from persons with varicella, because a person with varicella is contagious for 24-48 hr before the rash is apparent. Herpes zoster is less infectious than varicella; nonetheless, transmission has been reported even in the absence of direct contact with the patient. Infection control practices, including caring for patients with varicella in isolation rooms with filtered air systems, are essential. All healthcare workers should have evidence of varicella immunity (Table 253-1). Unvaccinated healthcare workers without other evidence of immunity who have had a close exposure to VZV should be furloughed for days 8-21 after exposure because they are potentially infectious during this period.

Vaccine

Varicella is a vaccine-preventable disease. Varicella vaccine contains live, attenuated VZV (Oka strain) and is indicated for subcutaneous administration. In the United States, varicella vaccine is recommended for routine administration as a 2-dose regimen to healthy children at ages 12-15 mo and 4-6 yr. Catch-up vaccination with the 2nd dose is recommended for children and adolescents who received only 1 dose. Vaccination with 2 doses is recommended for all persons without evidence of immunity. The minimum interval between the 2 doses is 3 mo for persons 12 yr of age or younger and 4 wk for older children, adolescents, and adults. Administration of varicella vaccine within 4 wk of measles-mumps-rubella (MMR) vaccination is associated with a higher risk for breakthrough disease; therefore, it is recommended that the varicella and MMR vaccines either be administered simultaneously at different sites or be given at least 4 wk apart. Varicella vaccine can be administered as a monovalent vaccine (for all healthy persons ≥12 mo of age) or as the quadrivalent measles-mumps-rubella-varicella (MMRV) vaccine (for children age 12 mo through 12 yr only).

Varicella vaccine is contraindicated for persons who have a history of anaphylactic reaction to any component of the vaccine; pregnant women; persons with cell-mediated immune deficiencies, including those with leukemia, lymphoma, and other malignant neoplasms affecting the bone marrow or lymphatic systems; persons receiving immunosuppressive therapy; and persons who have a family history of congenital or hereditary immunodeficiency in 1st-degree relatives unless the immune competence of the potential vaccine recipient is demonstrated. Children with isolated humoral immunodeficiencies may receive varicella vaccine. The monovalent varicella vaccine has been used in clinical trial settings in children with acute lymphocytic leukemia and certain solid tumors who are in remission. Protocols are available that define the timing of vaccination in terms of the length of time a patient has been in remission while receiving maintenance chemotherapy; when to interrupt maintenance chemotherapy, including therapy with corticosteroids, before and after vaccination; and the minimal acceptable lymphocyte and platelet counts at the time of vaccination. Because of the risk of severe vaccine-related complications, use of the vaccine in these specific populations of children should only be considered in settings where these protocols can be followed, antiviral therapy with acyclovir is readily available, and physicians have expertise with use of the vaccine in these populations.

The vaccine should be considered for HIV-infected children with a CD4+ T-lymphocyte percentage ≥15%. These children should receive 2 doses of vaccine, 3 mo apart. Specific guidelines for immunizing these children should be reviewed before vaccination. Data indicate that varicella vaccine is 100% effective in preventing herpes zoster among children infected with HIV. MMRV should not be administered as a substitute for the component vaccines in HIV-infected children.

Zoster vaccine is licensed for use as a single immunization for prevention of herpes zoster and to decrease the frequency of postherpetic neuralgia among individuals 50 yr of age and older. It is not indicated for the treatment of zoster or postherpetic neuralgia.

Vaccine-Associated Adverse Events

Varicella vaccine is safe and well tolerated. The incidence of injection site complaints observed ≤3 days after vaccination was slightly higher after dose 2 (25%) than after dose 1 (22%). A mild vaccine-associated varicellaiform rash was reported in approximately 1-5% of healthy vaccinees, consisting of 6-10 papular-vesicular, erythematous lesions with peak occurrence 8-21 days after vaccination. Serious adverse reactions confirmed to be caused by the vaccine strain are rare and include pneumonia, hepatitis, meningitis, recurrent herpes zoster, severe rash, and 2 deaths. Transmission of vaccine virus to susceptible contacts is a very rare event (9 documented occurrences from healthy vaccine recipients, all in the presence of a rash in the vaccine recipient). MMRV vaccine is associated with a greater risk for febrile seizures 5-12 days after the 1st dose among children 12-23 mo of age compared with

<table>
<thead>
<tr>
<th>Table 253-1</th>
<th>Evidence of Immunity to Varicella</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Evidence of immunity to varicella consists of any of the following:</strong></td>
<td></td>
</tr>
<tr>
<td>• Documentation of age-appropriate vaccination with a varicella vaccine:</td>
<td></td>
</tr>
<tr>
<td>• Preschool-age children (i.e., age ≥12 mo): 1 dose</td>
<td></td>
</tr>
<tr>
<td>• School-age children, adolescents, and adults: 2 doses*</td>
<td></td>
</tr>
<tr>
<td>• Laboratory evidence of immunity† or laboratory confirmation of disease</td>
<td></td>
</tr>
<tr>
<td>• Birth in the United States before 1980‡</td>
<td></td>
</tr>
<tr>
<td>• Diagnosis or verification of a history of varicella disease by a healthcare provider§</td>
<td></td>
</tr>
<tr>
<td>• Diagnosis or verification of a history of herpes zoster by a healthcare provider¶</td>
<td></td>
</tr>
</tbody>
</table>

*For children who received their 1st dose at younger than age 13 yr and for whom the interval between the 2 doses was 28 or more days, the 2nd dose is considered valid.
†Commercial assays can be used to assess disease-induced immunity, but they lack sensitivity to always detect vaccine-induced immunity (i.e., they might yield false-negative results).
‡For healthcare personnel, pregnant women, and immunocompromised persons, birth before 1980 should not be considered evidence of immunity.
§Verification of history or diagnosis of typical disease can be provided by any healthcare provider (e.g., school or occupational clinic nurse, nurse practitioner, physician assistant, or physician). For persons reporting a history of, or reporting with, atypical or mild cases, assessment by a physician or his/her designee is recommended, and 1 of the following should be sought: (1) an epidemiologic link to a typical varicella case or to a laboratory-confirmed case or (2) evidence of laboratory confirmation if it was performed at the time of acute disease. When such documentation is lacking, persons should not be considered as having a valid history of disease, because other diseases might mimic mild atypical varicella.
¶Verification of history or diagnosis of disease can be provided by any healthcare provider.
simultaneous MMR and varicella vaccines (1 extra febrile seizure for every 2,500 children vaccinated).

**Postexposure Prophylaxis**

Vaccine given to healthy children within 3 or 5 days after exposure (as soon as possible is preferred) is effective in preventing or modifying varicella. Varicella vaccine is now recommended for postexposure use and for outbreak control. Oral acyclovir administered late in the incubation period may modify subsequent varicella in the healthy child; however, its use in this manner is not recommended until it can be further evaluated.

High-titer anti-VZV immune globulin as postexposure prophylaxis is recommended for immunocompromised children, pregnant women, and newborns exposed to varicella. Since 2012 the product licensed for use in the United States is Varizig. Varizig is distributed in the United States by FFF Enterprises, Temecula, California (1-800-843-7477) or ASD Healthcare, Frisco Texas (800-746-6273). The recommended dose is 1 vial (125 units) for each 10 kg increment of body weight (maximum: 625 units), except for infants weighing ≤2 kg who should receive 0.5 vial. Varizig should be given intramuscularly as soon as possible but may be efficacious up to 10 days after exposure.

Newborns whose mothers demonstrate varicella 5 days before to 2 days after delivery should receive Varizig (0.5 vial for those weighing ≤2 kg and 1 vial for those weighing >2 kg). Varizig is also indicated for pregnant women and immunocompromised persons without evidence of varicella immunity; hospitalized premature infants born at <28 wks of gestation (or weight <1,000 g) who were exposed to varicella, regardless of maternal varicella immunity; and hospitalized premature infants born at ≥28 wk of gestation who were exposed to varicella and whose mothers have no evidence of varicella immunity. If possible, adults should be tested for VZV IgG antibodies before Varizig administration, because many adults with no clinical history of varicella are immune. Anti-VZV antibody prophylaxis may ameliorate disease but does not eliminate the possibility of progressive disease and does not ensure that varicella is not transmitted to close susceptible contacts; patients should be monitored and treated with acyclovir if necessary once lesions develop.

Close contact between a susceptible high-risk patient and a patient with herpes zoster is also an indication for Varizig prophylaxis. Passive antibody administration or treatment does not reduce the risk for herpes zoster or alter the clinical course of varicella or herpes zoster when given after the onset of symptoms.

Although licensed pooled IVIG preparations contain anti-VZV antibodies, the titer varies from lot to lot. In situations in which administration of Varizig does not appear possible, IVIG can be administered (400 mg/kg administered once within 10 days of exposure). Immunocompromised patients who have received high-dose IVIG (>400 mg/kg) for other indications within 2-3 wk before VZV exposure can be expected to have serum antibodies to VZV.

*Bibliography is available at Expert Consult.*
Bibliography
Infectious mononucleosis is the best-known clinical syndrome caused by Epstein-Barr virus (EBV). It is characterized by systemic somatic complaints consisting primarily of fatigue, malaise, fever, sore throat, and generalized lymphadenopathy. Originally described as glandular fever, it derives its name from the mononuclear lymphocytosis with atypical-appearing lymphocytes that accompany the illness. Other infections may cause infectious mononucleosis-like illnesses.

**ETIOLOGY**

EBV is a double-stranded DNA virus that is a member of the γ-herpesviruses and causes >90% of cases of infectious mononucleosis. Two distinct types of EBV, type 1 and type 2 (also called type A and type B), have been characterized and have 70–85% sequence homology. EBV-1 is more prevalent worldwide, although EBV-2 is more common in Africa than in the United States and Europe. Both types lead to persistent, lifelong, latent infection. Dual infections with both types have been documented among immunocompromised persons. EBV-1 induces in vitro growth transformation of B cells more efficiently than does EBV-2, but no type-specific disease manifestations or clinical differences have been identified. Coacquisition of multiple EBV genotypes has been shown by heteroduplex tracking assays to occur commonly in otherwise healthy patients with infectious mononucleosis. However, only a single genotype tends to be cultured. It is unknown if this represents isolation of a predominant strain or if the strains that are not able to be cultured, using the transformation assay, are defective.

As many as 5–10% of infectious mononucleosis-like illnesses are caused by primary infection with cytomegalovirus, *Toxoplasma gondii*, adenovirus, hepatitis virus, primary HIV, and possibly rubella virus. In the majority of EBV-negative infectious mononucleosis-like illnesses, the exact cause remains unknown.

**EPIDEMIOLOGY**

EBV infects more than 95% of the world's population. It is transmitted primarily via oral secretions and may be transmitted via penetrative sexual intercourse. Among children, transmission may occur by exchange of saliva from child to child, such as occurs between children in out-of-home childcare. Nonintimate contact, environmental sources, or fomites do not contribute to spread of EBV.

EBV is shed in oral secretions consistently for more than 6 mo after acute infection and then intermittently for life. As many as 20–30% of healthy EBV-infected persons excrete virus at any particular time. Immunosuppression permits reactivation of latent EBV; 60–90% of EBV-infected immunosuppressed patients shed the virus. EBV is also found in male and female genital secretions and, especially for EBV-2, is spread through sexual contact.

Infection with EBV in developing countries and among socioeconomically disadvantaged populations of developed countries usually occurs during infancy and early childhood. In central Africa, almost all children are infected by 3 yr of age. Among more affluent populations in industrialized countries, half of the population is infected by 6–8 yr of age with approximately 30% of infections during adolescence and young adulthood. In the United States, seroprevalence increases with age, from approximately 54% for 6–8 yr olds to 83% for 18–19 yr olds. Seroprevalence at each age is substantially higher for Mexican-Americans and non-Hispanic blacks than non-Hispanic whites. Large differences are seen by family income, with highest seroprevalence in children of families with lowest income.

The epidemiology of the illness of infectious mononucleosis is related to the age of acquisition of EBV infection. Primary infection with EBV during childhood is usually asymptomatic or mild and indistinguishable from other childhood infections; the clinical syndrome of infectious mononucleosis is practically unknown in undeveloped regions of the world. Primary EBV infection in adolescents and adults manifests in 30–50% of cases as the classic triad of fatigue, pharyngitis, and generalized lymphadenopathy, which constitute the major clinical manifestations of infectious mononucleosis. This syndrome may be seen at all ages but is rarely apparent in children younger than 4 yr of age, when most EBV infections are asymptomatic, or in adults older than 40 yr of age, when most individuals have already been infected by EBV. The true incidence of the syndrome of infectious mononucleosis is unknown but is estimated to occur in 20–70 per 100,000 persons/yr; in young adults, the incidence increases to approximately 100 per 100,000 persons/yr. The prevalence of serologic evidence of past EBV infection increases with age; almost all adults in the United States are seropositive.

**PATHOGENESIS**

After acquisition in the oral cavity, EBV initially infects crypt epithelial cells, which may contribute to the symptoms of pharyngitis. After
intracellular viral replication and cell lysis with release of new virions, virus spreads to contiguous structures such as the salivary glands, with eventual viremia and infection of B lymphocytes in the peripheral blood and the entire lymphoreticular system, including the liver and spleen. The atypical lymphocytes that are characteristic of infectious mononucleosis are CD8 T lymphocytes, which exhibit both suppressor and cytotoxic functions that develop in response to the infected B lymphocytes. This relative as well as absolute increase in CD8 lymphocytes results in a transient reversal of the normal 2:1 CD4/CD8 (helper/suppressor) T-lymphocyte ratio. Many of the clinical manifestations of infectious mononucleosis may result, at least in part, from cytokine release from the host immune response, which is effective in reducing the EBV load to <1 copy/10^5 circulating B lymphocytes, equivalent to <10 copies/µg of DNA from whole blood. The EBV load is more variable among immunocompromised persons and can be >4,000 copies/µg of DNA.

Epithelial cells of the uterine cervix may become infected by sexual transmission of the virus, although local symptoms have been described after sexual transmission. EBV is consistently found intracellularly in smooth muscle cells of leiomyosarcomas of immunocompromised persons, but not in leiomyosarcomas of immunocompetent persons.

EBV, like the other herpesviruses, establishes lifelong latent infection after the primary illness. The latent virus is carried in oropharyngeal epithelial cells and systemically in memory B lymphocytes as multiple episomes in the nucleus. The viral episomes replicate with cell division and are distributed to both daughter cells. Viral integration into the cell genome is not typical. Only a few viral proteins, including the EBV-determined nuclear antigens (EBNAs), are produced during latency. These proteins are important in maintaining the viral episome during the latent state. Progression to viral replication begins with production of EBV early antigens (EAs), proceeds to viral DNA replication, is followed by production of viral capsid antigen (VCA), and culminates in cell death and release of mature virions. Reactivation with viral replication occurs at a low rate in populations of latently infected cells and is responsible for intermittent viral shedding in oropharyngeal secretions of infected individuals. Reactivation is apparently asymptomatic and not recognized to be accompanied by distinctive clinical symptoms.

**ONCOGENESIS**

EBV was the first human virus to be associated with malignancy. EBV infection may result in a spectrum of proliferative disorders ranging from self-limited, usually benign disease such as infectious mononucleosis to aggressive, nonmalignant proliferations such as the virus-associated hemophagocytic syndrome to lymphoid and epithelial cell malignancies. Benign EBV-associated proliferations include oral hairy leukoplakia, primarily in adults with AIDS, and lymphoid interstitial pneumonitis, primarily in children with AIDS. Malignant EBV-associated proliferations include nasopharyngeal carcinoma, Burkitt lymphoma, Hodgkin disease, lymphoproliferative disorders, and leiomyosarcoma in immunodeficient states, including AIDS. There is no firm evidence of development of EBV quasispecies that would contribute to the pathogenesis of EBV-positive malignancies.

**Nasopharyngeal carcinoma** occurs worldwide but is 10 times more common in persons in southern China, where it is the most common malignant tumor among adult men. It is also common among whites in North Africa and Inuits in North America. Patients usually present with cervical lymphadenopathy, eustachian tube blockage, and nasal obstruction with epistaxis. All malignant cells of undifferentiated nasopharyngeal carcinoma contain a high copy number of EBV episomes. Persons with undifferentiated and partially differentiated, nonkeratinizing nasopharyngeal carcinomas have elevated EBV antibody titers that are both diagnostic and prognostic. High levels of immunoglobulin (Ig) A antibody to EA and VCA may be detected in asymptomatic individuals and can be used to follow response to tumor therapy (Table 254-1). Cells of well-differentiated, keratinizing nasopharyngeal carcinomas contain a low number of or no EBV genomes; these persons have EBV serologic patterns similar to those of the general population.

CT and MR images are helpful in both identifying and defining masses in the head and neck. The diagnosis is established by biopsy of the mass or of a suspicious cervical lymph node. Surgery is important for staging and diagnosis. Radiation therapy is effective for control of the primary tumor and regional nodal metastases. Chemotherapy with 5-fluourouracil, cisplatin, and methotrexate is effective but not always curative. The prognosis is good if the tumor is localized.

**Endemic (African) Burkitt lymphoma**, often found in the jaw, is the most common childhood cancer in equatorial East Africa and New

Table 254-1  Correlation of Clinical Status and Serologic Responses to Epstein-Barr Virus Infection

<table>
<thead>
<tr>
<th>CLINICAL STATUS</th>
<th>HETEROPHILE ANTIBODIES (QUALITATIVE TEST)</th>
<th>IgM-VCA</th>
<th>IgG-VCA</th>
<th>EA-D</th>
<th>EA-R</th>
<th>EBNA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative reaction</td>
<td>–</td>
<td>&lt;1:8*</td>
<td>&lt;1:10*</td>
<td>&lt;1:10*</td>
<td>&lt;1:2.5*</td>
<td></td>
</tr>
<tr>
<td>Susceptible</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Acute primary infection:</td>
<td>distinguishable</td>
<td>1:32 to 1:256</td>
<td>1:160 to 1:640</td>
<td>1:40 to 1:160</td>
<td>–</td>
<td>– to 1:2.5</td>
</tr>
<tr>
<td>infectious mononucleosis</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Recent primary infection:</td>
<td>distinguishable</td>
<td>±</td>
<td>– to 1:32</td>
<td>1:320 to 1:1280</td>
<td>1:40 to 1:160</td>
<td>–</td>
</tr>
<tr>
<td>infectious mononucleosis</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Remote infection</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Reactivation:</td>
<td>distinguishable</td>
<td>–</td>
<td>1:40 to 1:160</td>
<td>–</td>
<td>– to 1:40</td>
<td>1:10 to 1:40</td>
</tr>
<tr>
<td>immunosuppressed or</td>
<td>distinguishable</td>
<td>–</td>
<td>1:320 to 1:1280</td>
<td>–</td>
<td>1:80 to 1:320</td>
<td>– to 1:160</td>
</tr>
<tr>
<td>immunocompromised</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Burkitt lymphoma</td>
<td>–</td>
<td>–</td>
<td>1:320 to 1:1280</td>
<td>–</td>
<td>1:80 to 1:320</td>
<td>1:10 to 1:80</td>
</tr>
<tr>
<td>Nasopharyngeal carcinoma</td>
<td>–</td>
<td>–</td>
<td>1:320 to 1:1280</td>
<td>–</td>
<td>1:40 to 1:160</td>
<td>1:20 to 1:160</td>
</tr>
</tbody>
</table>

The data were obtained from numerous studies. Individual responses outside the characteristic range may occur.

Or the lowest test dilution.

In young children and adults with asymptomatic seroconversion, the anti–early antigen response may be mainly to the EA-R component.

A minority of individuals will have the anti–early antigen response mainly to the EA-D component.

A minority of individuals will have the anti–early antigen response mainly to the EA-R component.

–, Negative; +, positive; EA-D, diffuse staining component of early antigen; EA-R, cytoplasmic restricted component of early antigen; EBNA, EBV-determined nuclear antigens; EBV, Epstein-Barr virus; IgG, immunoglobulin G; IgM, immunoglobulin M; VCA, viral capsid antigen.

Guinea (see Chapter 496.2). The median age at onset is 5 yr. These regions are holoendemic for *Plasmodium falciparum* malaria and have a high rate of EBV infection early in life. The constant malarial exposure acts as a B-lymphocyte mitogen that contributes to the polyclonal B-lymphocyte proliferation with EBV infection, impairs T-lymphocyte surveillance of EBV-infected B lymphocytes, and increases the risk for developing Burkitt lymphoma. Approximately 98% of cases of endemic Burkitt lymphoma contain the EBV genome compared with only 20% of nonendemic (sporadic or American) Burkitt lymphoma cases. Individuals with Burkitt lymphoma have unusually and characteristically high levels of antibody to VCA and EA that correlate with the risk for developing tumor (see Table 254-1).

All cases of Burkitt lymphoma, including those that are EBV-negative, are monoclonal and demonstrate chromosomal translocation of the c-myc protooncogene to the constant region of the immunoglobulin heavy-chain locus, t(8;14), to the k constant light-chain locus, t(2;8), or to the λ constant light-chain locus, t(8;22). This results in the deregulation and constitutive transcription of the c-myc gene with overproduction of a normal c-myc product that autosuppresses c-myc production on the untranslocated chromosome.

The incidence of Hodgkin disease peaks in childhood in developing countries and in young adulthood in developed countries. Levels of EBV antibodies are consistently elevated preceding development of Hodgkin disease; only a small minority of patients is seronegative for EBV. Infection with EBV increases the risk for Hodgkin disease by a factor of 2-4, with the risk of developing Hodgkin disease peaking at 2.4 yr following infectious mononucleosis. EBV is associated with more than half of cases of mixed cellularity Hodgkin disease and approximately one quarter of cases of the nodular sclerosing subtype, and is rarely associated with lymphocyte-predominant Hodgkin disease. Immunohistochemical studies have localized EBV to the Reed-Sternberg cells and their variants, the pathognomonic malignant cells of Hodgkin disease.

Failure to control EBV infection may result from host immunologic deficits. The prototype is the X-linked lymphoproliferative syndrome (Duncan syndrome), an X chromosome-linked recessive disorder of the immune system associated with severe, persistent, and sometimes fatal EBV infection (see Chapter 123). Approximately 65% of these male patients die of disseminated and fulminating lymphoproliferation involving multiple organs at the time of primary EBV infection. Surviving patients acquire hypogammaglobulinemia, B-cell lymphoma, or both. Most patients die by 10 yr of age.

Numerous congenital and acquired immunodeficiency syndromes are associated with an increased incidence of EBV-associated B-lymphocyte lymphoma, especially central nervous system lymphoma, and leiomyosarcoma. The incidence of lymphoproliferative syndromes parallels the degree of immunosuppression. A decline in T-cell function evidently permits EBV to escape from immune surveillance. Congenital immunodeficiencies predisposing to EBV-associated lymphoproliferation include the X-linked lymphoproliferative syndrome, common-variable immunodeficiency, ataxia-telangiectasia, Wiskott-Aldrich syndrome, and Chédiak-Higashi syndrome. Individuals with acquired immunodeficiencies resulting from anticancer chemotherapy, immunosuppression after solid organ or bone marrow transplantation, or HIV infection have a significantly increased risk for EBV-associated lymphoproliferation. The lymphomas may be focal or diffuse and are usually histologically polyclonal but may become monoclonal. Their growth is not reversed on cessation of immunosuppression.

EBV is found intracellularly in all of the smooth muscle cells of leiomyosarcomas occurring in immunocompromised persons, including HIV-infected patients and transplant recipients, but not in leiomyosarcomas occurring in immunocompetent persons.

EBV is also associated with carcinoma of the salivary glands. Other tumors putatively associated with EBV include some T-lymphocyte lymphomas (including lethal midline), angioimmunoblastic lymphadenopathy-like lymphoma, thymomas and thymic carcinomas derived from thymic epithelial cells, supraglottic laryngeal carcinomas, lymphoepithelial tumors of the respiratory tract and gastrointestineal tract, and gastric adenocarcinoma. The precise contribution of EBV to these various malignancies is not well defined.

**CLINICAL MANIFESTATIONS**

The incubation period of infectious mononucleosis in adolescents is 30-50 days. In children, it may be shorter. The majority of cases of primary EBV infection in infants and young children are clinically silent. In older patients, the onset of illness is usually insidious and vague. Patients may complain of malaise, fatigue, acute or prolonged (>1 wk) fever, headache, sore throat, nausea, abdominal pain, and myalgia. This prodromal period may last 1-2 wk. Lytic infection of B lymphocytes and crypt epithelial cells results in high salivary levels and oral shedding. The complaints of sore throat and fever gradually increase until patients seek medical care. Splenic enlargement may be rapid enough to cause left upper quadrant abdominal discomfort and tenderness, which may be the presenting complaint.

The classic physical examination findings are generalized lymphadenopathy (90% of cases), splenomegaly (50% of cases), and hepatomegaly (10% of cases). Lymphadenopathy occurs most commonly in the anterior and posterior cervical nodes and the submandibular lymph nodes and less commonly in the axillary and inguinal lymph nodes. Epitrochlear lymphadenopathy is particularly suggestive of infectious mononucleosis. Symptomatic hepatitis or jaundice is uncommon, but elevated liver enzymes are very common. Splenomegaly to 2-3 cm below the costal margin is typical (15-65% of cases) and is seen in most cases by ultrasonography; massive enlargement is uncommon.

The sore throat is often accompanied by moderate to severe pharyngitis with marked tonsillar enlargement, occasionally with exudates (Fig. 254-1). Palatal petechiae at the junction of the hard and soft palate are frequently seen. The pharyngitis resembles that caused by streptococcal infection. Other clinical findings may include rashes and edema of the eyelids.

Rashes are usually maculopapular and have been reported in 3-15% of patients. Patients with infectious mononucleosis treated with ampicillin or amoxicillin may experience “ampicillin rash,” which may occur with other β-lactam antibiotics. This morbilliform, vasculitic rash is probably immune mediated and resolves without specific treatment. EBV is also associated with Gianotti-Crosti syndrome, a symmetric rash on the cheeks with multiple erythematous papules, which may coalesce into plaques and persist for 15-50 days. The rash has the appearance of atopic dermatitis and may appear on the extremities and buttocks.

Infants coinfected with HIV acquire EBV infection at an earlier age, have higher EBV plasma loads that are slower to resolve, and more frequently develop pneumonia and hepatosplenomegaly and require hospitalization compared to HIV-negative infants.

**DIAGNOSIS**

The diagnosis of infectious mononucleosis implies primary EBV infection. A presumptive diagnosis may be made by the presence of typical clinical symptoms with atypical lymphocytosis in the peripheral blood.

![Figure 254-1 Tonsillitis with membrane formation in infectious mononucleosis. (Courtesy of Alex J. Steigman, MD.)](image)
The diagnosis is usually confirmed by serologic testing, either for heterophile antibody or specific EBV antibodies.

Culture of EBV is tedious and requires 4–6 wk. The culture method is the transformation assay, which is performed by cocultivating oropharyngeal or genital secretions, peripheral blood (10–30 mL), or tumor with human umbilical cord lymphocytes. The cultures are observed for 6 wk for signs of cell transformation: proliferation and rapid growth, mitotic figures, large vacuoles, granular morphology, and cell aggregation. EBV immortalizes the umbilical cord cells, resulting in cell lines that harbor the EBV strain isolated from the patient and can be maintained in vitro in perpetuity.

### Differential Diagnosis

Infectious mononucleosis-like illnesses may be caused by primary infection with cytomegalovirus, T. gondii, adenovirus, hepatitis virus, HIV, or possibly rubella virus. Cytomegalovirus infection is a particularly common cause in adults. Streptococcal pharyngitis may cause sore throat and cervical lymphadenopathy indistinguishable from that of infectious mononucleosis but is not associated with hepatosplenomegaly. Approximately 5% of cases of EBV-associated infectious mononucleosis have positive throat cultures for group A Streptococcus, representing pharyngeal streptococcal carriage. Failure of a patient with streptococcal pharyngitis to improve within 48–72 hr should evoke suspicion of infectious mononucleosis. The most serious problem in the diagnosis of acute illness arises in the occasional patient with extremely high or low white blood cell counts, moderate thrombocytopenia, and even hemolytic anemia. In these patients, bone marrow examination and hematologic consultation are warranted to exclude the possibility of leukemia.

### Laboratory Tests

In >90% of cases there is leukocytosis of 10,000–20,000 cells/μL, of which at least two thirds are lymphocytes; atypical lymphocytes usually account for 20–40% of the total number. The atypical cells are mature T lymphocytes that have been antigenically activated. Compared with regular lymphocytes microscopically, atypical lymphocytes are larger overall, with larger, eccentrically placed indented and folded nuclei with a lower nuclear-to-cytoplasm ratio. Although atypical lymphocytosis may be seen with many of the infections usually causing lymphocytosis, the highest degree of atypical lymphocytes is classically seen with EBV infection. Other syndromes associated with atypical lymphocytosis include acquired cytomegalovirus infection (in contrast to congenital cytomegalovirus infection), toxoplasmosis, viral hepatitis, rubella, roseola, mumps, tuberculosis, typhoid, Mycoplasma infection, and malaria, as well as some drug reactions. Mild thrombocytopenia to 50,000–200,000 platelets/μL occurs in more than 50% of patients, but only rarely is associated with purpura. Mild elevation of hepatic transaminases occurs in approximately 50% of uncomplicated cases, but is usually asymptomatic without jaundice.

### Heterophile Antibody Test

Heterophile antibodies agglutinate cells from species different from those in the source serum. The transient heterophile antibodies seen in infectious mononucleosis, also known as Paul-Bunnell antibodies, are IgM antibodies detected by the Paul-Bunnell-Davidsohn test for sheep red cell agglutination. The heterophile antibodies of infectious mononucleosis agglutinate sheep or, for greater sensitivity, horse red cells but not guinea pig kidney cells. This adsorption property differentiates this response from the heterophile response found in patients with serum sickness, rheumatic diseases, and some normal individuals. Titers of >1:28 or >1:40, depending on the dilution system used, after adsorption with guinea pig cells are considered positive.

Heterophile antibody tests are positive in 75% of cases in the 1st wk and 90–95% of cases in the 2nd wk. Results of the sheep red cell agglutination test are often positive for several months after infectious mononucleosis; those of the horse red cell agglutination test may be positive for as long as 2 yr. The most widely used method is the qualitative rapid slide test using horse erythrocytes. It detects heterophile antibody in 90% of cases of EBV-associated infectious mononucleosis in adolescents and adults but in only up to 50% of cases in children younger than 4 yr of age because they typically develop a lower titer. From 5–10% of cases of infectious mononucleosis syndromes are not caused by EBV and are not uniformly associated with a heterophile antibody response. The false-positive rate is <10%, usually resulting from erroneous interpretation. If the heterophile test result is negative and an EBV infection is suspected, EBV-specific antibody testing is indicated. Nonetheless, a positive heterophile test, together with classic clinical manifestations of mononucleosis, helps confirm the diagnosis in adolescents and adults. Primary HIV infection may also be associated with a positive heterophile test and a mononucleosis-like clinical picture.

### Specific Epstein-Barr Virus Antibodies

EBV-specific antibody testing is useful to confirm acute EBV infection, especially in heterophile-negative cases, or to confirm past infection and determine susceptibility to future infection. Several distinct EBV antigen systems have been characterized for diagnostic purposes (Fig. 254-2 and see Table 254-1). The EBNA, EA, and VCA antigen systems are most useful for diagnostic purposes. The acute phase of infectious mononucleosis is characterized by rapid IgM and IgG antibody responses to VCA in all cases and an IgG response to EA in most cases. The IgM response to VCA is transient but can be detected for at least 4 wk and occasionally up to 3 mo. The laboratory must take steps to remove rheumatoid factor, which may cause a false-positive IgM VCA result. The IgG response to VCA usually peaks late in the acute phase, declines slightly over the next several weeks to months, and then persists at a relatively stable level for life.

Anti-EA antibodies are usually detectable for several months but may persist or be detected intermittently at low levels for many years. Antibodies to the diffuse-staining component of EA, EA-D, are found transiently in 80% of patients during the acute phase of infectious mononucleosis and reach high titers in patients with nasopharyngeal carcinoma. Antibodies to the cytoplasmic–restricted component of EA, EA-R, emerge transiently in the convalescence from infectious mononucleosis and often attain high titers in patients with EBV-associated Burkitt lymphoma, which in the terminal stage of the disease may be exceeded by antibodies to EA-D. High levels of antibodies to EA-D or EA-R may be found also in immunocompromised patients with persistent EBV infections and active EBV replication. Anti-EBNA antibodies are the last to develop in infectious mononucleosis and gradually

![Figure 254-2 Schematic of the development of antibodies to various Epstein-Barr virus antigens in patients with infectious mononucleosis. Antibody titers are calculated as geometric mean values expressed as reciprocals of the serum dilution. The immunoglobulin M (IgM) response to viral capsid antigen (VCA) is divided because of the significant differences noted according to age of the patient. IgG, immunoglobulin G. (Reprinted with permission from Jenson HB: Epstein-Barr virus. In Detrick B, Hamilton RG, Folds JD, editors: Manual of molecular and clinical laboratory immunology, ed 7. Washington, DC, 2006, American Society for Microbiology.)](image-url)
appear 3–4 mo after the onset of illness and remain at low levels for life. Absence of anti-EBNA when other antibodies are present implies recent infection, whereas the presence of anti-EBNA implies infection occurring more than 3–4 mo previously. The wide range of individual antibody responses and the various laboratory methods used can occasionally make interpretation of an antibody profile difficult. The detection of IgM antibody to VCA is the most valuable and specific serologic test for the diagnosis of acute EBV infection and is generally sufficient to confirm the diagnosis.

**TREATMENT**

There is no specific treatment for infectious mononucleosis. The mainstays of management are rest, encouraging adequate fluid and nutrition intake, and symptomatic treatment with acetaminophen or nonsteroidal antiinflammatory agents to manage fever, throat discomfort, and malaise. Bed rest is necessary only when the patient has debilitating fatigue. As soon as there is definite symptomatic improvement, the patient should be allowed to begin resumption of normal activities. Because blunt abdominal trauma may predispose patients to splenic rupture, it is customary and prudent to advise against participation in contact sports and strenuous athletic activities during the 1st 2-3 wk of illness or while splenomegaly is present.

Short courses of corticosteroids (<2 wk) may be helpful for selected complications of infectious mononucleosis, but this use has not been evaluated critically. Some appropriate indications include incipient airway obstruction, thrombocytopenia with hemorrhaging, autoimmune hemolytic anemia, seizures, and meningitis. A recommended regimen is prednisone 1 mg/kg/day (maximum: 60 mg/day) or equivalent for 7 days and tapered over another 7 days. There are no controlled data showing efficacy of corticosteroids in any of these conditions. In view of the potential and unknown hazards of immunosuppression for a virus infection with oncogenic complications, corticosteroids should not be used in uncomplicated cases of infectious mononucleosis.

Antiviral therapy is not recommended. Therapy with high doses of acyclovir, with or without corticosteroids, decreases viral replication and oropharyngeal shedding during the period of administration but does not reduce the severity or duration of symptoms or alter the eventual outcome.

**COMPLICATIONS**

Very few patients with infectious mononucleosis experience complications. The most feared complication is subcapsular splenic hemorrhage or splenic rupture, which occurs most frequently during the 2nd wk of the disease at a rate of <0.5% of cases in adults; the rate in children is unknown but is probably much lower. Rupture is commonly related to trauma, which is often mild, and is rarely fatal. Swelling of the tonsils and oropharyngeal lymphoid tissue may be substantial and may cause airway obstruction that manifests as drooling, stridor, and interference with breathing. Airway compromise with progressive symptoms occurs in <5% of cases and is a common indication for hospitalization with infectious mononucleosis. It may be managed by elevating the head of the bed, intravenous hydration, humidified air, and systemic corticosteroids. Respiratory distress with incipient or actual airway occlusion should be managed by tonsilloadenoidectomy and endotracheal intubation for 12–24 hr in an intensive care setting.

Many uncommon and unusual neurologic conditions are reported to be associated with EBV infectious mononucleosis. Headache is present in about half of cases, with severe neurologic manifestations, such as seizures and ataxia, in 1–5% of cases. Perceptual distortions of sizes, shapes, and spatial relationships, known as the Alice-in-Wonderland syndrome (metamorphosis), may be a presenting symptom. There may be meningitis with nuchal rigidity and mononuclear cells in the cerebrospinal fluid, facial nerve palsy, transverse myelitis, andencephalitis. Most patients with encephalitis from EBV, however, do not demonstrate the common symptoms of infectious mononucleosis.

Guillain–Barre syndrome or Reye syndrome may follow acute illness. Hemolytic anemia, often with a positive Coombs test result and with cold agglutinins specific for red cell antigen i, occurs in 3% of cases. The onset is typically in the 1st 2 wk of illness and lasts for <1 mo. Aplastic anemia is a rare complication that usually presents 3–4 wk after the onset of illness, usually with recovery in 4–8 days, but some cases do require bone marrow transplantation. Mild thrombocytopenia and neutropenia are common, but severe thrombocytopenia (<20,000 platelets/µL) or severe neutropenia (<1,000 neutrophils/µL) is rare. Myocarditis or interstitial pneumonia may occur, both resolving in 3–4 wk. Other rare complications include pancreatitis, parotitis, and orchitis.

**PROGNOSIS**

The prognosis for complete recovery is excellent. The major symptoms typically last 2–4 wk followed by gradual recovery within 2 mo of onset of symptoms. Individuals often harbor multiple strains of EBV and second infections with a different type of EBV (type 1 or type 2) have been demonstrated in immunocompromised persons, but symptoms or second clinical episodes of infectious mononucleosis have not been documented. Cervical lymphadenopathy and fatigue may resolve more slowly. Prolonged and debilitating fatigue, malaise, and some disability that may wax and wane for several weeks to 6 mo are common complaints even in otherwise unremarkable cases. Occasional persistence of fatigue for a few years after infectious mononucleosis is well recognized. There is no convincing evidence linking EBV infection or EBV reactivation to chronic fatigue syndrome (see Chapter 121).

**PREVENTION**

It is impractical to try to prevent EBV infection because the virus is ubiquitous and the majority of the population is EBV-positive. A recombinant EBV subunit glycoprotein 350 candidate vaccine in a 3 dose regimen shows promise to prevent infectious mononucleosis and potentially EBV-associated malignancies as well.

*Bibliography is available at Expert Consult.*


Human cytomegalovirus (CMV) is ubiquitous in the population, and once infected, individuals remain persistently infected for life with intermittent excretion of infectious virus. Although CMV rarely causes symptoms in normal individuals, it is an important cause of morbidity, and in some cases death, in immunocompromised hosts. CMV remains a well-recognized cause of disease in the newborn infant following intrauterine infection (congenital CMV) and the allograft recipients undergoing posttransplantation immunosuppression. CMV has emerged as the most common opportunistic infection in HIV/AIDS patients prior to the advent of highly active retroviral therapy. Case reports also indicate that invasive CMV infections can be observed in patients treated with immunosuppressive biologics such as anti–tumor necrosis factor antibodies. In each of these clinical situations, the association of disease with CMV infection has been linked to high levels of virus replication and end-organ disease, usually following virus dissemination. In contrast, there is likely another group of disease states associated with chronic effects of persistent CMV infection that reflects the robust inflammatory response induced by this virus. Such associations have included coronary artery disease, transplant vasculopathy and cardiac allograft loss, tubular sclerosis and renal allograft loss, exacerbations of inflammatory bowel disease, and possibly some cancers such as glioblastoma.

THE VIRUS AND ITS INTERACTION WITH THE HOST
CMV is the largest of the human herpesvirus with an estimated size of 190 nm. The 230-kb double-stranded DNA genome is approximately
50% larger than the herpes simplex virus genome and encodes more than 100 unique virion proteins and an unknown number of nonstructural proteins. Viral DNA replication takes place in the nucleus of the infected cell followed by virus assembly in both the nucleus and cytoplasm. The structure of the virus is typical of herpesviruses and includes a complex envelope composed of host cell–derived membrane studded with virion glycoproteins, an amorphous area between the envelope and the capsid called the tegument layer, and an icosahedral capsid that contains the virion DNA. The tegument layer is highly immunogenic and induces strong adaptive immune responses, including CMV–specific CD8+ cytotoxic T lymphocytes that are thought to play a pivotal role in controlling CMV replication in the infected host. Likewise, the protein components of the viral envelope are also immunogenic and believed to induce protective antibody responses that can be most closely correlated with virus neutralization. In vivo, CMV appears to replicate in nearly all tissue and cell types, whereas in vitro productive virus replication (production of infectious progeny) occurs in primary cells derived from epithelial tissue and the dermis. Literature from nearly 3 decades ago suggested that each strain of CMV isolated from epidemiologically unrelated individuals was genetically unique, a finding suggesting that an infinite number of distinct viruses existed in the human population. New evidence suggests that CMV exists as genetically diverse swarms within an individual because CMV DNA synthesis is fraught with error rates that are much higher than has been thought; alternately an individual may acquire a library of CMV variants during each exposure and infection. An important finding supportive of this latter possibility is that reinfection of previously infected individuals with new strains of CMV is commonplace. These observations have led many to argue that CMV must express an armamentarium of immune evasion functions that allow it to remain hidden from protective host immunity. This relationship between host and virus is best illustrated by the finding that a persistently infected individual over years can maintain a stable virus load, unwavering antiviral antibody responses, and, in some cases, up to 15% of a total peripheral blood CD8+ cytotoxic T-lymphocyte activity dedicated to recognition of CMV-infected cells.

**Epidemiology**

CMV infections are acquired through several settings: (1) community exposure, (2) nosocomial transmission, and (3) intrauterine infection. Community acquisition occurs throughout life and is linked by exposure to CMV present in saliva and urine. Peaks in exposure occur during childhood and in adolescents and young adults, presumably in the latter cases secondary to sexual activity. Common routes of infection of the young infant include perinatal exposure to infected genital secretions during birth and ingestion of breast milk containing CMV. Breastfeeding is the most common route of CMV infection in early childhood. Ingestion of breast milk from seropositive women results in a rate of infection of approximately 60-70% in infants. Infection is most common during the first 6 mo of breastfeeding, but the risk continues for the duration of breastfeeding. Infants infected through breast milk excrete virus in the saliva and urine for prolonged periods of time measured in months to years and thus serve as a reservoir of virus for spread to other infants, children, and adults. After this period of intense exposure to CMV during the 1st yr of life, infection in the remainder of childhood and early teenage years depends on specific exposures, such as enrollment in group childcare facilities and/or exposure to infected, similarly aged siblings. Up to 50% of young infants and children attending group care facilities can be excreting CMV, a source of virus that can result in infection of uninfected children enrolled in the facility, and in some cases, the workers in the facility. Furthermore, once infected, infants can then readily transmit virus to their parents and siblings. Throughout childhood and early adulthood, CMV is transmitted by exposure to saliva and urine. However, in adolescence and early adulthood there is a spike in infection, possibly associated with sexual exposure. CMV is considered a sexually transmitted infection.

Nosocomial infections with CMV are well described and follow exposure to blood products containing CMV and less commonly through allograft transplantation following transplantation of an organ from a CMV infected donor. Prior to improvements in blood banking that limited the number of leukocytes in red blood transfusions, transmission of CMV by blood transfusion was not uncommon and was closely related to the volume of blood that was transfused. Transfusion-acquired CMV infections often resulted in symptomatic illness, with laboratory findings including hepatitis and thrombocytopenia in children and adults. In newborns lacking antibodies to CMV secondary to being born to women without seroimmunity to CMV or extreme prematurity, severe, sometimes fatal infections have developed. Similarly, immunocompromised patients who received CMV containing blood were also at risk for severe infection. Current methodologies of leukocyte depletion and the use of blood products from CMV seronegative donors have greatly decreased the incidence of transfusion-associated CMV infections. Finally, CMV transmission through infected allografts is well described, and infections arising from CMV transferred in the allograft are a major cause of morbidity in the early and late period after transplantation. Severe infections and graft loss are more often associated with mismatches between the donor and recipient, for instance, if the donor has a history of CMV infection (and is therefore positive for CMV) and the recipient has not been exposed to CMV (and is therefore negative for CMV), there is a D+/R− mismatch. Even with effective antiviral therapy, CMV infection remains linked to long-term graft dysfunction and graft loss, a particularly important problem in cardiac and lung transplant recipients.

Congenital CMV infection (present at birth) occurs following intrauterine transmission of CMV. Rates of congenital infection between 0.5-1.0% have been routinely reported in the United States. Rates as high as 2% in some areas in Asia and Africa have also been described. CMV is thought to be transferred to the developing fetus following hematogenous spread of the virus to the placenta, presumably followed by cell-free transfer of virus to the fetal blood system. The rate of transmission to the fetus is approximately 30% in women undergoing primary infection during pregnancy, whereas in utero infections also occur in previously immune women (nonprimary infection) albeit at a reduced rate on the order of 1-2%. This later rate is an estimate because a precise rate following nonprimary maternal infection has not been established. It is important to note that although the rate of transmission of CMV is more frequent following primary maternal infection, the absolute number of congenitally infected infants born to women with nonprimary infections in most populations outnumber those resulting from primary maternal infection by 3-4-fold. This is particularly true in Africa, South America, and Asia, where maternal seroimmunity to CMV often exceeds 95%. Interestingly, these populations also have the highest rates of congenital CMV infections. The source of nonprimary infection is also somewhat controversial. Older reports suggested it followed reactivation (recurrence) of virus infection in seroimmune women, whereas more recent literature has demonstrated that reinfection by genetically distinct strains of CMV occurs in previously infected women and that these strains can be transmitted to the developing fetus. In some studies, the reinfection rates are approximately 15-20% with annualized rates as high as 25%. Thus, immunity to CMV is far from protective, although it appears to decrease the risk of transmission to the developing fetus.

**Mechanisms of Disease Associated with Cytomegalovirus Infections**

The mechanism(s) of disease associated with CMV infections remain undefined for most clinical syndromes that follow CMV infection. Several reasons have contributed to the overall lack of understanding of the pathogenesis of CMV infections and include (1) the asymptomatic nature of infections in almost all normal individuals, (2) the complexity of the underlying disease processes in immunocompromised hosts that often confounds the assignment of specific manifestations of CMV infection, (3) limitations of observational studies in humans, and (4) the species-specific tropism of human CMV. Although CMV replicates in a limited number of cell types in vitro, CMV inclusions, antigens, and nucleic acids can be demonstrated in almost organ systems and cell types in individuals with severe, disseminated infections. The virus does
not exhibit specific cellular or organ system tropism in vivo. Hematogenous dissemination is usually associated with cell-associated virus, and significant levels of plasma virus are usually detected only in severely immunocompromised hosts. Virus and viral DNA can be recovered from neutrophils, monocytes, and endothelial cells. High levels of virus replication can result in end-organ disease, presumably secondary to direct virus-mediated cellular damage. These manifestations of CMV infections are thought to result from uncontrolled virus replication and dissemination secondary to deficits in innate and adaptive immune responses to CMV. In some cases, clinical disease has been observed in patients without significant levels of virus replication, a finding suggesting indirect mechanisms of disease such as immunopathologic responses to CMV. Such a mechanism was clearly operative in patients with immune recovery vitreitis, a pathologic T-lymphocyte-mediated response to CMV in HIV/AIDS patients with CMV retinitis that closely followed the reconstitution of their virus-specific T-lymphocyte responses following active retroviral therapy. Likewise, the level of virus replication has not been closely correlated with several chronic diseases thought to be linked to CMV, an observation that is consistent with indirect mechanisms of disease such as immunopathologic responses.

From early observations in patients with invasive CMV infections in allograft recipients it was apparent that immunosuppressive therapies that resulted in altered T-lymphocyte function predisposed these patients to severe infections. Definitive evidence consistent with this mechanism was provided by a clinical study that demonstrated that in vitro expanded, CMV-specific cytotoxic T lymphocytes could limit invasive infection in hematopoietic cell transplant recipients. Invasive infections such as retinitis and colitis in HIV/AIDS patients with very low CD4+ T-lymphocyte counts also clearly demonstrated the importance of T-lymphocyte responses and invasive CMV infections. Other studies in solid organ transplant recipients have demonstrated that the passive transfer of immune globulins containing high titers of anti-CMV antibodies could provide some degree of protection from invasive disease, a finding that was consistent with the proposed role of antiviral antibodies in limiting CMV dissemination and disease in animal models of invasive CMV infections. The importance of innate immune responses such as natural killer cells and γδ T lymphocytes in limiting invasive infections has been well documented in representative animal models, but definitive evidence for a key role in resistance to CMV infections in humans is limited. Lastly, effector molecules such as γ interferon appear to play an important role in controlling local CMV infections in animal models, but evidence of a similar role in humans has not been shown experimentally.

The control of acute CMV infection is clearly dependent on an effective adaptive immune response; however, even a vigorous T-lymphocyte response is not sufficient to eliminate CMV from the infected host as CMV persists for the lifetime of the host either as a low-level chronic infection or as a latent infection with limited expression of its genome. The inability of the host to clear CMV remains incompletely understood, but the large array of immune evasion functions encoded by this virus likely contributes to the blunted innate and adaptive immune response. These functions include inhibition of apoptotic functions of infected cells, inhibition of interferon-regulated responses, inhibition of natural killer cell activation, downregulation of class I major histocompatibility complex expression, inhibition of class II major histocompatibility complex function, and mechanisms to limit antibody recognition of envelope proteins such as carbohydrate masking of antibody recognition sites and extensive variation in amino acid sequences in virion envelope proteins. Although each of these functions by itself could be expected to have limited effects on virus clearance by the immune system, when acting in concert they likely provide the virus an advantage that leads to its persistence.

**CLINICAL MANIFESTATIONS**

In the overwhelming majority of normal patients with acute CMV infections there are no specific symptoms or clinical findings. In patients with symptomatic, acute CMV infection, clinical findings are consistent with a mononucleosis-like syndrome, with fatigue and occasionally cervical adenopathy. Up to 20% of heterophile antibody negative cases of mononucleosis could be attributed to CMV. Laboratory findings could include mild elevation of hepatic transaminases and decreased platelet counts.

**Immunocompromised Host**

The clinical presentation of CMV infection in immunocompromised hosts often reflects the magnitude of the immunodeficiency. Profoundly immunocompromised hosts such as hematopoietic cell allograft recipients can present with disseminated infection and clinical manifestations reflecting the involvement of multiple organ systems including liver, lung, gastrointestinal tract, and rarely the central nervous system. Organ-threatening and life-threatening disease is not infrequent. In less-immunocompromised patients such as most solid organ transplant recipients, CMV infection can present with fever, hematologic abnormalities including leukopenia and thrombocytopenia, and mild hepatocellular dysfunction. In contrast to renal and liver solid organ transplant recipients, heart–lung and lung transplant recipients are at high risk for severe manifestations from CMV infection, presumably because the transplanted organ is a site of virus replication and disease. Prior to the use of antivirals for prophylaxis of allograft recipients, clinical disease usually developed between 30 and 60 days posttransplantation. More recently, prolonged antiviral prophylaxis has nearly eliminated CMV disease in most solid-organ transplants but late manifestations of CMV disease can be seen after discontinuation of the antiviral prophylaxis. These late manifestations are most worrisome in hematopoietic cell recipients, as they may signal deficits in graft function leading to invasive CMV infections. Finally, long-term graft function has been reported to be influenced by CMV infection. This has been most well studied in the renal allograft recipients but has been seen perhaps most dramatically in heart transplant recipients, where CMV is believed to play a major role in transplant vascular sclerosis, a vasculopathy of the coronary arteries in the allograft, leading to loss of the transplanted heart.

**Congenital Infection**

Congenital infection with CMV can present with symptomatic infections (Table 255-1) in approximately 10% of infected newborns, whereas 90% of infected infants will have no clinical manifestations of infection in the newborn period. Severe multorgan disease is

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**Table 255-1** Findings in Infants with Symptomatic Congenital Cytomegalovirus Infection Identified Through Newborn Screening Program

<table>
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<tr>
<th>FINDINGS</th>
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<tr>
<td>2 Clinical findings</td>
<td>59</td>
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<td>Elevated alanine aminotransferase (&gt;80 IU/mL)</td>
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<td>Thrombocytopenia (&lt;100,000/mL)</td>
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<td>54</td>
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*Findings in 70 infants with symptomatic congenital CMV infection identified during the newborn screening program for infants with congenital CMV infection performed at the University of Alabama Hospitals over an approximate 20 yr interval.
infrequent and occurs in less than 5% of infants with congenital CMV infections. The clinical findings of infants with symptomatic congenital CMV infections can include hepatosplenomegaly, petechial rashes, jaundice, and in some cases microcephaly. These findings were utilized for natural history studies to classify infants as having symptomatic or asymptomatic infections; however, several authors have included intrauterine growth restriction as a finding of symptomatic congenital CMV infection. Laboratory findings include direct hyperbilirubinemia, elevation of hepatic transaminases, thrombocytopenia, anemia, and abnormal findings on cranial ultrasonography. If cerebrospinal fluid is obtained, there can be evidence of encephalitis with elevation of mononuclear cell number and in some cases, elevation of cerebrospinal fluid protein. A small number of symptomatically infected infants (<10%) will be found to have chorioretinitis. Finally, because hearing loss is the most common long-term sequela associated with congenital CMV infection, the failure of an infant to pass a newborn hearing screening exam should raise the possibility of congenital CMV infection. Hearing loss in the older infant and young child should also alert the clinician to the possibility of congenital CMV infection, as approximately 50% of infants with hearing loss associated with congenital CMV infection will pass an initial hearing screening exam but develop hearing loss in later infancy and early childhood.

An organized plan for follow-up is an important aspect in the clinical management of infants with congenital CMV infection. Because permanent sequelae are limited to disorders of the nervous system, long-term follow-up should include appropriate assessment of development and neuromuscular function in infected infants, with referral to specialized care if necessary. Hearing loss will develop in approximately 11% of infected infants, and in some infants hearing loss will progress during infancy. Thus, audiologic testing and follow-up are mandatory in these patients. Other sequelae such as vision loss are infrequent, but vision testing and comprehensive eye examinations should be included in the care plan.

Perinatal Infection
Perinatal infections can be acquired during birth or following ingestion of CMV-containing breast milk. In almost all cases, perinatal infections are not associated with any clinical manifestations of infection and, perhaps more importantly, have not been associated with any long-term sequelae. In rare cases, such as is seen in breast milk transmission of CMV to extremely premature infants or infants born to nonimmune women, perinatal infection can result in severe, disseminated infections associated with end-organ disease and death. These more severe infections are thought to develop in infants who lack transplacentally acquired antiviral antibodies either secondary to extreme prematurity or being the product of a mother lacking anti-CMV antibodies.

DIAGNOSIS
In the nonimmunocompromised individual, diagnosis of CMV infection requires evidence of a primary infection. Serologic reactivity for CMV is lifelong following primary infection; therefore, the presence of immunoglobulin (Ig) G antibody to CMV does not provide evidence of infection. In addition, IgM reactivity for CMV can be detected for prolonged periods after acute infection and cannot be used to reliably estimate the duration of infection. Furthermore, recovery of virus from body fluids such as saliva or urine does not in itself permit diagnosis of CMV infection, because persistently infected individuals can intermittently shed virus. In the immunocompromised host, CMV can frequently be recovered from patients in the absence of evidence of invasive CMV infection. Thus, assignment of CMV as a cause of disease in this patient population must be made carefully, and other potential causes of symptoms and clinical findings in these patients must also be considered. Serologic assays are of limited value in the transplant recipient secondary to impact of immunosuppression on antibody responses in the allograft recipient. Furthermore, IgM antibodies can be produced following a nonprimary infection in these patients. Sequential viral load measurements by polymerase chain reaction in relevant body fluids such as blood and measurements of CMV DNA in biopsy tissue can be of great value in establishing CMV as a cause of disease in allograft recipients.

Congenital Infections
The diagnosis of congenital CMV infections requires the recovery of replicating virus and/or viral nucleic acids within the 1st 3 wk of life. Sources of virus and viral nucleic acids include urine, saliva, and blood. Methods of detection include routine virus culture combined with immunofluorescence and polymerase chain reaction. Although quantification of virus in various specimens can suggest the likelihood of long-term sequelae such as hearing loss for a population of infected newborns, the predictive value for the individual patient is limited. A considerable amount of effort has been devoted to identifying screening assays that would be suitable for populations of newborn infants. Newborn screening using saliva has proven sensitive and specific and is now performed for newborn screening in some institutions. Early studies suggested that congenitally infected newborn infants could be identified by CMV-specific IgM reactivity and that elevated levels of CMV-specific IgM correlated with severity of disease. Subsequent studies have demonstrated that although of some value, the limited sensitivity of most assays employed to detect newborn IgM also limit their clinical utility.

Noncongenital Infections
In nonimmunocompromised patients, demonstration of CMV-specific IgG seroconversion or the presence of CMV-specific IgM antibodies represents evidence of a newly acquired CMV infection. IgM anti-CMV antibody reactivity can persist for months depending on the sensitivity of the particular assay. The use of the IgG avidity assays in which CMV-specific binding antibodies are eluted with increasing concentrations of chaotropic agents such as urea can be used to estimate the duration of infection. This assay has been used almost exclusively in the management of CMV infections during pregnancy to aid in defining primary maternal infections. Detection of CMV in urine, saliva, and blood and in tissue specimens obtained at biopsy can be most reliably accomplished by polymerase chain reaction–based methods, and because findings can be quantified, treatment responses can be monitored. However, conventional culture of CMV using human dermal fibroblasts often combined with immunofluorescence detection of CMV-encoded immediate early antigens also remains standard in many institutions. Routine histologic stains allow detection of characteristic nuclear (and cytoplasmic) inclusions (owl-eye inclusions) in tissue specimens.

TREATMENT
Treatment of immunocompromised hosts with invasive CMV disease limits both the morbidity and mortality in the patient with disseminated CMV infections with end-organ disease. This has been shown in allograft transplant recipients and patients with HIV/AIDS. Similarly, antiviral prophylaxis can limit the development of clinically important CMV disease in allograft recipients. Several agents are currently licensed for CMV infections, including ganciclovir and foscarnet. In some transplant centers, high-titered CMV immunoglobulins are included as a component of prophylaxis. Treatment with CMV immunoglobulins alters the natural history of CMV infection in renal and liver allograft recipients. Currently, the effectiveness of antiviral agents in prophylaxis has resulted in less-frequent use of these biologics.

Treatment of congenitally (symptomatic and asymptomatic but at risk for hearing loss) infected infants with ganciclovir has been studied in clinical trials; many infected infants have been treated off-label with this agent because of severe CMV infections. The study conducted by the Collaborative Antiviral Study Group sponsored by the National Institutes of Health suggested that 6 wk of ganciclovir treatment could limit hearing loss and possibly improve developmental outcome in symptomatically infected infants. In addition, infants with severe perinatal CMV infection following breast milk ingestion have been successfully treated with ganciclovir. Preliminary evidence suggests
that 6 mo of oral valganciclovir may be more effective and less toxic than intravenous ganciclovir in infants with symptomatic CMV infection.

PREVENTION

Passive Immunoprophylaxis

Passive transfer of anti-CMV antibodies has been utilized to limit disease but not infection in allograft recipients. A similar approach has also been considered for prevention of intrauterine disease. An uncontrolled trial of human immunoglobulin suggested that passive transfer of anti-CMV antibodies to pregnant women undergoing primary CMV infection may limit transmission and disease. Unfortunately, another study that was controlled failed to confirm this first study.

Active Immunoprophylaxis

A number of different vaccine platforms have been explored, including replicating attenuated CMV as vaccines, protein-based vaccines, heterologous virus vectored CMV vaccines, and DNA vaccines. In all cases, some level of immunity was induced in volunteers. Larger-scale trials have been carried out using replication competent, attenuated CMV vaccines and adjuvant recombinant protein vaccines. However, there has been little evidence that current approaches will be adequate to attenuate a replicating CMV and yet retain sufficient immunogenicity to induce protective responses. More progress has been made in use of adjuvant recombinant proteins. An adjuvant recombinant glycoprotein B, a major protein component of the envelope and target of neutralizing antibodies, has been shown to induce virus-neutralizing antibodies and CD4+ T-lymphocyte proliferative responses. Moreover, this vaccine reduced virus acquisition by approximately 50% in a small trial carried out in young women. However, closer examination of this vaccine trial revealed that protection was very short-lived and that the effectiveness of the vaccine, although statistically significant, was not convincingly demonstrated because of the small numbers of subjects in the trial. Yet, this was perhaps the first evidence that active immunization could effect some level of protection. Because of the potentially large population that may be targeted by a successful vaccine, it should be anticipated that more candidate vaccines will be tested in the near future. Finally, a major question that will face all vaccine programs is whether existing immunity in seropositive women can be augmented to a level to prevent damaging infection in their offspring. The maternal population with existing immunity to CMV prior to childbearing age is responsible for the greatest number of congenitally infected infants in almost all regions of the world.

Counseling

Studies of the natural history of CMV repeatedly demonstrate that transmission requires close, often direct, contact with infected material, such as secretions from the oral or genitourinary tract. Although only limited data suggest that it can be transmitted on fomites, infectivity can persist for hours on surfaces such as toys. Limiting exposure to such secretions and attention to hygiene such as handwashing can drastically limit acquisition of CMV. Counseling is very effective in the prevention of CMV infection in women of childbearing age. In fact, counseling programs are more effective in limiting CMV infection during pregnancy than any vaccine that has been tested to date. Sexual transmission is an important route of infection, and CMV is considered to be a sexually transmitted infection. Limiting sexual transmission through education and counseling should be considered in sexually active individuals.

Acquisition of CMV by hospital workers and other healthcare providers was shown to be less than that of age-matched individuals in the general public. Importantly, these studies were carried out prior to universal precautions that are in place in most hospitals today. Thus, patient education with an emphasis on describing the sources of infectious virus in communities and attention to general hygiene could dramatically reduce CMV spread in the community.

Bibliography is available at Expert Consult.
Bibliography


Infectious Diseases

Chapter 256

Roseola (Human Herpesviruses 6 and 7)

Mary T. Caserta

Human herpesvirus 6 (HHV-6A and HHV-6B) and human herpesvirus 7 (HHV-7) cause ubiquitous infection in infancy and early childhood. HHV-6B is responsible for the majority of cases of roseola infantum (exanthema subitum or sixth disease) and is associated with other diseases, including encephalitis, especially in immunocompromised hosts. A small percentage of children with roseola have primary infection with HHV-7.

ETIOLOGY

HHV-6A, HHV-6B, and HHV-7 are the sole members of the Roseolovirus genus in the Betaherpesvirinae subfamily of human herpesviruses. Human cytomegalovirus, the only other β-herpesvirus, shares limited sequence homology with HHV-6 and HHV-7. Morphologically all human herpesviruses are composed of an icosahedral nucleocapsid, protein-dense tegument, and lipid envelope. Within the nucleocapsid, HHV-6 and HHV-7 both contain large, linear, double-stranded DNA genomes that encode more than 80 unique proteins.

Initially, 2 strain groups of HHV-6 were recognized, HHV-6 variant A and HHV-6 variant B. Despite sharing highly conserved genomes with approximately 90% sequence identity, the 2 variants could be distinguished by restriction fragment length polymorphisms, reactivity with monoclonal antibodies, differential cell tropism, and epidemiology. Because of these differences, the 2 were reclassified as separate species in the genus Roseolovirus by the International Committee on the Taxonomy of Viruses in 2012.

Although the frequency of detection of HHV-6A DNA differs among studies, HHV-6B is the overwhelmingly predominant virus found in both normal and immunocompromised hosts by both culture and polymerase chain reaction (PCR). Primary infection with HHV-6A has been detected by PCR in children in Africa. It is not clear whether the differences in the detection of HHV-6A DNA and HHV-6B DNA relate to different tissue tropism, differences in mode of age of acquisition, differences in the ability to cause human disease, or geographic location of the population studied.

EPIDEMIOLOGY

Primary infection with HHV-6B is acquired rapidly by essentially all children following the loss of maternal antibodies in the 1st few mo of infancy, 95% of children being infected with HHV-6 by 2 yr of age. The peak age of primary HHV-6B infection is 6–9 mo of life, with infections occurring sporadically and without seasonal predilection or contact with other ill individuals. Infection with HHV-7 is also widespread but occurs later in childhood and at a slower rate; only 50% of children have evidence of prior infection with HHV-7 by 3 yr of age. Seroprevalence reaches 75% at 3–6 yr of age. In a small study of children with primary HHV-7 infection, the mean age of the patients was 26 mo, significantly older than that of children with primary HHV-6 infection.

Preliminary data suggest that the majority of children acquire primary infection with HHV-6 from the saliva or respiratory droplets of asymptomatic adults or older children. However, congenital infection with HHV-6 occurs in 1% of newborns. Two mechanisms of vertical transmission of HHV-6 have been identified, transplacental infection and chromosomal integration. HHV-6 is unique among the human herpesviruses in that it is integrated at the telomere end of human chromosomes at a frequency of 0.2–2.2% of the population and is passed from parent to child via the germline. Chromosomal
integration has been identified as the major mechanism by which HHV-6 is vertically transmitted, accounting for 86% of congenital infections, with one third resulting from HHV-6A, a percentage much higher than in primary infection in the United States. The clinical consequences of chromosomal integration or transplacental infection with HHV-6 have yet to be determined. In 1 series of infants identified with HHV-6 congenital infection, no evidence of disease was present in the early neonatal period. Congenital infection with HHV-7 has not been demonstrated, and primary infection is presumed to be spread by the saliva of asymptomatic individuals. DNA of both HHV-6 and HHV-7 has been identified in the cervical secretions of pregnant women, suggesting an additional role for sexual or perinatal transmission of these viruses. Breast milk does not appear to play a role in transmission of either HHV-6 or HHV-7.

**PATHOLOGY/PATHOGENESIS**

Primary HHV-6B infection causes a viremia that can be demonstrated by coculture of the patient’s peripheral blood mononuclear cells with mitogen-stimulated cord blood mononuclear cells. HHV-6 has a recognizable cytopathic effect, consisting of the appearance of large refractile mononucleated or multinucleated cells with intracytoplasmic and/or intranuclear inclusions. Infected cells exhibit a slightly prolonged life span in culture; however, lytic infection predominates. HHV-6 infection also induces apoptosis of T cells and may lead to cell expiration via loss of mitochondrial membrane potential as well as alteration of interferon and retinoic acid–induced cell death signals. In vitro, HHV-6 can infect a broad range of cell types, including primary T cells, monocytes, natural killer cells, dendritic cells, and astrocytes. HHV-6 has also been documented to infect B-cell, megakaryocytic, endothelial, and epithelial cell lines. Human astrocytes, oligodendrocytes, and microglia have been infected with HHV-6 ex vivo. The broad tropism of HHV-6 is consistent with the recognition that CD46, a complement regulatory protein present on the surface of all nucleated cells, is a cellular receptor for HHV-6. Recent data also suggest that CD134 is a selective receptor for HHV-6B and may explain some of the differences in tissue tropism noted between HHV-6A and HHV-6B. The CD4 molecule has been identified as a receptor for HHV-7. HHV-7 has been demonstrated to reactivate HHV-6 from latency in vitro. Whether this phenomenon occurs in vivo is not clear.

Primary infection with HHV-6 and HHV-7 is followed by lifelong latency or persistence of virus at multiple sites. HHV-6 exists in a true state of viral latency in monocytes and macrophages. The detection of replicating HHV-6 in cultures of primary CD34⁺ hematopoietic stem cells has also been described, suggesting that cellular differentiation is a trigger of viral reactivation. This observation is clinically significant because HHV-6 may cause either primary or reactivated infection during hematopoietic stem cell transplantation (HSCT). Additionally, HHV-6 and HHV-7 infection may be persistent in salivary glands, and DNA of both HHV-6 and HHV-7 can be routinely detected in the saliva of both adults and children. HHV-6 DNA has been identified in the cerebrospinal fluid (CSF) of children, both during and subsequent to primary infection, as well as in brain tissue from immunocompetent adults at autopsy, implicating the central nervous system as an additional important site of either viral latency or persistence. HHV-7 DNA has also been found in adult brain tissue but at a significantly lower frequency.

**CLINICAL MANIFESTATIONS**

Roseola infantum (exanthem subitum, or sixth disease) is an acute, self-limited disease of infancy and early childhood. It is characterized by the abrupt onset of high fever, which may be accompanied by fussiness. The fever usually resolves acutely after 72 hr (“crisis”) but may gradually fade over a day (“lysis”) coincident with the appearance of a faint pink or rose-colored, nonpruritic, 2-3 mm morbilliform rash on the trunk (Fig. 256-1). The rash usually lasts 1-3 days but is often described as evanescent and may be visible only for hours, spreading...
from the trunk to the face and extremities. Because the rash is variable in appearance, location, and duration, it is not distinctive. Associated signs are few but can include mild injection of the pharynx, palpebral conjunctivae, or tympanic membranes and enlarged subcubital nodes. In Asian countries, ulcers at the uvulopalatoglossal junction (Nagayama spots) are commonly reported in infants with roseola.

High fever (mean: 39.7°C [103.5°F]) is the most consistent finding associated with primary HHV-6B infection. Rash detected either during the illness or following defervescence has been reported in approximately 20% of infected children in the United States. Additional symptoms and signs include irritability, inflamed tympanic membranes, rhinorrhea and congestion, gastrointestinal complaints, and encephalopathy. Symptoms of lower respiratory tract involvement such as cough are identified significantly less frequently in children with primary HHV-6B infection than in children with other febrile illnesses. The mean duration of illness caused by primary HHV-6B infection is 6 days, with 15% of children having fever for 6 or more days. Primary infection with HHV-6B accounts for a significant burden of illness on the healthcare system; 1 study found that 24% of visits to emergency departments by infants between 6 and 9 mo of age were because of primary HHV-6B infection. A population-based study of primary HHV-6B infection confirmed that 93% of infants had symptoms and were more likely to visit a physician than noninfected infants. Fever was less likely to be present with HHV-6B infection in children younger than 6 mo of age but was significantly more common in older infants and children.

Much less is known about the clinical manifestations of HHV-7 infection. Primary infection with HHV-7 has been identified in a small number of children with roseola in whom the illness is indistinguishable from that caused by HHV-6B. Secondary cases of roseola caused by infection with HHV-7 have also been reported. Additionally, primary infection with HHV-7 may be asymptomatic or may cause a nonspecific febrile illness lasting approximately 3 days.

LABORATORY FINDINGS

The most characteristic laboratory findings noted in children with primary HHV-6B infection are lower mean numbers of total white blood cells (8,900/µL), lymphocytes (3,400/µL), and neutrophils (4,500/µL), than in febrile children without primary HHV-6B infection. Similar hematologic findings have been reported during primary infection with HHV-7. Thrombocytopenia, elevated serum transaminase values, and atypical lymphocytes have also been noted sporadically in children with primary HHV-6B infection.

Results of CSF analyses reported in patients with encephalitis thought to be caused by HHV-6 have been normal or demonstrated only minimal CSF pleocytosis with mild elevations of protein, especially early in the course of the disease, which may progress with time. Areas of hyperintense signal on T2-weighted and fluid attenuation inversion recovery images of the hippocampus, uncus, and amygdala have been found on MRI, as well as increased metabolism within the hippocampus on positron emission tomography scanning.

DIAGNOSIS

Although roseola is generally a benign self-limited disease, its diagnosis can exclude other, more serious disorders that cause fever and rash. A history of 3 days of high fever in an otherwise nontoxic 10 mo old infant with a blanching maculopapular rash on the trunk suggests a diagnosis of roseola. Likewise, a specific diagnosis of HHV-6 is not usually necessary except in situations in which the manifestations of the infection are severe or unusual and might benefit from antiviral therapy.

The diagnosis of primary infection with either HHV-6 or HHV-7 is confirmed by demonstrating the presence of actively replicating virus in the patient’s blood sample coupled with seroconversion. Viral culture is the gold standard method to document active viral replication. Unfortunately, culture is expensive, time-consuming, and available only in research laboratories. Two other methods used to identify active HHV-6 replication are the detection of viral DNA by PCR on cell cultures or reverse transcriptase PCR on peripheral blood mononuclear cell samples designed to detect viral transcription and protein production. Quantitative PCR for HHV-6 genome copy numbers on various specimens is also frequently reported and is commercially available. However, the role of this methodology is not clear, as a specific value of DNA that can discriminate between patients with viremia and those who are culture negative has not been determined. Complicating the use of molecular assays for the detection of active replication of HHV-6 is the recognition that individuals with chromosomally integrated HHV-6 have persistent HHV-6 DNA in plasma, peripheral blood mononuclear cells, and CSF in the absence of disease and replicating virus.

Serologic methods including indirect immunofluorescence assays, enzyme-linked immunosorbent assays, neutralization assays, and immunoblot have been described for the measurement of concentrations of antibodies to HHV-6 and HHV-7 in serum or plasma and are commercially available. Although immunoglobulin G antibody produced early in infection with HHV-6, assays designed to measure this response have not proved useful in the diagnosis of primary or reactivated infection. The absence of immunoglobulin M antibody in an infant older than 6 mo of age combined with the presence of replicating virus is strong evidence of primary infection with either HHV-6 or HHV-7. Alternatively, the demonstration of seroconversion between acute and convalescent samples also confirms primary infection but is not clinically useful in the acute care setting. Unfortunately, serologic assays have not been found reliable in the detection of HHV-6 reactivation and cannot be used to differentiate between infection with HHV-6A and HHV-6B. Additionally, limited antibody cross-reactivity has been demonstrated between HHV-6 and HHV-7, complicating the interpretation of serologic assays, especially if low titers are reported.

Differential Diagnosis

Primary infection with either HHV-6B or HHV-7 usually causes an undifferentiated febrile illness that may be very difficult to distinguish from other common viral infections of childhood. This difficulty also applies to the early stages of roseola, before the development of rash. Once the rash is present, roseola may be confused with other exanthematous diseases of childhood, especially measles and rubella. Children with rubella often have a prodrome characterized by mild illness with low-grade fever, sore throat, arthralgia, and gastrointestinal complaints, unlike those with roseola. On physical examination, subcutaneous and posterior auricular lymph nodes are prominent up to 1 wk before the rash of rubella is evident and persist during the exanthematous phase. Additionally, the rash of rubella usually begins on the face and spreads to the chest, like that in measles. The associated symptoms of measles virus infection include cough, coryza, and conjunctivitis, with high fever coincident with the development of rash, unlike in roseola. Roseola may also be confused with scarlet fever, though the latter is rare in children younger than 2 yr of age and causes a characteristic sandpaper-like rash concurrent with fever.

Roseola may be confused with illness caused by enterovirus infections, especially in the summer and fall months. Drug hypersensitivity reactions may also be difficult to distinguish from roseola. Antibiotics are frequently prescribed for children with fever from roseola before the appearance of rash. A child who then demonstrates rash after the resolution of fever may erroneously be labeled as being drug allergic.

COMPLICATIONS

Convulsions are the most common complication of roseola and are recognized in up to one third of patients. Seizures are also the most common complication of children with primary HHV-6B infection, occurring in approximately 15%, with a peak age of 12-15 mo. Children with primary HHV-6B infection are also reported to have a higher frequency of partial seizures, prolonged seizures, postictal paralysis, and repeated seizures than are children with febrile seizures
not associated with HHV-6. In a study limited to children with primary HHV-6B infection and seizures, 30% of patients had prolonged seizures, 29% had focal seizures, and 38% had repeated seizures. A prospective study of children 2–35 mo of age with suspected encephalitis or severe febrile illness with convulsions found that 17% had primary infection with either HHV-6 or HHV-7, and status epilepticus was the most common presentation. Among children with febrile status epilepticus (FSE), primary or reactivated infection with HHV-6B or HHV-7 has been identified in approximately one third.

An association between recurrent seizures and reactivated or persistent infection of the central nervous system by HHV-6 has also been suggested. Studies evaluating brain tissue specimens implicate HHV-6 in as many as 35% of patients with temporal lobe epilepsy, high viral loads being found in the hippocampus or lateral temporal lobe regions. HHV-6 protein production has also been identified in a small number of resected tissue specimens. Primary astrocytes obtained from these samples had undetectable levels of a glutamate transporter, suggesting the loss of ability to control glutamate levels as a possible mechanism for the development of recurrent seizures. Contrary to these findings, limited clinical data suggest that there may be a decreased risk of recurrent seizures after primary infection with HHV-6 and febrile seizures than of febrile seizures from other causes. Additionally, children with FSE associated with HHV-6B and HHV-7 had similar seizure characteristics and a similar proportion of electroencephalography and MRI hippocampal abnormalities as children with FSE not associated with HHV-6B or HHV-7, suggesting a shared pathogenesis to other etiologies of FSE. Further study is needed to determine if there is a link between HHV-6 and HHV-7 infection and epilepsy.

Case reports and small patient series have described additional complications in children with primary HHV-6B infection, including encephalitis, acute disseminated demyelination, autoimmune encephalitis, acute cerebellitis, hepatitis, and myocarditis. Late-developing long-term sequelae, including developmental disabilities and autistic-like features, are reported rarely in children who have central nervous system symptoms during primary HHV-6B infection.

Reactivation of HHV-6 has been reported in several different populations with and without disease with the use of various methods of detection. The best documentation of HHV-6 reactivation has been in immunocompromised hosts, especially those patients who have undergone HSCT. Such reactivation occurs in approximately 50% of patients, typically at 2–4 wk after transplantation. Many of the clinical complications seen following HSCT have been associated with HHV-6B reactivation, including fever, rash, delayed engraftment of platelets or monocytes, and graft–versus-host disease with variable degrees of support in the literature for each.

HHV-6B reactivation has also been reported as a cause of encephalitis in both normal and immunocompromised hosts. A distinct syndrome of posttransplant acute limbic encephalitis (PALE) has been described primarily in patients following HSCT, especially cord blood stem cell transplantation; it is characterized by short-term memory dysfunction, confusion, and insomnia with seizures noted either clinically or on prolonged electroencephalography monitoring. HHV-6B DNA has been identified in the CSF in the majority of these patients with additional evidence of reactivation by detection of HHV-6B DNA in plasma. HHV-6 proteins were identified in the astrocytes of the hippocampus in 1 postmortem specimen, consistent with active HHV-6B infection at the time of death. The development of PALE is associated with increased mortality and long-term neurocognitive sequelae.

**TREATMENT**

Supportive care is usually all that is needed for infants with roseola. Parents should be advised to maintain hydration and may use antipyretics if the child is especially uncomfortable with the fever. Specific antiviral therapy is not recommended for routine cases of primary HHV-6B or HHV-7 infection. Unusual or severe manifestations of primary or presumed reactivated HHV-6B infection such as encephalitis/PALE, especially in immunocompromised patients, may benefit from treatment. Ganciclovir, foscarnet, and cidofovir all demonstrate inhibitory activity against HHV-6 in vitro similar to their activity against cytomegalovirus. Case reports suggest that all 3 drugs, alone or in combination, can decrease HHV-6 viral replication, as evidenced by decreased viral loads in plasma and CSF. However, clinical data regarding efficacy are sparse and contradictory, with no randomized trials to guide use. Additionally, in vitro resistance of HHV-6 to all 3 drugs has been described. Despite these drawbacks, treatment with ganciclovir or foscarnet as first-line agents has been recommended for a minimum of 3 wk in patients with PALE. Foscarnet appears to be most likely to have activity against HHV-7 on the basis of in vitro testing, but no clinical data are available.

**PROGNOSIS**

Roseola is generally a self-limited illness associated with complete recovery. The majority of children with primary infections with HHV-6B and HHV-7 also recover uneventfully without sequelae. Although seizures are a common complication of primary infection with HHV-6B and HHV-7, the risk of recurrent seizures does not appear to be higher than that associated with other causes of simple febrile seizures.

**PREVENTION**

Primary infections with HHV-6 and HHV-7 are widespread throughout the human population with no current means of interrupting transmission.

*Bibliography is available at Expert Consult.*
Bibliography
Human herpesvirus 8 (HHV-8) was first identified in tissue specimens from patients with Kaposi sarcoma (KS). Because of this association, it is also known as Kaposi sarcoma–associated herpesvirus. HHV-8 has since been recognized as the etiologic agent of 2 additional lymphoproliferative disorders: primary effusion–based lymphoma (PEL) and multicentric Castleman disease.

ETIOLOGY
HHV-8 is a $\gamma_2$-human herpesvirus similar to Epstein-Barr virus. The virus contains a large DNA genome encoding 85-95 unique proteins. Infection is followed by both lytic and latent viral states with different degrees of viral replication associated with distinct disease manifestations.

EPIDEMIOLOGY
The prevalence of infection with HHV-8 varies both geographically and by population and roughly matches the epidemiology of KS. HHV-8 infection is endemic in Africa and parts of South America, with infection rates of up to 30-60% by adolescence. Seroprevalence >20% has also been found in regions bordering the Mediterranean. In contrast, infection rates <5% are noted in North America, central Europe, and Asia. However, within geographic regions, the prevalence
of infection varies with risk behaviors, rates of 30–75% being found among men who have sex with men in North America and Europe. HHV-8 DNA can be detected in saliva, blood, and tissues. Based upon large-scale epidemiologic studies, the current consensus is that saliva is the major mode of transmission. Other less-common routes of HHV-8 transmission include blood transfusion, bone marrow transplantation, and solid organ transplantation. Vertical transmission may occur in regions where HHV-8 is highly endemic, but the risk appears low.

PATHOLOGY AND PATHOGENESIS

HHV-8 contains multiple genes that impact cell-cycle regulation and the host immune response. Viral proteins interfere with the function of the tumor suppressor molecules p53 and retinoblastoma protein, induce the expression of proangiogenesis factors vascular endothelial growth factor A and vascular endothelial growth factor receptor-2, and lead to upregulation of the human mammalian target of rapamycin pathway, which is instrumental in the control of cell growth and metabolism. HHV-8 also encodes a homolog of human interleukin-6, which can bind and activate cytokine receptors and serve as a host cell autocrine growth factor. Additionally, viral proteins are associated with the constitutive expression of the transcription factor nuclear factor-κB. All of these proteins may be potential targets for therapeutic intervention.

CLINICAL MANIFESTATIONS

Although subclinical infection appears to be common, symptomatic primary HHV-8 infection has been described in immunocompetent children. Patients commonly had fever and a maculopapular rash or a mononucleosis-like syndrome, with full recovery the rule. In immunocompromised patients, primary infection has been associated with fever, rash, splenomegaly, pancytopenia, and lymphoid hyperplasia, and may be quite severe. Additionally, preliminary data suggest that transfusion-associated primary infection with HHV-8 is associated with an increased risk of mortality.

KS has several different clinical forms; each includes multifocal, angiogenic lesions arising from vascular endothelial cells infected with HHV-8. Classic KS is an indolent disorder seen in elderly men with limited involvement of the skin of the lower extremities. Endemic KS is more aggressive, occurring in children and young people, primarily in Africa, and can include visceral involvement as well as widespread cutaneous lesions (patches, plaques, or nodules). Posttransplantation KS and AIDS-related KS are the most severe forms, with disseminated lesions, often in the gastrointestinal tract and lungs, in addition to the skin.

Primary effusion–based lymphoma is a rare disease caused by HHV-8 that is seen most commonly in HIV-infected individuals. It consists of lymphomatous invasion of the serosal surfaces of the pleura, pericardium, and peritoneum. Similarly, multicentric Castleman disease is an unusual lymphoproliferative disorder characterized by anemia, thrombocytopenia, generalized lymphadenopathy, and constitutional symptoms and frequently associated with HHV-8 infection and a high degree of viral replication.

DIAGNOSIS

Serologic assays, including immunofluorescence and enzyme-linked immunosorbent assays, are the primary methods of diagnosing infection with HHV-8. However, testing has limited sensitivity, specificity, and reproducibility and is primarily a research tool with no universally recognized standard assays. Additionally, the loss of antibodies over time, referred to as seroreversion, has been described, further complicating serodiagnosis. Immunohistochemistry and molecular methods are available for the detection of the HHV-8 genome in tissue samples and are utilized in the diagnosis of KS, PEL, and multicentric Castleman disease.

TREATMENT

Treatment for KS, PEL, and multicentric Castleman disease is multifaceted and includes attempts to control malignant proliferations with traditional chemotherapeutic regimens and biologic agents as well as agents aimed at specific cellular pathways targeted by HHV-8 proteins. Highly active antiretroviral treatment (HAART) is a mainstay of both prevention and therapy for HHV-8 related disease in HIV-infected patients. In HIV associated KS, treatment with HAART alone is often used for the control of mild disease, while HAART plus chemotherapy is utilized for more severe disease. In transplantation-associated KS, the first line of treatment includes decreasing immunosuppression, often in association with a switch from calcineurin inhibitors to sirolimus (rapamycin) to block the mammalian target of rapamycin pathway. Severe disease frequently requires the use of traditional chemotherapy as well. The role of specific antiviral antiviral treatment is unclear. Oral valganciclovir decreases both the quantity and frequency of detection of HHV-8 in saliva, and ganciclovir treatment has been associated with decreased rates of development of KS in HIV-infected individuals. However, results of using antivirals in the treatment of established disease have been generally disappointing. The prognosis for PEL tends to be poor despite the use of traditional chemotherapy, while rituximab (anti-CD20) shows promise in the treatment of multicentric Castleman disease, both alone and in combination with chemotherapy. Rituximab treatment may worsen concurrent KS.

Bibliography is available at Expert Consult.
Bibliography
Influenza viral infections cause a broad array of respiratory illnesses that are responsible for significant morbidity and mortality in children. Influenza A viruses also have the potential to cause periodic global pandemics with even higher penetrance of illness than seasonal epidemics.

**ETIOLOGY**

Influenza viruses are large, single-stranded RNA viruses belonging to the family Orthomyxoviridae, which includes 3 genera (or types): A, B, and C. Influenza A and B viruses are the primary human pathogens, causing seasonal epidemics, while influenza virus type C is a sporadic cause of predominantly mild upper respiratory tract illness. Influenza A viruses are further divided into subtypes based on 2 surface proteins that project as spikes from the lipid envelope, the hemagglutinin (HA) and neuraminidase (NA) proteins (Fig. 258-1). Strain variants are identified by antigenic differences in their HA and NA and are designated by the geographic area from which they were originally isolated, isolate number, and year of isolation—for example, influenza A/Victoria/361/2011(H3N2). The HA and NA antigens from influenza B and C viruses do not receive subtype designations, as there is less variation among influenza B and C antigens.

**EPIDEMIOLOGY**

Influenza has generally been thought to be transmitted primarily via respiratory droplets, but transmission via contact with secretions and small-particle aerosols may also occur. The incubation period is short, ranging from 12-72 hr. Seasonal influenza incidence peaks during colder months in temperate climates and circulates throughout
Influenza 1599

WB Saunders, principles and practice of infectious diseases GL, Bennet JE, Dolin R, editors: enza viruses, including avian influenza and swine influenza. In Mandell pandemic virus was likely the result of direct adaptation of an avian was estimated to have killed an estimated 50 million people. The 1918 severe pandemic in recorded history occurred in 1918, when the virus by an influenza A[H1N1] virus designated (A[H1N1]pdm09). The most global pandemics have occurred: in 1918 (caused by an influenza A[H1N1] virus), 1957 (A[H2N2]), 1968 (A[H3N2]), and 2009 (caused by an influenza A[H1N1] virus designated (A[H1N1]pdm09). The most severe pandemic in recorded history occurred in 1918, when the virus was estimated to have killed an estimated 50 million people. The 1918 pandemic virus was likely the result of direct adaptation of an avian influenza virus to the human host, rather than from reassortment. The 2009 pandemic stemmed from reassortment of genes from swine, avian, and human viruses (Fig. 258-2). This resulted in the emergence of a novel influenza A(H1N1) virus that spread quickly from North America across the globe, and has replaced the previously circulating seasonal H1N1 viruses.

In addition to the 2009 H1N1 pandemic, several other novel influenza strains, all originating in animals, have recently caused outbreaks of human infections. Avian influenza A[H5N1], a virulent avian influenza strain that was first identified in 1997, has caused more than 600 documented cases in 15 countries, with a 60% mortality rate. Another novel avian influenza, A(H7N9)—which first caused an outbreak of human infections in China during the spring of 2013 and second larger outbreak beginning fall 2014—also appears highly virulent; it has been fatal in more than one third of cases. In addition, a novel influenza A(H3N2v) virus caused more than 300 confirmed human infections in the United States from 2011-2013. Influenza viruses that normally circulate in swine are designated variant ("v") viruses when detected in humans. In contrast to avian influenza A[H5N1] and A[H7N9], this H3N2v influenza virus caused generally mild illness, primarily in children with swine contact at agricultural fairs. However, none of these viruses has exhibited sustained, efficient human-to-human transmission.

**Seasonal Influenza**

An estimated 20,000 children younger than 5 yr of age are hospitalized annually in the United States as a result of seasonal influenza-associated
comparisons, with hospitalization and mortality rates greatest in infants. Since 2004, the annual number of reported influenza-associated pediatric deaths in the United States has ranged from 34-149 during regular influenza seasons (it was 348 during the 2009 H1N1 pandemic). Influenza disproportionately affects children with specific chronic conditions, such as underlying pulmonary, cardiac, or neurologic and neuromuscular disorders. Very young children, especially those younger than 2 yr of age, and children with chronic medical conditions are more likely to develop severe influenza-related complications, including viral and bacterial pneumonia, respiratory failure, and death. However, while children with underlying medical conditions are at higher risk of complications, many healthy children are hospitalized with influenza, and nearly half of pediatric influenza-associated deaths are in children that have no known underlying medical condition.

Hospitals represent a small fraction of influenza-associated healthcare use; the proportion of outpatient visits resulting from influenza ranges from 10-25% annually in children younger than 5 yr of age. Influenza may also be underdiagnosed. Many who seek medical care for influenza do not have laboratory testing performed and do not receive a diagnosis of influenza. Children with primary influenza infection have higher influenza viral loads and more prolonged viral shedding than adults, making children extremely effective transmitters of infection. Nosocomial outbreaks of influenza can cause significant morbidity.

Every year, 3-4 influenza virus types or subtypes typically cocirculate, including H3N2, H1N1, and B viruses. Although 1 subtype usually predominates in any given season, it is difficult to predict which will be predominant. Thus, the influenza vaccine varies annually and contains 3 or 4 antigens representing the expected circulating types.

**PATHOGENESIS**

Influenza viruses infect the respiratory tract epithelium, primarily the ciliated columnar epithelial cells, by using the HA to attach to sialic acid residues. Virus is then adsorbed and virus replication occurs, usually within 4-6 hr. Infectious virus is then released, infecting neighboring cells and allowing the virus to spread rapidly. Influenza virus is rarely detected in extrapulmonary sites. With primary infection, virus replication continues for 10-14 days. Influenza virus causes a lytic infection of the respiratory epithelium with loss of ciliary function, decreased mucus production, and desquamation of the epithelial layer. These changes permit secondary bacterial invasion, either directly through the epithelium or, in the case of the middle ear space, through obstruction of the normal drainage through the eustachian tube.

The exact immune mechanisms involved in termination of primary infection and protection against reinfection are complex. Induction of cytokines that inhibit viral replication, such as interferon and tumor necrosis factor, as well as other host defenses, such as cell-mediated immune responses and local and humoral antibody defenses, all likely play a role. Secretory antibodies produced by the respiratory mucosa immunoglobulin A antibodies are thought to be an effective and immediate response generated during influenza infection. Serum antibody levels inhibiting HA activity can usually be detected by the 2nd wk after infection. These antibodies are also generated by vaccines, and high HA inhibition titers correlate with protection.

**CLINICAL MANIFESTATIONS**

The onset of influenza illness is often abrupt, with a predominance of systemic symptoms including fever, myalgias, chills, headache, malaise, and anorexia. Coryza, pharyngitis, and dry cough are also usually present at the onset of illness but may be less prominent than systemic symptoms. Respiratory manifestations can include isolated upper respiratory tract illness, including croup, or progression to lower tract disease, such as bronchiolitis or pneumonia. More than any other respiratory virus, influenza virus causes systemic manifestations such as high temperature, myalgia, malaise, and headache.

Abdominal pain, vomiting, and diarrhea may also occur in children; in some studies, diarrhea was reported to be more often associated with 2009 H1N1 compared with seasonal influenza. Influenza is a less-distinct illness in younger children and infants. The infected young infant or child may be highly febrile and toxic in appearance, prompting a full diagnostic work-up. The typical duration of the febrile illness is 2-4 days. Cough may persist for longer periods, and evidence of small airway dysfunction is often found weeks later. Owing to the high transmissibility of influenza, other family members or close contacts of an infected person often experience a similar illness.

**COMPLICATIONS**

Otitis media and pneumonia are common complications of influenza in young children. Acute otitis media may be seen in up to 25% of cases of documented influenza. Pneumonia accompanying influenza may be a primary viral process or a secondary bacterial infection (usually *Staphylococcus aureus*) facilitated through damaged respiratory epithelium. Unusual clinical manifestations of influenza include acute myositis seen with influenza type B, marked by muscle weakness and pain, particularly in the calf muscles, and myoglobinuria. Influenza types A and B are reported to cause myocarditis. Toxic shock syndrome can be associated with toxin-producing *Staphylococcus* colonization. Central nervous system complications, such as encephalitis, myelitis, and Guillain-Barré syndrome, can occur and are seen more commonly in children than adults. Although it has essentially disappeared in the United States, Reye syndrome can result with the use of salicylates during influenza type B infection (see Chapter 361). Influenza is particularly severe in children with underlying cardiopulmonary disease, including congenital and acquired valvular disease, cardiomyopathy, bronchopulmonary dysplasia, asthma, cystic fibrosis, and neuromuscular diseases affecting the accessory muscles of breathing. Pregnant women are at special risk for severe influenza. In children receiving cancer chemotherapy and children with immunodeficiency, virus is shed for longer periods, with higher risk of complications.

**LABORATORY FINDINGS**

The clinical laboratory abnormalities associated with influenza are nonspecific. Relative leukopenia is frequently seen. Chest radiographs may show evidence of atelectasis or infiltrate.

**DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS**

The diagnosis of influenza depends on epidemiologic, clinical, and laboratory considerations. In the context of an epidemic, the clinical diagnosis of influenza in a young child who has fever without a focus, malaise, and respiratory symptoms may be made with some certainty; however, clinical presentation is often indistinguishable from other respiratory viruses, including respiratory syncytial virus, parainfluenza virus, human metapneumovirus, adenovirus, and even rhinovirus. Although confirmation of influenza virus infection by diagnostic testing is not required for clinical decisions to prescribe antiviral medications, prompt suspicion or diagnosis of influenza may allow for early antiviral therapy to be initiated and may reduce inappropriate use of antibiotics. A number of diagnostic tests may be used for laboratory confirmation of influenza (Table 258-1).

Although rapid influenza diagnostic tests are often employed because of their ease of use and fast results, they can have suboptimal sensitivity to detect influenza virus infection, particularly for novel influenza viruses. Sensitivities of rapid diagnostic tests are generally 50-70%, although a range of 10-80% has been reported, compared to viral culture or reverse-transcription polymerase chain reaction. Specificities are higher, approximately 95-100%. Therefore, false-negative results occur more often than false-positive results. The interpretation of negative results should take into account the clinical characteristics and the patient's risk for complications. If there is clinical suspicion for influenza in a patient at high risk for complications (Table 258-2), early empiric treatment should be given regardless of a negative rapid diagnostic test result, and another type of test (e.g., reverse-transcription
Influenza Virus Testing Methods

<table>
<thead>
<tr>
<th>METHOD</th>
<th>ACCEPTABLE SPECIMENS</th>
<th>TEST TIME</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rapid influenza diagnostic tests</td>
<td>Nasopharyngeal (NP) swab, throat swab, nasal wash, nasal aspirate</td>
<td>&lt;30 min</td>
<td>Rapid turnaround; suboptimal sensitivity</td>
</tr>
<tr>
<td>Immunofluorescence, direct (DFA) or indirect (IFA) antibody staining</td>
<td>NP swab or wash, bronchial wash, nasal or endotracheal aspirate</td>
<td>1-4 hr</td>
<td>Relatively rapid turnaround; requires laboratory expertise and experience</td>
</tr>
<tr>
<td>RT-PCR* (single and multiplex; real-time and other RNA-based) and other molecular assays</td>
<td>NP swab, throat swab, NP or bronchial wash, nasal or endotracheal aspirate, sputum</td>
<td>Varied (generally 1-6 hr)</td>
<td>Excellent sensitivity, relatively rapid turnaround</td>
</tr>
<tr>
<td>Rapid cell culture (shell vials culture)</td>
<td>NP swab, throat swab, NP or bronchial wash, nasal or endotracheal aspirate, sputum</td>
<td>1-3 days</td>
<td>Culture isolates important for strain information and antiviral resistance monitoring</td>
</tr>
<tr>
<td>Viral cell culture (conventional)</td>
<td>NP swab, throat swab, NP or bronchial wash, nasal or endotracheal aspirate, sputum</td>
<td>3-10 days</td>
<td></td>
</tr>
<tr>
<td>Serologic tests (antibody detection)</td>
<td>Paired acute and convalescent sera</td>
<td>N/A (not performed during acute infection)</td>
<td>Not generally recommended for routine patient diagnosis</td>
</tr>
</tbody>
</table>

*Reverse transcription polymerase chain reaction

Adapted from Centers for Disease Control and Prevention (CDC): Rapid diagnostic testing for influenza: information for health care professionals; available at http://www.cdc.gov/flu/professionals/diagnosis/rapidclin.htm#table

Children and Adolescents Who Are at Higher Risk for Influenza Complications


Although all children younger than 5 yr of age are considered at higher risk for complications from influenza, the highest risk is for those younger than 2 yr of age, with the highest hospitalization and death rates among infants younger than 6 mo of age.

Polymerase chain reaction, direct fluorescent antibody, or viral culture may be performed for confirmation.

TREATMENT

Two classes of antiviral drugs are licensed for treatment of influenza in children. The NA inhibitors, oseltamivir and zanamivir, may be used for treatment of children from the ages of 2 wk and 7 yr, respectively (Table 258-3). These drugs are generally given either by inhalation (zanamivir) or oral administration (oseltamivir). In December 2012, the FDA approved the use of oseltamivir for the treatment of influenza in infants as young as 2 wk of age, and the Centers for Disease Control and Prevention (CDC) and American Academy of Pediatrics recommend its use in all infants. Investigational intravenous zanamivir is also available for compassionate use under an emergency investigational new drug request.

The second class of drugs, adamantanes, includes amantadine and rimantadine, which are effective only against influenza A viruses. These 2 antivirals are not effective against influenza type B strains and are not approved for use in children younger than 5 yr of age. Genetic mutations have conferred widespread adamantane resistance among circulating influenza A (H3N2) and A(H1N1)pdm09 viruses; therefore, this class of antivirals is not currently recommended for use. Many H5N1 viruses and the H7N9 avian influenza viruses detected in 2013 and 2014 are also resistant to amantadine and rimantadine. It is important to review annual recommendations and updates published by the CDC before prescribing influenza antiviral medications.

When initiated early in the course of uncomplicated influenza illness, antiviral agents can reduce the duration of symptoms and the likelihood of complications. Among hospitalized patients, observational studies suggest that early treatment reduces disease severity and mortality. Most data regarding potential benefit are for adults; however, a few studies support the use of antiviral agents in children. Clinical benefit is greatest when antiviral treatment is administered early, especially within 48 hr of influenza illness onset. Although early treatment is desired, treatment as early as possible, even more than 48 hr from onset, is recommended for hospitalized patients, patients with complicated or progressive illness, and patients at high risk for
Table 258-3  Centers for Disease Control and Prevention Recommended Dosage and Schedule of Influenza Antiviral Medications for Treatment and Chemoprophylaxis

<table>
<thead>
<tr>
<th>ANTIVIRAL AGENT</th>
<th>USE</th>
<th>CHILDREN</th>
<th>ADULTS*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osimertinib (Tagrisso)</td>
<td>Treatment (5 days)</td>
<td>If child is younger than 1 yr old*: 3 mg/kg/dose twice daily†  If child is 1 yr or older, dose varies by child’s weight: 15 kg or less, the dose is 30 mg twice a day &gt;15-23 kg, the dose is 45 mg twice a day &gt;23-40 kg, the dose is 60 mg twice a day &gt;40 kg, the dose is 75 mg twice a day</td>
<td>75 mg twice daily</td>
</tr>
<tr>
<td>Zanamivir (Relenza)</td>
<td>Chemoprophylaxis (7 days)</td>
<td>For children age 7 yr and older: 10 mg (two 5-mg inhalations) twice daily For children age 5 yr and older: 10 mg (two 5-mg inhalations) once daily</td>
<td>10 mg (two 5-mg inhalations) twice daily 10 mg (two 5-mg inhalations) once daily</td>
</tr>
</tbody>
</table>

Current for 2013-2014 influenza season, United States.

*Influenza complications (see Table 258-2). Decisions about starting antiviral treatment should not wait for laboratory confirmation of influenza. Currently, for hospitalized patients and patients with severe or complicated illness, treatment with oral or enterically administered oseltamivir (and not inhaled zanamivir) is recommended. The recommended treatment course for uncomplicated influenza is 2 doses per day of an NA inhibitor medication for 5 days; however, the optimal duration and dose are uncertain for severe or complicated influenza and longer courses of treatment (e.g., 10 days of treatment) may be considered.

Clinical judgment, on the basis of the patient’s disease severity, age, underlying medical conditions, likelihood of influenza, and time since onset of symptoms, is important when making antiviral treatment decisions for outpatients at high risk for complications. Antiviral treatment also can be considered for any previously healthy, symptomatic outpatient not at high risk with confirmed or suspected influenza on the basis of clinical judgment, if treatment can be initiated within 48 hr of illness onset.

Drug resistance can develop commonly during a course of amantadine or rimantadine therapy and has also been reported to emerge in patients receiving oseltamivir treatment. Antiviral medications should be considered an adjunct to vaccination.

SUPPORTIVE CARE

Adequate fluid intake and rest are important components in the management of influenza. Bacterial superinfections are relatively common and should be appropriately treated with antibiotic therapy. Bacterial superinfection should be suspected with recrudescence of fever, prolonged fever, or deterioration in clinical status. With uncomplicated influenza, children should start to feel better after the 1st 48-72 hr of symptoms.

PROGNOSIS

The prognosis for recovery from uncomplicated influenza is generally excellent, although full return to normal level of activity and freedom from cough usually requires weeks rather than days. Fatigue may also persist for weeks. However, severe influenza disease can be associated with hospitalizations and death, even among previously healthy children.

PREVENTION

Influenza vaccination is the best means of preventing severe disease caused by influenza. In studies of children who are fully vaccinated, influenza vaccine was approximately 50-80% effective in reducing the risk of laboratory-confirmed influenza illness. Vaccine effectiveness can vary from year to year and among different age and risk groups. Recommendations for use of the influenza vaccine have broadened as the impact of influenza is appreciated in such groups as pregnant women and young infants. Starting in the 2008-2009 influenza season, the Advisory Committee on Immunization Practices (ACIP) recommended that all children from 6 mo to 18 yr of age be vaccinated for influenza unless they have a specific contraindication to receiving the
Vaccination should be given as soon as vaccine is available, preferably before the onset of influenza circulation in the community, so that there is time for antibodies to reach protective levels. The ACIP publishes guidelines for vaccine use each year when the vaccines are formulated and released. These guidelines are widely publicized but appear initially in the Morbidity and Mortality Weekly Report published by the CDC.

**Chemoprophylaxis**

Routine use of antiviral medications for chemoprophylaxis is not recommended. Examples for which the use of chemoprophylaxis may be considered to prevent influenza after exposure to an infectious person include: (1) unvaccinated persons at high risk of influenza complications, (2) persons for whom vaccine is contraindicated or expected to have low effectiveness, and (3) residents/patients in care facilities during institutional influenza outbreaks. NA inhibitors or adamantanes may be used for chemoprophylaxis of influenza; however, adamantanes are not currently recommended because of widespread adamantane resistance. Table 258-3 shows the recommendations for dosage and duration of treatment and chemoprophylaxis for the 2012-2013 influenza season, but updated recommendations from the ACIP and CDC should be consulted every season (http://www.cdc.gov/flu). In general, if chemoprophylaxis can be started within 48 hr of exposure to an infectious person, postexposure chemoprophylaxis for persons at high risk of influenza complications (see Table 258-2) is recommended for at least 7 days after the most recent exposure. An alternative to chemoprophylaxis for some persons after a suspected exposure is close monitoring and early initiation of antiviral treatment if symptoms develop. For control of outbreaks with seasonal influenza in long-term care facilities and hospitals, antiviral chemoprophylaxis should be considered for exposed vaccinated and unvaccinated high-risk patients, as well as unvaccinated healthcare providers. The CDC and the Infectious Disease Society of America recommend chemoprophylaxis for a minimum of 2 wk and up to 1 wk after the last known case is identified, whichever is longer.

*Bibliography is available at Expert Consult.*

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**Vaccines**

There are 2 main categories of seasonal influenza vaccines available for children, inactivated influenza vaccine (IIV) and live-attenuated influenza vaccine (LAIV). Previously referred to as the trivalent inactivated vaccine, IIV is given intramuscularly; it uses killed virus components and cannot cause influenza virus infection. The LAIV vaccine uses weakened influenza virus and is administered as an intranasal spray. Starting in 2014-2015, ACIP and CDC recommended the use of the LAIV nasal spray vaccine for healthy children 2 through 8 yr of age, when it is immediately available and when no contraindications or precautions to that vaccine exist. LAIV is not recommended for children younger than 2 yr of age or children who are at higher risk of developing influenza complications. In addition, special vaccination instructions for children 6 mo to 8 yr of age should be followed: depending on vaccination history, some children will require 2 doses of seasonal influenza vaccine (administered a minimum of 4 wk apart) to optimize immune response (Fig. 258-3). Influenza vaccines have an excellent safety profile, with the most common side effects being soreness, redness, tenderness, or swelling from the injection, and nasal congestion after the nasal spray.

Inactivated and live-attenuated seasonal influenza vaccines become available in the late summer and early fall of each year. The formulation reflects the strains of influenza viruses that are expected to circulate in the coming winter. Beginning in the 2013-2014 season, IIVs were available in both trivalent and quadrivalent formulations. The trivalent vaccine (IIV3) contains 2 influenza A strains and 1 influenza B strain; the quadrivalent vaccine (IIV4) contains a second influenza B strain of an antigenically distinct lineage. In addition to IIV and LAIV vaccines, a third vaccine category, recombinant hemagglutinin influenza vaccine, became available as a trivalent formulation in the 2013-2014 season.

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**Figure 258-3** Influenza vaccine dosing algorithm for children 6 mo through 8 yr of age. *(From Centers for Disease Control and Prevention (CDC): Summary recommendations: prevention and control of influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices—United States, 2014-15. Available at http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6332a3.htm.)*

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Has the child ever received influenza vaccine?  
No/Don’t know → 2 doses*

Yes → Did the child receive a total of 2 or more doses of seasonal influenza vaccine since July 1, 2010?  
No/Don’t know → 2 doses†

Yes → 1 dose

* Doses should be administered at least 4 wk apart.

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**Table 258-3** shows the recommendations for dosage and duration of treatment and chemoprophylaxis for the 2012-2013 influenza season, but updated recommendations from the ACIP and CDC should be consulted every season (http://www.cdc.gov/flu). In general, if chemoprophylaxis can be started within 48 hr of exposure to an infectious person, postexposure chemoprophylaxis for persons at high risk of influenza complications (see Table 258-2) is recommended for at least 7 days after the most recent exposure. An alternative to chemoprophylaxis for some persons after a suspected exposure is close monitoring and early initiation of antiviral treatment if symptoms develop. For control of outbreaks with seasonal influenza in long-term care facilities and hospitals, antiviral chemoprophylaxis should be considered for exposed vaccinated and unvaccinated high-risk patients, as well as unvaccinated healthcare providers. The CDC and the Infectious Disease Society of America recommend chemoprophylaxis for a minimum of 2 wk and up to 1 wk after the last known case is identified, whichever is longer.

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Bibliography


Parainfluenza viruses (PIVs) are common causes of acute respiratory illness in infants and children and are important causes of lower respiratory tract disease in young children and immunocompromised persons. These viruses cause a spectrum of upper and lower respiratory tract illnesses but are particularly associated with croup (laryngotracheitis or laryngotracheobronchitis), bronchiolitis, and pneumonia.

**ETIOLOGY**

The PIVs are members of the Paramyxoviridae family. Four PIVs cause illness in humans, classified as types 1-4, with diverse manifestations of infection. Type 4 is divided into 2 antigenic subgroups, A and B. PIVs have a nonsegmented, single-stranded RNA genome with a lipid-containing envelope derived from budding through the cell membrane. The major antigenic moieties are the HN and F envelope spike glycoproteins, which exhibit hemagglutinin-neuraminidase and fusion functions, respectively.
Children are likely to excrete virus from the oropharynx for 2-3 wk, but excretion can be more prolonged even in immunocompetent children; in immunocompromised patients, excretion may persist for months. Primary infection does not confer permanent immunity, and reinfections are common throughout life. Reinfections are generally mild and self-limited.

**EPIDEMIOLOGY**

By 5 yr of age, most children have experienced primary infection with PIV types 1, 2, and 3. PIV-3 infections often occur in the 1st 6 mo of life, with half of children estimated to be infected by age 1 year, and 90-100% by age 5 yr. PIV-1 and PIV-2 are more common after infancy, with 60-75% infected by age 5 yr. Although PIV-4 is not recognized as often, about half of children have antibody by the age of 5 yr. In the United States and temperate climates, PIV-1 has typically been reported to have biennial epidemics in the fall, sometimes noted to alternate years in which the serotype is most prevalent with PIV-2 (Fig. 259-1). PIV-2 has also been reported to cause yearly outbreaks. PIV-3 is endemic throughout the year but typically peaks in late spring. In years with less PIV-1 activity, the PIV-3 season has been observed to extend longer or to have a second peak in the fall (Fig. 259-1). The epidemiology of PIV-4 is less-well defined, because it is difficult to grow in tissue culture and was often excluded from previous studies, but newer studies show it to have an irregular epidemic pattern.

PIVs are spread primarily from the respiratory tract by inhalation of large respiratory droplets or contact with infected secretions. PIVs are notable for causing outbreaks of respiratory infections in hospital wards, clinics, neonatal nurseries, and other institutional settings. The incubation period from exposure to symptom onset is 2-6 days.

**PATHOGENESIS**

PIVs replicate in the respiratory epithelium. The propensity to cause illness in the upper large airways is presumably related to preferential replication in the larynx, trachea, and bronchi in comparison with other viruses. Some PIVs induce cell-to-cell fusion. During the budding process, cell membrane integrity is lost, and viruses can induce cell death through the process of apoptosis. In children, the most severe illness coincides with the time of maximal viral shedding. However, disease severity is likely related to the host immune response to infection as much as to direct cytopathic effects of the virus. Virus-specific immunoglobulin A antibody levels correlate with protection from PIV infection. Circulating serum antibody is also likely to play a role in protection against PIV acquisition and progression to severe infection. Patients with compromised cellular immunity have severe, prolonged disease, suggesting that T cells are critical to controlling and terminating PIV infection.
Region, is characteristic of croup, differential considerations include "steeple sign," consisting of progressive narrowing of the subglottic abscess, and subglottic hemangioma. Although the radiographic "steeple sign," consisting of progressive narrowing of the subglottic region, is characteristic of croup, differential considerations include acute epiglottitis, thermal injury, angioedema, and bacterial tracheitis.

The indications for antibiotics are limited to well-documented secondary bacterial infections of the middle ear(s) or lower respiratory tract.

TREATMENT

There are no specific antiviral medications approved for the treatment of PIV infections. For croup, the possibility of rapid respiratory compromise should influence the acuity of care given (see Chapter 385). Humidified air has not been shown to be effective. Corticosteroids, including dexamethasone orally or by injection and budesonide via nebulizer, improve symptoms within 6 hr after treatment, lessen the need for other medications, and shorten hospital stays. In general, because of its safety, efficacy, and cost-effectiveness, a single dose of oral dexamethasone (0.6 mg/kg) is preferred as part of the management of croup in the office or emergency room setting. A single dose of intra-muscular dexamethasone or budesonide (2 mg [2 mL solution] via nebulizer) may provide an alternative to dexamethasone for children with severe respiratory distress or vomiting. The dose may be repeated, but this should not be necessary on a routine basis, and there are no guidelines to compare outcomes of single- and multiple-dose treatment schedules. Moderate to severe symptoms that persist for more than a few days should prompt investigation for other causes of airway obstruction.

For obstructive airway symptoms associated with moderate to severe croup, nebulized epinephrine (either racemic epinephrine 2.25%, 0.5 mL in 2.5 mL of saline, or L-epinephrine, 1:1,000 dilution in 5 mL of saline) is recommended and may also provide temporary symptomatic improvement. Children should be observed for at least 2 hr after receiving epinephrine treatment for return of obstructive symptoms. Repeated treatments may be provided, depending on the duration of symptoms. Oxygen should be administered for hypoxia, and supportive care with analgesics and antipyretics is reasonable for fever and discomfort associated with PIV infections. The indications for antibiotics are limited to well-documented secondary bacterial infections of the middle ear(s) or lower respiratory tract.

Ribavirin has some antiviral activity against PIVs in vitro and in animal models. Inhaled ribavirin has been given to severely immunocompromised children with PIV pneumonia, although the majority of data indicate that it is not effective, particularly for PIV pneumonia when given late in the course of illness. It is unclear whether treatment given early to prevent progression to pneumonia may be beneficial, although there have been anecdotal reports of successful use of aerosolized ribavirin for this purpose in children with severe combined immunodeficiency and transplant recipients. DAS181, a novel sialidase fusion protein inhibitor, has shown clinical potential when used for treatment of PIV lower respiratory tract disease among solid organ and hematopoietic stem cell transplant recipients, with reported improvement in viral load and symptoms following initiation of therapy. Other promising strategies for drug development include hemagglutinin-neuraminidase inhibitors, transcription inhibitors, and synthetic small interfering RNAs.

Complications

Eustachian tube obstruction can lead to secondary bacterial invasion of the middle ear space and acute otitis media in 30-50% of PIV
infections. Similarly, obstruction of the paranasal sinuses can lead to sinusitis. The destruction of cells in the upper airways can lead to secondary bacterial invasion and resultant bacterial tracheitis, and antecedent PIV infection of lower airways may predispose to bacterial pneumonia. Nonrespiratory complications of PIV are rare but include aseptic meningitis, encephalitis, acute disseminated encephalomyelitis, rhabdomyolysis, myocarditis, and pericarditis.

**PROGNOSIS**
The prognosis for full recovery from PIV infection in the normal child is excellent, with no long-term pulmonary sequelae.

**PREVENTION**
Vaccine development has focused largely on live-attenuated intranasal PIV-3 vaccines. The candidates include a cold-adapted virus of human origin (cp45), an attenuated bovine PIV-3, and newer constructs using the bovine PIV-3 vaccine with insertion of human PIV-3 HN and F genes and the F and G proteins of respiratory syncytial virus. Reverse genetics technology has led to development of a live-attenuated investigational PIV-3 vaccine virus (rcp45) derived from complementary DNA, as well as complementary DNA–derived chimeric bovine/human PIV-3 virus constructs; these candidates are well tolerated and immunogenic in infants and young children. Although less advanced, candidate PIV-1 and PIV-2 vaccines have been developed and are undergoing phase 1 clinical studies in children ([www.clinicaltrials.gov](http://www.clinicaltrials.gov)). The measure of protection afforded by vaccines will be difficult to assess, because symptomatic reinfection occurs and the frequency of serious infection in the general population is low. Nonetheless, it is clear that prevention of acute respiratory illness caused by PIVs, particularly lower respiratory tract infections among infants and young children, is a worthwhile goal.

*Bibliography is available at Expert Consult.*
Bibliography


Respiratory syncytial virus (RSV) is the major cause of bronchiolitis (see Chapter 391) and viral pneumonia in children younger than 1 yr of age and is the most important respiratory tract pathogen of early childhood.

**ETIOLOGY**

RSV is an enveloped RNA virus with a single-stranded negative-sense genome that replicates entirely in the cytoplasm of infected cells and matures by budding from the apical surface of the cell membrane. Because this virus has a nonsegmented genome, it cannot undergo antigenic shift by reassortment like the influenza viruses do. The virus belongs to the family Paramyxoviridae, along with parainfluenza and measles viruses, and is in the subfamily Pneumovirinae, which also contains the human metapneumovirus (see Chapter 261). It is the only member of the genus *Pneumovirus* that infects humans. There are 2 antigenic subgroups of RSV, distinguished based primarily on variation in 1 of the 2 surface proteins, the G glycoprotein that is responsible for attachment. This antigenic variation caused by point mutations from infidelity of the virus RNA polymerase may to some degree contribute to the frequency with which RSV reinfects children and adults.

RSV replicates in a wide variety of cell line monolayer cultures in vitro, and in HeLa or HEp-2 cells produces characteristic syncytial cytopathology, from which the virus derives its name. Interestingly, it is now known that the virus does not cause large syncytia in polarized epithelial cells in vitro, and it is not clear whether syncytium formation occurs to any significant degree in vivo.

**EPIDEMIOLOGY**

RSV is distributed worldwide and appears in yearly epidemics. In temperate climates, these epidemics occur each winter over 4-5 mo. During the remainder of the year, infections are sporadic and much less common. In the Northern hemisphere, epidemics usually peak in January, February, or March, but peaks have been recognized as early as December and as late as June. Some areas in the United States, such as Florida, report a moderate incidence year-round. In the Southern hemisphere, outbreaks also occur during winter months in that hemisphere. RSV outbreaks often overlap with outbreaks of influenza and human metapneumovirus but are generally more consistent from year to year and result in more disease overall, especially among infants younger than 6 mo of age. In the tropics, the epidemic pattern is less clear. This pattern of widespread annual outbreaks and the high incidence of infection during the 1st 3-4 mo of life are unique among human viruses.

Transplacentally acquired anti-RSV maternal immunoglobulin G serum antibodies, if present in high concentration, appear to provide partial but incomplete protection. These immunoglobulin Gs may account for the lower severity of RSV infections during the 1st 4-6 wk of life, except among infants born prematurely, who receive less maternal immunoglobulin. Breastfeeding provides substantial protection against severe disease, an effect that may persist only to female infants and not male infants. RSV is one of the most contagious viruses that affect humans. Infection is nearly universal among children by their 2nd birthday. Reinfection occurs at a rate of at least 10-20% per epidemic throughout childhood, with a lower frequency among adults. In situations of high exposure, such as daycare centers, attack rates are nearly 100% among previously uninfected infants and 60-80% for second and subsequent infections.

Reinfection may occur as early as a few weeks after recovery, but usually takes place during subsequent annual outbreaks. Antigenic variation is not required for reinfection, as shown by the fact that a proportion of adults inoculated repeatedly with the same experimental preparation of wild-type virus could be reinfected multiple times. The immune response of infants is poor in quality, magnitude, and durability. The severity of illness during reinfection in childhood is usually lower and appears to be a function of partial acquired immunity, more robust airway physiology, and increased age.

Asymptomatic RSV infection is unusual in young children. Most infants experience coryza and pharyngitis, often with fever and frequently with otitis media caused by a virus in the middle ear or bacterial superinfection following eustachian tube dysfunction. The lower respiratory tract is involved to a varying degree with bronchiolitis and bronchopneumonia in about a third of children. The hospitalization rate for RSV infection in otherwise healthy infants is typically 0.5-4%, depending on region, gender, socioeconomic status, exposure to cigarette smoke, gestational age, and family history of atopy. The admitting diagnosis is usually bronchiolitis with hypoxia, although this condition is often indistinguishable from RSV pneumonia in infants, and, indeed, the 2 processes frequently coexist. All RSV diseases of the lower respiratory tract (excluding croup) have their highest incidence at 6 wk to 7 mo of age and decrease in frequency thereafter. The syndrome of bronchiolitis is much less common after the 1st birthday. The terminology used for diagnosis of virus-associated wheezing illnesses in toddlers is confusing, as these illnesses are variably termed wheezing-associated respiratory infection, “wheezy bronchitis,” exacerbation of reactive airways disease, or asthma attack. Because many toddlers wheeze during RSV infection but do not go on to have lifelong asthma, it is best to use the diagnostic term asthma only later in life. Acute viral
pneumonia is a recurring problem throughout childhood, although RSV becomes less prominent as the etiologic agent after the 1st yr. RSV plays a causative role in an estimated 40-75% of cases of hospitalized bronchiolitis, 15-40% of cases of childhood pneumonia, and 6-15% of cases of croup.

Bronchiolitis and pneumonia resulting from RSV are more common in boys than in girls by a ratio of approximately 1.5:1. Other risk factors with similar impact include 1 or more siblings in the home, white race, rural residence, maternal smoking, and maternal education <12 yr. The medical factors in infants associated with highest risk are chronic lung disease of prematurity, congenital heart disease, immunodeficiency, and prematurity. Still, most infants admitted to the hospital because of RSV infection do not have strong, easily identifiable risk factors. Therefore, any strategy for prophylaxis focused only on individuals with strong risk factors probably could prevent only approximately 10% of hospitalizations, even if the prophylaxis was 100% effective in treated high-risk individuals.

The incubation period from exposure to first symptoms is approximately 3-5 days. The virus is excreted for variable periods, probably depending on severity of illness and immunologic status. Most infants with lower respiratory tract illness shed infectious virus for 1-2 wk after hospital admission. Excretion for 3 wk, and even longer, has been documented. Spread of infection occurs when large, infected droplets, either airborne or conveyed on hands or other fomites, are inoculated in the nasopharynx of a susceptible subject. RSV is probably introduced into most families by young schoolchildren undergoing reinfection. Typically, in the space of a few days, 25-50% of older siblings and 1 or both parents acquire upper respiratory tract infections, but infants become more severely ill with fever, otitis media, or lower respiratory tract disease.

Nosocomial infection during RSV epidemics is an important concern. Virus is usually spread from child to child on the hands of caregivers or other fomites. Adults undergoing reinfection also have been implicated in spread of the virus. Contact precautions are sufficient to prevent spread when compliance is meticulous, as the virus is not usually spread by small particle aerosol. In practice, however, adherence to isolation procedures by caregivers often is not complete.

**PATHOGENESIS**

Bronchiolitis is caused by obstruction and collapse of the small airways during expiration. Infants are particularly apt to experience small airway obstruction because of the small size of their normal bronchi- oles; airway resistance is proportional to 1/radius. There has been relatively little pathologic examination of RSV disease in the lower airways of otherwise healthy subjects. Airway narrowing likely is caused by virus-induced necrosis of the bronchiolar epithelium, hypersecretion of mucus, and round-cell infiltration and edema of the surrounding submucosa. These changes result in formation of mucus plugs obstructing bronchioles, with consequent hyperinflation or collapse of the distal lung tissue. In interstitial pneumonia, the infiltration is more generalized, and epithelial shedding may extend to both the bronchi and the alveoli. In older subjects, smooth muscle hyperreactivity may contribute to airway narrowing, but the airways of young infants typically do not exhibit a high degree of reversible smooth muscle hyperreactivity during RSV infection.

Several facts suggest that elements of the host response may cause inflammation and contribute to tissue damage. The immune response required to eliminate virus-infected cells is a double-edged sword, reducing the cells producing virus but causing host cell death in the process. A large number of soluble factors, such as cytokines, chemokines, and leukotrienes, are released in the process, and skewing of the patterns of these responses may predispose some individuals to more severe disease. There is also evidence that genetic factors may predispose to more severe bronchiolitis.

Children who received a formalin-inactivated, parenterally administered RSV vaccine in the 1960s experienced more severe and more frequent bronchiolitis upon subsequent natural exposure to wild-type RSV than did their age-matched controls. Several children died during naturally acquired RSV infection after vaccination. This event has greatly inhibited progress in RSV vaccine development, because of both an incomplete understanding of the mechanism and a reluctance to test new experimental vaccines that might induce the same type of response.

Some studies have identified the presence of both RSV and human metapneumovirus viral RNA in airway secretions in a significant proportion of infants requiring assisted ventilation and intensive care. It may be that coinfection is associated with more severe disease. Positive results of polymerase chain reaction (PCR) analysis must be interpreted carefully because this positivity can remain for prolonged periods after infection, even when infectious virus can no longer be detected.

It is not clear how often superimposed bacterial infection plays a pathogenic role in RSV lower respiratory tract disease. RSV bronchiolitis in infants is probably exclusively a viral disease, although there is evidence that bacterial pneumonia can be triggered by respiratory viral infection, including with RSV. A large clinical study of pneumococcal vaccine showed that childhood vaccination reduced the incidence of viral pneumonia by approximately 30%, suggesting viral-bacterial interactions that we currently do not fully understand.

**CLINICAL MANIFESTATIONS**

Typically, the first sign of infection in infants with RSV is rhinorrhea. Cough may appear simultaneously but more often does so after an interval of 1-3 days, at which time there may also be sneezing and a low-grade fever. Soon after the cough develops, the child who experiences bronchiolitis begins to wheeze audibly. If the disease is mild, the symptoms may not progress beyond this stage. Auscultation often reveals diffuse fine inspiratory crackles and expiratory wheezes. Rhinorrhea usually persists throughout the illness, with intermittent fever. Chest radiograph findings at this stage are frequently normal.

If the illness progresses, cough and wheezing worsen and air hunger ensues, with increased respiratory rate, intercostal and subcostal retractions, hyperexpansion of the chest, restlessness, and peripheral cyanosis. Signs of severe, life-threatening illness are central cyanosis, tachypnea of >70 breaths/min, listlessness, and apneic spells. At this stage, the chest may be significantly hyperexpanded and almost silent to auscultation because of poor air movement.

Chest radiographs of infants hospitalized with RSV bronchiolitis have normal findings in approximately 30% of cases, with the other 70% showing hyperexpansion of the chest, peribronchial thickening, and interstitial infiltrates. Segmental or lobar consolidation is unusual and pleural effusion is rare.

In some infants, the course of the illness may resemble that of pneumonia, the prodromal rhinorrhea and cough being followed by dyspnea, poor feeding, and listlessness, with a minimum of wheezing and hyperexpansion. Although the clinical diagnosis is pneumonia, wheezing is often present intermittently and the chest radiographs may show air trapping.

Fever is an inconstant sign in RSV infection. In young infants, particularly those who were born prematurely, periodic breathing and apneic spells have been distressingly frequent signs, even with relatively mild bronchiolitis. Apnea is not necessarily caused by respiratory exhaustion, but rather appears to be a consequence of alterations in central control of breathing.

RSV infections in profoundly immunocompromised hosts may be severe at any age of life. The mortality rates associated with RSV pneumonia in the 1st few wk after hematopoietic stem cell or solid organ transplantation in both children and adults are high. RSV infection does not seem to be more severe in HIV-infected patients with reasonable control of HIV disease, although these patients may shed virus for prolonged periods.

**DIAGNOSIS**

Bronchiolitis is a clinical diagnosis. RSV can be suspected with varying degrees of certainty on the basis of the season of the year and the presence of the virus in the community. Other epidemiologic features that
may be helpful are the presence of colds in older household contacts and the age of the child. The other respiratory viruses that attack infants frequently during the 1st few mo of life are parainfluenza virus type 3, human metapneumovirus, enteroviruses, coronaviruses, and influenza viruses. Rhinovirus is frequently found in the respiratory tract of children, and there is growing evidence that this virus may contribute significantly to lower respiratory tract disease.

Routine laboratory tests are of minimal diagnostic use in most cases of bronchiolitis or pneumonia caused by RSV. The white blood cell count is normal or elevated, and the differential cell count may be normal with either a neutrophilic or mononuclear predominance. Hypoxemia as measured by pulse oximetry or arterial blood gas analysis is frequent and tends to be more marked than anticipated from the clinical findings. A normal or elevated blood CO₂ value in a patient with a markedly elevated respiratory rate is a sign of respiratory failure.

The most important diagnostic concern is to identify bacterial or chlamydial involvement. When bronchiolitis is not accompanied by infiltrates on chest radiographs, there is little likelihood of a bacterial component. In infants 1-4 mo of age, interstitial pneumonitis may be caused by Chlamydia trachomatis (see Chapter 226). With C. trachomatis pneumonia there may be a history of conjunctivitis, and the illness tends to be of subacute onset. Coughing and inspiratory crackles may be prominent; wheezing is not. Fever is usually absent.

Lobar consolidation without other signs or with pleural effusion should be considered of bacterial etiology until proved otherwise. Other signs suggesting bacterial pneumonia are neutrophilia, neutropenia in the presence of severe disease, ileus or other abdominal signs, high temperature, and circulatory collapse. In such instances, antibiotics should be initiated.

Definitive diagnosis of RSV infection is based on the detection in respiratory secretions of live virus by cell culture. The presence of viral RNA (detected by a molecular diagnostic test using reverse transcription PCR) or viral antigens (detected by a rapid diagnostic test, usually a membrane blotting test incorporating antibody detection of viral proteins) is strongly supportive in the right clinical setting. The antigen test is less sensitive than culture, whereas reverse transcription PCR analysis is more sensitive than culture. An aspirate of mucus or a nasopharyngeal wash from the child's posterior nasal cavity is the optimal specimen. Nasopharyngeal or throat swabs are less preferable but acceptable. A tracheal aspirate is unnecessary, but endotracheal tube lavage fluid from patients intubated for mechanical ventilation can be tested. The specimen should be placed on ice, taken directly to the laboratory, and processed immediately for culture, antigen detection, or PCR analysis. The virus is thermolabile, so it degrades over relatively short periods of time unless frozen at a low temperature such as −80°C (−112°F) in freezers used in research settings.

TREATMENT

The treatment of uncomplicated cases of bronchiolitis is symptomatic. Humidified oxygen and suctioning are usually indicated for hospitalized infants who are hypoxic. Many infants are slightly to moderately dehydrated, and therefore fluids should be carefully administered in amounts somewhat greater than those for maintenance. Often, intravenous or tube feeding is helpful when sucking is difficult because of tachypnea.

There is disagreement among experts regarding the usefulness of aerosolized saline or hypertonic saline, ephedrine or β₂-agonists in RSV bronchiolitis. Most patients do not receive lasting benefit from prolonged therapy, which is associated with a relatively high frequency of side effects. Corticosteroid therapy is not indicated except in older children with an established diagnosis of asthma, because its use is associated with prolonged virus shedding and is of no proven clinical benefit.

In nearly all instances of bronchiolitis, antibiotics are not useful, and their inappropriate use contributes to development of antibiotic resistance. Interstitial pneumonia in infants 1-4 mo old may be caused by C. trachomatis, and macrolide therapy may be indicated for that infection.

Ribavirin is an antiviral agent delivered through an oxygen hood, face mask, or endotracheal tube with use of a small-particle aerosol generator most of the day for 3-5 days. Early small trials of its use suggested a modest beneficial effect on the course of RSV pneumonia, with some reduction in the duration of both mechanical ventilation and hospitalization. However, subsequent studies failed to document a clear beneficial effect of ribavirin, and therefore this drug is no longer used for routine therapy of RSV disease. The monoclonal antibody palivizumab is licensed for prophylaxis in high-risk infants during the RSV season, and does prevent about half of the expected hospitalizations in that population. Small clinical trials using the palivizumab as a therapy during established infection have not shown benefit to date.

PROGNOSIS

The mortality rate of hospitalized infants with RSV infection of the lower respiratory tract is very low in the developed world. Almost all deaths occur among young, premature infants or infants with underlying disease of the neuromuscular, pulmonary, cardiovascular, or immunologic system. It is estimated, however, that more than 100,000 children worldwide in resource-poor settings die each year from RSV. In addition, thousands of elderly patients die of RSV infection each year in the United States.

Many children with asthma have a history of bronchiolitis in infancy. There is recurrent wheezing in 30-50% of children with severe RSV bronchiolitis in infancy. The likelihood of recurrence is increased in the presence of an allergic diathesis (e.g., eczema, hay fever, or a family history of asthma). With a clinical presentation of bronchiolitis in a patient older than 1 yr of age, there is an increasing probability that, although the episode may be virus induced, this is likely the first of multiple wheezing attacks that will later be diagnosed as hyperreactive airways disease or asthma. Asthma is difficult to diagnose in the 1st yr of life. It is not fully clear at this time whether early, severe RSV wheezing disease causes some cases of asthma or whether subjects destined to suffer asthma present with symptoms first when provoked by RSV infection during infancy. However, results from a recent long-term follow-up study of infants who received palivizumab prophylaxis suggested that prevention of severe RSV infection reduces the incidence of reactive airways disease later in life.

PREVENTION

In the hospital, the most important preventive measures are aimed at blocking nosocomial spread. During RSV season, high-risk infants should be separated from all infants with respiratory symptoms. Gowns, gloves, and careful handwashing should be used for the care of all infants with suspected or established RSV infection. A high level of compliance with contact isolation is essential. Viral laboratory tests are adequate for diagnosis in the setting of acute disease when levels of virus are high, but they are not designed to detect low levels of virus. Therefore, contact precaution isolation should be observed for most patients admitted for acute disease assigned for the duration of hospitalization; rapid antigen tests should not be used to determine whether or not a patient still requires isolation. Ideally, patients with RSV or metapneumovirus infections are housed separately, because coinfection may be associated with more severe disease.

Passive Immunoprophylaxis

Administration of palivizumab (15 mg/kg IM once a month), a neutralizing humanized murine monoclonal antibody against RSV, is recommended for protecting high-risk children against serious complications from RSV disease. Immunoprophylaxis reduces the frequency and total days of hospitalization for RSV infections in high-risk infants in about half of cases. Palivizumab is administered monthly from the beginning to the end of the RSV season. The American Academy of Pediatrics Committee on Infectious Diseases issued "Modified Recommendations for Use of Palivizumab for Prevention of Respiratory Syncytial Virus Infections" in 2014. Palivizumab prophylaxis may be considered for the following infants and children:

- Infants born before 29 wk of gestation in the 1st yr of life
- Infants born before 32 wk of gestation, who have chronic lung disease of prematurity (required >21% FIO₂ [fraction of inspired oxygen] for ≥28 days after birth), in the 1st yr of life
Infants younger than 1 yr of age with hemodynamically significant congenital heart disease
Children 24 mo of age or younger with profound immunocompromising conditions during RSV season
Infants in the 1st yr of life who have either congenital abnormalities of the airway or neuromuscular disease that compromises handling of respiratory secretions
Administration in the 2nd yr of life is recommended for children who required 28 or more days of oxygen after birth and who have ongoing treatment for chronic pulmonary disease (oxygen, steroids, diuretics)

The American Academy of Pediatrics 2012 Red Book recommendations also give the following specific guidelines on implementation of prophylaxis. Recommendations for initiation and termination of prophylaxis reflect current descriptions from the Centers for Disease Control and Prevention of RSV seasonality in different geographic locations within the United States. Typically, prophylaxis is initiated July 1 in southeast Florida, September 15 in north-central and southwest Florida, and November 1 in most other areas of the United States. Regardless of the month in which the 1st dose is administered, the recommendation for a maximal number of 5 doses for all geographic locations is emphasized for infants with hemodynamically significant congenital heart disease, chronic lung disease of prematurity, or birth before 32 wk, 0 days of gestation. A maximal number of 3 doses is recommended for infants with a gestational age of 32 wk, 0 days to 34 wk, 6 days without hemodynamically significant congenital heart disease or chronic lung disease of prematurity who qualify for prophylaxis. Infants born from 32 wk, 0 days through 34 wk, 6 days of gestation who qualify for prophylaxis under the new recommendations should receive prophylaxis only until they reach 90 days of age or a maximum of 3 doses (whichever comes first).

**Vaccine**
There is no licensed vaccine against RSV. The challenge for development of live virus vaccines has been to produce attenuated vaccine strains that infect infants in the nasopharynx after topical inoculation without producing unacceptable symptoms, that remain genetically stable during shedding, and that induce protection against severe disease following reinfection. The most promising live-attenuated virus candidates have been engineered in the laboratory from cold-passaged strains of RSV, according to a basic strategy that yielded the live poliovirus and influenza virus vaccine strains. A variety of nonreplicating experimental vaccines are being tested in early clinical trials. Plans are underway to study some of the new vaccine candidates in maternal immunization trials. The rationale of such studies is to test whether boosting the serum level of RSV-neutralizing antibodies in the mother can enhance immunity in neonates following transplacental transfer of maternal antibodies to the infant.

*Bibliography is available at Expert Consult.*
Bibliography
Human metapneumovirus (HMPV) is a respiratory virus that was first identified in 2001 and has emerged as one of the most common causes of serious lower respiratory tract illness in children throughout the world.

**ETIOLOGY**

HMPV is an enveloped, single-stranded nonsegmented negative-sense RNA genome of the Paramyxoviridae family, which is divided into 2 subfamilies, Pneumovirinae and Metapneumovirinae. The Pneumovirinae subfamily includes the 2 genera Metapneumovirus and Pneumovirus, which includes respiratory syncytial virus (RSV). HMPV and the avian pneumoviruses are highly related and are separated into the separate genus Metapneumovirus because the gene order in the nonsegmented genome is slightly altered and because avian pneumoviruses/HMPVs lack the genes for 2 nonstructural proteins, NS1 and NS2, that are encoded at the 3' end of RSV genomes. These proteins are thought to counteract host type I interferons. The absence of NS1/NS2 in the metapneumoviruses may contribute to an overall slightly reduced pathogenicity relative to wild-type RSV strains.

Full-length sequences of a number of HMPV genomes have been determined. The genome encodes 9 proteins in the order 3'-N-P-M-F-M2-(orf1 and 2)-SH-G-L-5'. The genome also contains noncoding 3' leader, 5' trailer, and intergenic regions, consistent with the organization of most paramyxoviruses, with a viral promoter contained in the 3' end of the genome. The F (fusion), G (glycosylated), and SH (short hydrophobic) proteins are integral membrane proteins on the surfaces of infected cells and virion particles. The F protein is a classic type I integral membrane viral fusion protein that contains 2 heptad repeats in the extracellular domain that facilitate membrane fusion. There is a predicted protein cleavage site near a hydrophobic fusion peptide that likely is cleaved by an extracellular protease, activating the F protein for fusion. The predicted attachment (G) protein of HMPV exhibits the basic features of a glycosylated type II mucin-like protein. The HMPV G protein differs from the RSV G protein in that it lacks a cysteine noose structure. This protein may inhibit innate immune responses. The internal proteins of the virus appear similar in function to those of other paramyxoviruses.

**EPIDEMIOLOGY**

HMPV outbreaks occur in annual epidemics during late winter and early spring in temperate climates, often overlapping with the second half of the annual RSV epidemic (Fig. 261-1). Sporadic infections occur year round. The usual period of viral shedding is likely to be many days or even several weeks after primary infection in infants. The incubation period is approximately 3-5 days. Humans are the only source of virus, as there is no known animal or environmental reservoir. Transmission occurs by close or direct contact with contaminated secretions involving large-particle aerosols, droplets, or contaminated surfaces. Nosocomial infections have been reported, and contact isolation with excellent handwashing for healthcare providers is critical in medical settings. This virus affects the elderly, immunocompromised patients, and patients with reactive airways disease more severely than otherwise healthy individuals.

**PATHOLOGY**

Infection is usually limited to the superficial layer of airway epithelial cells and is associated with a local inflammatory infiltrate consisting of lymphocytes and macrophages. Immunocompromised individuals have evidence of both acute and organizing injuries during prolonged infection.

**PATHOGENESIS**

Infection occurs via inoculation of the upper respiratory tract. Infection can spread rapidly to the lower respiratory tract, but it is not clear whether the dissemination is mediated by cell-to-cell spread or aspiration of infected materials from the upper tract. Severe lower respiratory tract illness, especially wheezing, occurs mainly during the 1st yr of life, at a time when the airways are of a small diameter and high resistance. Maternal serum neutralizing antibodies that cross the placenta may afford a relative protection against severe disease for several weeks or months after birth. Once infection is established, it is likely that cytotoxic T cells recognize and eliminate virus-infected cells, thus terminating the infection but also causing some cytopathology. The virus appears to have specific mechanisms for inhibiting T-cell responses during acute infection. Individuals with an underlying predisposition to reactive airways disease (including adults) are susceptible to severe wheezing during reinfection later in life, suggesting that HMPV may cause smooth muscle hyperactivity, inflammation, or increased mucus
production in such individuals. Infection in otherwise healthy individuals resolves without apparent long-term consequences in most cases. HMPV infection is associated with exacerbations of asthma later in life.

**CLINICAL MANIFESTATIONS**

HMPV is associated with the common cold (complicated by otitis media in approximately 30% of cases) and with lower respiratory tract illnesses such as bronchiolitis, pneumonia, croup, and exacerbation of reactive airways disease. The profile of signs and symptoms caused by HMPV is very similar to that caused by RSV (Table 261-1). Approximately 5-10% of outpatient lower respiratory tract illnesses in otherwise healthy young children is associated with HMPV infection, which is second in incidence only to RSV. Children with RSV or HMPV infection require supplemental oxygen and medical intensive care at similar frequencies.

About half of the cases of HMPV lower respiratory tract illness in children occur in the 1st 6 mo of life, suggesting that young age is a major risk factor for severe disease. Both young adults and the elderly can have HMPV infection that requires medical care including hospitalization, but severe disease occurs at much lower frequencies in adults than in young children. Severe disease in older subjects is most common in immunocompromised patients and can be fatal. A significant number of both adult and pediatric patients with asthma exacerbations have HMPV infection; it is not clear whether the virus causes long-term wheezing. RSV and HMPV coinfections have been reported; coinfections may be more severe than infection with a single virus, resulting in pediatric intensive care unit admissions. It is difficult to define true coinfections because these viral genomes can be detected by reverse transcriptase polymerase chain reaction (PCR) in respiratory secretions for at least several weeks after illness, even when virus shedding has terminated.

**LABORATORY FINDINGS**

The virus can be visualized only with electron microscopy. The virus grows in primary monkey kidney cells or LLC-MK2 cell or Vero cell monolayer cultures, but efficient isolation of the virus requires an experienced laboratory technician. Conventional bright-field microscopy of infected cell monolayer cultures often reveals cytopathic effect only after multiple passages in cell culture. The characteristics of the cytopathic effect are not sufficiently distinct to allow identification of the virus on this basis alone, even by a trained observer. Direct antigen tests for identification of HMPV antigens in nasopharyngeal secretions are available but are less efficient than nucleic acid–based detection. Some laboratories have success with the use of immunofluorescence staining with monoclonal or polyclonal antibodies to detect HMPV in nasopharyngeal secretions and shell vial cultures or in monolayer cultures in which virus has been cultivated. The most sensitive test for identification of HMPV in clinical samples is reverse transcriptase PCR, usually performed with primers directed to conserved viral genes. Detection by this modality is also available in some multiplex PCR tests for panels of respiratory viruses. Real-time reverse transcriptase PCR tests offer enhanced sensitivity and specificity, including assays designed to detect viruses from the 4 known genetic lineages.

**DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS**

In temperate areas, the diagnosis should be suspected during the late winter in infants or young children with wheezing or pneumonia and a negative RSV diagnostic test result. The diseases caused by RSV and HMPV cannot be distinguished clinically. Many other common respiratory viruses, such as parainfluenza viruses, influenza viruses, adenoviruses, rhinoviruses, enteroviruses, and coronaviruses, can cause similar disease in young children. Some of these viruses can be identified by PCR genetic testing or conventional cell culture means.

**COMPLICATIONS**

Bacterial superinfection of the lower airways is unusual but does occur. The local complication of otitis media is common, likely a result of eustachian tube dysfunction caused by the virus.

**TREATMENT**

There is no specific treatment at this time for HMPV infection. Management consists of supportive care. The rate of bacterial lung infection or bacteremia associated with HMPV infection is not fully defined but is suspected to be low. Antibiotics are usually not indicated in treatment of infants hospitalized for HMPV bronchiolitis or pneumonia.
**SUPPORTIVE CARE**
Treatment is supportive and includes careful attention to hydration, monitoring of respiratory status by physical examination and measurement of oxygen saturation, use of supplemental oxygen, and, if necessary, mechanical ventilation.

**PROGNOSIS**
Most infants and children recover from acute HMPV infection without apparent long-term consequences. Many experts believe an association exists between severe HMPV infections in infancy and risk for recurrent wheezing or the development of asthma; however, it is not clear whether the virus causes these conditions or precipitates their first manifestations.

**PREVENTION**
The only method of prevention of HMPV infection is reduction of exposure. Contact precautions are recommended for the duration of HMPV-associated illness among hospitalized infants and young children. Patients known to have HMPV infection should be housed in single rooms or with a cohort of HMPV-infected patients. When feasible, it is wise to care for patients with RSV infection in a separate cohort from HMPV-infected patients, so as to prevent coinfection. Preventive measures include limiting exposure to contagious settings during annual epidemics (such as daycare centers) as much as possible and emphasis on hand hygiene in all settings, including the home, especially during periods when the contacts of high-risk children have respiratory infections. However, providers should keep in mind that infection is universal in the 1st several years of life. Therefore, reduction of exposure makes most sense during the 1st 6 mo of life, when infants are at highest risk for severe disease.

*Bibliography is available at Expert Consult.*
Bibliography


Adenoviruses

Human adenoviruses (HAdVs) are a common cause of human disease. Conjunctivitis is a familiar illness associated with HAdVs, but these viruses also cause upper and lower respiratory disease, pharyngitis, gastroenteritis, and hemorrhagic cystitis. HAdVs can cause severe disease in immunocompromised hosts. Outbreaks of febrile respiratory illness caused by HAdV-4 and HAdV-7 are a major source of morbidity in military barracks, with attack rates ranging from 25% to >90%. Spread of HAdV occurs by respiratory and fecal-oral routes. An important factor in HAdV transmission, especially in epidemics, is the ability of the nonenveloped particle to survive on inanimate objects in the environment. Nosocomial outbreaks have been reported.

ETIOLOGY

Adenoviruses were first isolated from human adenoidal surgical specimens in 1953. They are nonenveloped viruses with an icosahedral protein capsid. The double-stranded DNA genome is contained within the particle complexed with several viral proteins. Antigenic variability in surface proteins of the virion defines more than 50 serotypes grouped into 8 species. Species differ in their tissue tropism and target organs, causing distinct clinical infections (Table 262-1). HAdVs can be shed from the gastrointestinal tract for prolonged periods and can establish chronic low-level infection of the tonsils and adenoids.

CLINICAL MANIFESTATIONS

HAdVs cause a variety of common clinical syndromes in both immunocompetent and immunocompromised hosts. These syndromes are difficult to distinguish reliably from similar illnesses caused by other pathogens, such as respiratory syncytial virus, human metapneumovirus, human rhinovirus, rotavirus, group A streptococcus, and other common viral and bacterial pathogens.

Acute Respiratory Disease

Respiratory tract infections are common manifestations of HAdV infections in children and adults. HAdVs cause an estimated 5-10% of all childhood respiratory disease. Primary infections in infants may manifest as bronchiolitis or pneumonia. HAdV pneumonia may manifest as features more typical of bacterial disease (lobar infiltrates, high fever, parapneumonic effusions). HAdV-14 has recently emerged as a significant cause of severe acute respiratory disease in military and civilian populations, in some cases leading to hospitalization and death. Pharyngitis caused by HAdV typically includes symptoms of coryza, sore throat, and fever. The virus can be identified in 15-20% of

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Table 262-1 Adenovirus Types with Associated Infections

**ETIOLOGY**

Adenoviruses are nonenveloped viruses with an icosahedral protein capsid. The double-stranded DNA genome is contained within the particle complexed with several viral proteins. Antigenic variability in surface proteins of the virion defines more than 50 serotypes grouped into 8 species. Species differ in their tissue tropism and target organs, causing distinct clinical infections. HAdVs can be shed from the gastrointestinal tract for prolonged periods and can establish chronic low-level infection of the tonsils and adenoids.

**EPIDEMIOLOGY**

HAdVs circulate worldwide and cause endemic infections year-round in immunocompetent hosts. Asymptomatic infections are also common. Only about one third of all known HAdV types are associated with clinically apparent disease. The most prevalent types in recent surveillance studies are HAdV types 3, 2, 1, and 5. Epidemics of conjunctivitis (often severe), pharyngitis, and respiratory disease occur, especially in schools and military settings. Outbreaks of febrile respiratory illness caused by HAdV-4 and HAdV-7 are a major source of morbidity in military barracks, with attack rates ranging from 25% to >90%. Spread of HAdV occurs by respiratory and fecal-oral routes. An important factor in HAdV transmission, especially in epidemics, is the ability of the nonenveloped particle to survive on inanimate objects in the environment. Nosocomial outbreaks have been reported.

**PATHOGENESIS**

HAdVs bind to cell surface receptors and trigger internalization by endocytosis. Acidification of the endosome induces conformational changes in the capsid, leading to eventual translocation of the genome to the cell nucleus. Viral messenger RNA transcription and genomic replication occur in the nucleus. Lysis of the cell releases new infectious particles and causes damage to epithelial mucosa, sloughing of cell debris, and inflammation. Host responses to HAdV infection include the recruitment of neutrophils, macrophages, and natural killer cells to the site of infection and the elaboration by these cells of a number of cytokines and chemokines. This host immune response is likely to contribute to the symptoms of HAdV infection, but specific mechanisms of pathogenesis are poorly understood. The strict species specificity of the adenoviruses precludes the development of an animal model for HAdVs; consequently, mouse adenovirus is used to study adenovirus pathogenesis using a murine model.

**ETIOLOGY**

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**EPIDEMIOLOGY**

HAdVs circulate worldwide and cause endemic infections year-round in immunocompetent hosts. Asymptomatic infections are also common. Only about one third of all known HAdV types are associated with clinically apparent disease. The most prevalent types in recent surveillance studies are HAdV types 3, 2, 1, and 5. Epidemics of conjunctivitis (often severe), pharyngitis, and respiratory disease occur, especially in schools and military settings. Outbreaks of febrile respiratory illness caused by HAdV-4 and HAdV-7 are a major source of morbidity in military barracks, with attack rates ranging from 25% to >90%. Spread of HAdV occurs by respiratory and fecal-oral routes. An important factor in HAdV transmission, especially in epidemics, is the ability of the nonenveloped particle to survive on inanimate objects in the environment. Nosocomial outbreaks have been reported.

**PATHOGENESIS**

HAdVs bind to cell surface receptors and trigger internalization by endocytosis. Acidification of the endosome induces conformational changes in the capsid, leading to eventual translocation of the genome to the cell nucleus. Viral messenger RNA transcription and genomic replication occur in the nucleus. Lysis of the cell releases new infectious particles and causes damage to epithelial mucosa, sloughing of cell debris, and inflammation. Host responses to HAdV infection include the recruitment of neutrophils, macrophages, and natural killer cells to the site of infection and the elaboration by these cells of a number of cytokines and chemokines. This host immune response is likely to contribute to the symptoms of HAdV infection, but specific mechanisms of pathogenesis are poorly understood. The strict species specificity of the adenoviruses precludes the development of an animal model for HAdVs; consequently, mouse adenovirus is used to study adenovirus pathogenesis using a murine model.

**CLINICAL MANIFESTATIONS**

HAdVs cause a variety of common clinical syndromes in both immunocompetent and immunocompromised hosts. These syndromes are difficult to distinguish reliably from similar illnesses caused by other pathogens, such as respiratory syncytial virus, human metapneumovirus, human rhinovirus, rotavirus, group A streptococcus, and other common viral and bacterial pathogens.

**Acute Respiratory Disease**

Respiratory tract infections are common manifestations of HAdV infections in children and adults. HAdVs cause an estimated 5-10% of all childhood respiratory disease. Primary infections in infants may manifest as bronchiolitis or pneumonia. HAdV pneumonia may manifest as features more typical of bacterial disease (lobar infiltrates, high fever, parapneumonic effusions). HAdV-14 has recently emerged as a significant cause of severe acute respiratory disease in military and civilian populations, in some cases leading to hospitalization and death. Pharyngitis caused by HAdV typically includes symptoms of coryza, sore throat, and fever. The virus can be identified in 15-20% of
children with isolated pharyngitis, mostly in preschool children and infants.

**Ocular Infections**

Common follicular conjunctivitis caused by HAdV is self-limiting and requires no specific treatment. A more severe form, called *epidemic keratoconjunctivitis*, involves the cornea and conjunctiva. Pharyngoconjunctival fever is a distinct syndrome that includes a high temperature, pharyngitis, nonpurulent conjunctivitis, and preauricular and cervical lymphadenopathy.

**Gastrointestinal Infections**

HAdV can be detected in the stools of 5-10% of children with acute diarrhea. Most cases of acute diarrhea are self-limiting, although severe disease can occur. Enteric infection with HAdV is often asymptomatic, so the causative role in these episodes is frequently uncertain. HAdV may also cause mesenteric adenitis.

**Hemorrhagic Cystitis**

Hemorrhage cystitis consists of a sudden onset of hematuria, dysuria, frequency, and urgency with negative urine bacterial culture results. Urinalysis may show sterile pyuria in addition to red blood cells. This illness occurs more frequently in young males and typically resolves on its own in 1-2 wk.

**Other Complications**

Rarely, HAdVs are associated with myocarditis, hepatitis, or meningencephalitis in immunocompetent individuals.

**Adenoviruses in Immunocompromised Patients**

Immunocompromised persons are at high risk for severe disease caused by HAdV, particularly recipients of hematopoietic stem cell transplants (HSCTs) and solid organ transplants. These patients may experience primary HAdV infection, but reactivation of endogenous virus in a transplant recipient, as well as transmission of virus from a donor organ, may also occur. Organ failure as a consequence of pneumonia, hepatitis, gastroenteritis, and disseminated infection occurs primarily in these patients. HAdV infection in HSCT recipients commonly manifests as pulmonary or disseminated disease and is most likely to occur in the 1st 100 days after transplantation. Hemorrhagic cystitis can be severe in HSCT recipients. Infections caused by HAdV in solid organ transplanted recipients usually involve the transplanted organ. Immunocompromised children are at greater risk than immunocompromised adults for complicated HAdV infection, presumably because of a lack of preexisting immunity. Additional risk factors are T-cell–depleted grafts, high-level immunosuppression, and presence of graft-versus-host disease. Some experts advocate a preemptive screening approach to detect and treat HAdV infection early in immunocompromised patients, with the intent to prevent dissemination and severe illness in this vulnerable population.

**Diagnosis**

HAdV may be suspected as the etiology of an illness on the basis of epidemiologic or clinical features; neither of these categories is specific enough to firmly establish the diagnosis. The frequency of asymptomatic shedding of HAdV makes assigning causality to this pathogen difficult at times. Most HAdV serotypes grow well in culture, although this method requires 2-7 days and thus is not helpful for early identification. Cells from respiratory or ocular specimens can be tested using immunofluorescent staining with antibodies to detect HAdV protein. Commercially available enzyme-linked immunosassays can be used to rapidly detect HAdV in patient specimens, usually in stool. Molecular techniques, such as polymerase chain reaction, offer rapid, sensitive, and specific diagnosis of HAdV infections and are most useful clinically for the management of suspected HAdV infections in immunocompromised hosts. In these patients, measurement of *HAdV genome copy number* using quantitative real-time polymerase chain reaction can facilitate diagnosis, and repeated measurements can aid in assessing a patient’s response to treatment. Serology is generally useful only in epidemiologic investigations.

**Complications**

HAdV pneumonia can lead to respiratory failure requiring mechanical ventilation, especially in the immunocompromised patient. Secondary bacterial pneumonias do not appear to be as common following HAdV infection as they are after influenza infection, but data for this issue are limited. Severe HAdV pneumonia has been linked to chronic lung disease and bronchiolitis obliterans in a minority of cases. Epidemic keratoconjunctivitis is a sight-threatening form of HAdV infection. Nearly any form of HAdV infection can be fatal in an HSCT or solid organ transplant recipient. Refractory severe anemia requiring repeated blood transfusions can develop in HSCT recipients with hemorrhagic cystitis. Mortality rates of up to 60-80% have been reported in transplant recipients with disseminated HAdV or HAdV pneumonia.

**Treatment**

Supportive care is the mainstay of HAdV treatment in most cases. Patients with severe HAdV conjunctivitis should be referred for ophthalmologic consultation. No specific antiviral therapy produces a definite clinical benefit against HAdV infection. The nucleoside analog cidofovir has in vitro activity against most HAdV serotypes. Cidofovir is used topically to treat epidemic keratoconjunctivitis, often in conjunction with topical steroids or other immunosuppressive agents to limit the inflammatory component. Cidofovir may be used intravenously for HAdV infections in immunocompromised patients. Cidofovir is highly nephrotoxic; however, prehydration, concomitant administration of probenecid, and weekly dosing may alleviate renal toxicity. Clinical studies suggest benefit from cidofovir, but there are no prospective, randomized controlled trials of cidofovir for HAdV. In addition, no formal guidelines or recommendations for treatment exist. There are anecdotal descriptions of benefit from intravenous immunoglobulin. Adoptive immunotherapy involving the infusion of HAdV-specific T cells may also provide some benefit for immunocompromised patients with life-threatening HAdV infections, but this intervention is not yet considered standard therapy.

**Prevention**

Environmental and fomite transmission of HAdV occurs readily; therefore, simple measures such as handwashing and cleaning reduce spread. Live-attenuated HAdV-4 and HAdV-7 vaccines were used effectively in the United States military from the 1970s until 1999. Cessation of their use led to widespread outbreaks in barracks, and these vaccines have been reintroduced into military use. HAdVs are highly immunogenic and have been used as gene therapy vectors and vaccine vectors for other pathogens, including malaria and HIV, but no HAdV-specific vaccines are commercially available.

*Bibliography is available at Expert Consult.*
Bibliography
Human rhinoviruses (HRVs) are the most frequent cause of the common cold in both adults and children. Although rhinoviruses were once thought to cause only the common cold, it is now known that they are associated with lower respiratory infections in adults and children. Many HRVs do not grow in culture; studies using molecular diagnostic tools such as polymerase chain reaction (PCR) have revealed that HRVs are leading causes of both mild and serious respiratory illnesses in children.

**ETIOLOGY**
HRVs are members of the Picornaviridae family ("pico" = small; "rna" = RNA genome). Traditional methods of virus typing using immune
antiserum have identified approximately 100 serotypes, classified into HRVA and HRVB species on the basis of genetic sequence similarity. A novel group of HRVs, designated HRVCs, has been detected by reverse transcriptase PCR but has not been cultivated using conventional methods. Virus gene sequence analysis demonstrates that HRVCs are a genetically distinct and diverse species. The increased proportions of HRV reported in recent PCR-based studies are likely the result of detection of these previously unknown HRVC viruses in addition to improved detection of known HRVA and HRVB strains.

EPIDEMIOLOGY
Rhinoviruses are distributed worldwide. There is no proven correlation between serotypes and epidemiologic or clinical characteristics, although several studies suggest that HRV may be more strongly associated with lower respiratory infection and asthma than other HRVs. Multiple serotypes circulate in a community simultaneously, and particular HRV strains may be isolated during consecutive epidemic seasons, suggesting persistence in a community over an extended period. In temperate climates the incidence of HRV infection peaks in fall, with another peak in spring, but HRV infections occur year-round. HRVC appears to circulate with seasonal variation, exchanging dominance with HRVA. Rhinoviruses are the major infectious trigger for asthma among young children, and numerous studies have described a sharp increase in asthmatic attacks in this age group when school opens in the fall. Peak HRV incidence in the tropics occurs during the rainy season, from June to October.

Rhinoviruses are present in high concentrations in nasal secretions and can be detected in the lower airways. Rhinovirus particles are nonenveloped and quite hardy, persisting for hours to days in secretions on hands or other surfaces such as telephones, light switches, doorknobs, and stethoscopes. Transmission occurs when infected secretions carried on contaminated fingers are rubbed onto the nasal or conjunctival mucosa. Rhinoviruses are present in aerosols produced by talking, coughing, and sneezing. Children are the most important reservoir of the virus.

PATHOGENESIS
The majority of HRVs infect respiratory epithelial cells via intercellular adhesion molecule-1, but some HRV strains utilize the low-density lipoprotein receptor. The receptor for HRVCs is not known. Infection begins in the nasopharynx and spreads to the nasal mucosa and, in some cases, to bronchial epithelial cells in the lower airway. Rhinoviruses do not appear to cause significant direct cellular damage, so it is thought that many of the pathogenic effects are produced by the host immune response. Rhinovirus infection of bronchial epithelial cells in vitro induces the secretion of many inflammatory chemokines and cytokines. Both innate and adaptive immune mechanisms are important in HRV pathogenesis and clearance. HRV-specific nasal immunoglobulin (Ig) A can be detected on day 3 after infection, followed by the production of serum IgM and IgG after 7-8 days. Neutralizing IgG to HRV may prevent or limit the severity of illness following reinfection. Cross protection between antibodies to different HRV serotypes is limited in breadth and duration. Both allergen exposure and elevated IgE values predispose patients with asthma to more severe respiratory symptoms in response to HRV infection. Abnormalities in the host cellular response to HRV infection that result in impaired apoptosis and increased viral replication may be responsible for the severe and prolonged symptoms in individuals with asthma.

CLINICAL MANIFESTATIONS
Most HRV infections produce clinical symptoms, but approximately 15% are asymptomatic. Typical symptoms of sneezing, nasal congestion, rhinorrhea, and sore throat develop following an incubation period of 1-4 days. Cough and hoarseness are present in one third of cases. Fever is less common with HRV than with other common respiratory viruses, including influenza virus, respiratory syncytial virus, and human metapneumovirus. Symptoms are frequently more severe and last longer in children, with 70% of children still reporting symptoms by day 10, compared with 20% of adults. Virus can be shed for as long as 3 wk.

HRVs are the most prevalent agents associated with acute wheezing, otitis media, and hospitalization for respiratory illness in children and are an important cause of severe pneumonia and exacerbation of asthma or chronic obstructive pulmonary disease in adults. HRV-associated hospitalizations are more frequent in young infants than in older children and in children with a history of wheezing or asthma. HRV infection in immunocompromised hosts may be life threatening. Certain strains or species of HRV, namely HRVC, may be more pathogenic than others.

DIAGNOSIS
Culturing HRV is labor intensive and of relatively low yield; HRV has only been cultivated in polarized primary airway epithelial cell culture, a highly specialized method. Sensitive and specific diagnostic methods based on reverse transcriptase PCR are commercially available. However, because reverse transcriptase PCR tests do not identify the HRV types, it can be difficult to distinguish prolonged shedding from newly acquired infection. An important caveat of HRV detection is the fact that HRV infection can be asymptomatic, and thus the presence of the virus does not prove causality in all cases. Serology is impractical because of the great number of HRV serotypes. Presumptive clinical diagnosis based on symptoms and seasonality is not specific, because many other viruses cause similar clinical illnesses. Bacterial culture or antigen testing may exclude streptococcal pharyngitis. Rapid detection techniques for HRV might lessen the use of unnecessary antibiotics or procedures.

COMPLICATIONS
Possible complications of HRV infection include sinusitis, otitis media, asthma exacerbation, bronchiolitis, pneumonia, and, rarely, death. HRV-associated wheezing during infancy is a significant risk factor for the development of childhood asthma. This effect appears to remain until adulthood, but the mechanisms have not been elucidated. One large study determined that genetic variants at the 17q21 locus were associated with asthma in children who had experienced HRV wheezing illnesses during infancy. Further studies are required to determine the likely multiple genetic and environmental factors that contribute to HRV-related asthma.

TREATMENT
Supportive care is the mainstay of HRV treatment. The symptoms of HRV infection are commonly treated with analgesics, decongestants, antihistamines, or antitussives. Data are limited on the effectiveness of such nonprescription cold medications for children. If bacterial superinfections are highly suspected or diagnosed, antibiotics may be appropriate. Antibiotics are not indicated for uncomplicated viral upper respiratory infection. Vaccines have not been successfully developed because of the numerous HRV serotypes and limited cross protection between serotypes.

PREVENTION
Good handwashing remains the mainstay of prevention of HRV infection and should be reinforced frequently, especially in young children, the predominant “vectors” for disease.

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Coronaviruses are increasingly recognized as important human pathogens. They cause up to 15% of common colds and have been implicated in more serious diseases, including croup, asthma exacerbations, bronchiolitis, and pneumonia. Evidence also suggests that coronaviruses may cause enteritis or colitis in neonates and infants and may be
underappreciated as agents of meningitis or encephalitis. Four coronaviruses are endemic in humans: human coronaviruses (HCoVs) 229E, OC43, NL63, and HKU1. In addition, 2 epidemics of previously unknown coronaviruses caused significant respiratory distress and high mortality rates among infected individuals. The discoveries of SARS-associated coronavirus (SARS-CoV) in 2003, the cause of severe acute respiratory syndrome (SARS), and of Middle East respiratory syndrome coronavirus (MERS-CoV) in 2012, support the potential for coronaviruses to emerge from animal hosts such as bats and become important human pathogens.

ETIOLOGY
Coronaviruses are enveloped viruses of medium to large size (80-220 nm) that possess the largest known single-stranded positive-sense RNA genomes. These viruses encode the protein nsp14-ExoN, which is the first known RNA proofreading enzyme and is likely responsible for the evolution of the large and complex coronavirus genome. Coronaviruses derive their name from the characteristic surface projections of spike protein, which give a corona or crown-like appearance on negative-stain electron microscopy. Coronaviruses are organized taxonomically by a lettering system based on genomic phylogenetic relationships. Alphacoronaviruses include human coronavirus 229E (HCoV-229E) and HCoV-NL63. Betacoronaviruses include 4 human pathogens and are commonly divided into 4 lineages, without formal taxonomic recognition. HCoV-OC43 and the HCoV-HKU1 are in lineage A, while SARS-CoV falls in lineage B. Lineages C and D were exclusively comprised of bat coronaviruses until the discovery of MERS-CoV, which aligns with lineage C. Gammacoronaviruses and deltacoronaviruses presently include exclusively nonhuman pathogens.

In 2002-2003, coronaviruses received international attention during the SARS outbreak, which was responsible for more than 800 deaths in 30 countries. SARS-CoV, a novel coronavirus at the time of the epidemic, was found to be the causative agent of SARS. The detection of SARS-like coronaviruses in a live animal market in the Guangdong province in Southern China, along with serologic evidence of exposure in food handlers in the same market, suggest that these markets may have facilitated the spread of SARS-CoV to humans from an animal reservoir. Subsequent studies identified SARS-like coronaviruses in fecal specimens from asymptomatic Chinese horseshoe bats that are very closely related, but not direct precursors to, SARS-CoV. Thus, although bats are thought to be a reservoir for SARS-like coronaviruses, the precise antecedent to SARS-CoV remains to be identified.

In June 2012, another novel coronavirus, MERS-CoV, was isolated from a man with acute pneumonia and renal failure in Saudi Arabia. To date, more than 500 cases have been confirmed in Saudi Arabia, Qatar, Jordan, United Arab Emirates, Oman, Kuwait, Yemen, United States (imported), and the United Kingdom; 145 of these patients died from their infection. MERS-CoV differs from SARS in that it seems to be less communicable, although human-to-human transmission has been confirmed. MERS-CoV has been shown to use dipeptidyl peptidase 4 as a cellular receptor, a difference compared to SARS-CoV, which utilizes ACE-2. With this receptor specificity, MERS-CoV is able to infect cells from several animal lineages, including human, pig, and bat, suggesting the possibility of movement between multiple species.

EPIDEMIOLOGY
Seroprevalence studies have demonstrated that antibodies against 229E and OC43 increase rapidly during early childhood, so that by adulthood 90-100% of persons are seropositive. Although less information is available for HKU1 and NL63, available studies demonstrate similar patterns of seroconversion to these viruses during early childhood. Although some degree of strain-specific protection may be afforded by recent infection, reinfections are common and occur despite the presence of strain-specific antibodies. Attack rates are similar in different age groups. Although infections occur throughout the year, there is a peak during the winter and early spring for each of these HCoVs. In the United States, outbreaks of OC43 and 229E have occurred in 2- to 3-year alternating cycles. Independent studies of viral etiologies of upper and lower respiratory infections during the same period, but from different countries, have confirmed that all known HCoVs have a worldwide distribution. Studies using both viral culture and polymerase chain reaction (PCR) multiplex assays demonstrate that coronaviruses often occur as coinfections with other respiratory viruses, including respiratory syncytial virus, adenovirus, rhinovirus, or human metapneumovirus. Volunteer studies demonstrated that OC43 and 229E are transmitted predominantly through the respiratory route. Droplet spread appears to be most important, although aerosol transmission may also occur.

There have been no identified natural or laboratory-acquired cases of SARS-CoV since 2004, but the mechanisms of introduction, spread, and disease remain important for potential animal-to-human transmission and disease. The primary mode of SARS-CoV transmission occurred through direct or indirect contact of mucous membranes with infectious droplets or fomites. Aerosol transmission was less common, occurring primarily in the setting of endotracheal intubation, bronchoscopy, or treatment with aerosolized medications. Fecal-oral transmission did not appear to be an efficient mode of transmission, but may have occurred because of the profuse diarrhea observed in some patients. The seasonality of SARS-CoV remains unknown. SARS-CoV is not highly infectious, with generally only 2-4 secondary cases resulting from a single infected adult. During the SARS epidemic, a small number of infected individuals, “superspreaders,” transmitted infection to a much larger number of persons, but the mechanism for this high degree of spread remains unknown. In contrast, persons with mild disease, such as children younger than 12 yr of age, rarely transmitted the infection to others. Infectivity correlated with disease stage; transmission occurred almost exclusively during symptomatic disease. During the 2003 outbreak, most individuals with SARS-CoV infection were hospitalized within 3-4 days of symptom onset. Consequently, most subsequent infections occurred within hospitals and involved either healthcare workers or other hospitalized patients. MERS-CoV may begin in an animal vector (camel, bat); although person-to-person contagion has been reported, it is thought to be a minor mechanism for acquisition of the MERS-CoV.

PATHOGENESIS
Coronaviruses are reported to cause minimal cytopathology. Studies with SARS-CoV in human airway epithelial cell cultures indicate that ciliated cells are principal targets for infection and that infected ciliated cells may be directly extruded or lost from the infected monolayer. Thus, the cytopathology from other HCoVs may be from direct cell infection and loss, although symptoms may also be from the host immune response. Infection with OC43 and 229E is associated with the elaboration of cytokines, including interleukin-8 and interferon-γ. In experimentally infected volunteers, serum-specific immunoglobulin A and immunoglobulin G antibody levels peak 12-14 days after infection but decline rapidly thereafter. At 1 year following experimental infection, there is only partial protection against reinfection with the homologous strain, suggesting a challenge for the development of successful vaccines against HCoVs.

CLINICAL MANIFESTATIONS
While all known HCoVs cause respiratory disease, the role of HCoVs in gastrointestinal and neurologic disease is less clear and remains to be proven. In addition to causing severe respiratory pathology, both SARS-CoV and MERS-CoV can cause renal failure, although this symptom is observed less frequently during SARS-CoV infections.

Respiratory Infections
Even though up to 50% of respiratory tract infections with OC43 and 229E are asymptomatic, coronaviruses are still responsible for up to 15% of common colds. Cold symptoms caused by HCoVs are indistinguishable from those caused by rhinoviruses and other respiratory viruses. The average incubation period is 2-4 days, with symptoms typically lasting 4-7 days. Rhinorrhea, cough, sore throat, malaise, and headache are the most common symptoms. Fever occurs in up to 60% of cases. Coronavirus NL63 is a cause of croup in children younger than 3 yr of age. Coronavirus infections are linked to episodes of wheezing in asthmatic children, albeit at a lower frequency and...
severity than observed with rhinovirus and respiratory syncytial virus infections. Lower respiratory tract infections, including bronchiolitis and pneumonia, are also reported in immunocompetent and immunocompromised children and adults. As with respiratory syncytial virus or rhinovirus, coronavirus detection in upper respiratory infections is frequently associated with acute otitis media and can be isolated from middle ear fluid.

Nonrespiratory Sequelae
There is some evidence to support a role for coronaviruses in human gastrointestinal disease, particularly in young children. Coronavirus-like particles have been detected by electron microscopy in the stools of infants with nonbacterial gastroenteritis. In addition, several outbreaks in neonatal intensive care units of gastrointestinal disease characterized by diarrhea, bloody stools, abdominal distention, bilious gastric aspirates, and classic necrotizing enterocolitis have also been associated with the presence of coronavirus-like particles in stools. In older children and adults, coronavirus-like viruses have been observed with similar frequency in symptomatic and asymptomatic individuals, making it difficult to discern if they are pathogenic in the gastrointestinal tract. Coronaviruses are well-known causes of neurologic disease in animals, including demyelinating encephalitis, but their role in causing human neurologic disease remains unclear. They have been detected by culture, in situ hybridization, and reverse transcriptase PCR (RT-PCR) in brain tissue from a few patients with multiple sclerosis. However, coronavirus RNA has also been recovered from the spinal fluid and brain tissue of adults without neurologic disease. HCoV-OC43 has been detected by RT-PCR in the spinal fluid and nasopharynx of one child with acute disseminated encephalomyelitis.

Severe Acute Respiratory Syndrome–Associated Coronavirus
SARS-CoV infections in teenagers and adults included a viral replication phase and an immunologic phase. During the viral replication phase there was a progressive increase in viral load that reached its peak during the 2nd wk of illness. The appearance of specific antibodies coincided with peak viral replication. The clinical deterioration that typified the 2nd and 3rd wk of illness was characterized by a decline in the viral load and evidence of tissue injury likely from cytokine-mediated immunity. The explanation for milder clinical disease in children younger than 12 yr of age has not been determined. Seroepidemiologic studies suggest that asymptomatic SARS-CoV infections were uncommon. The incubation period ranged from 1-14 days, with a median of 4-6 days. The clinical manifestations were nonspecific, most commonly consisting of fever, cough, malaise, coryza, chills or rigors, headache, and myalgia. Coryza was more common in children younger than 12 yr of age, whereas systemic symptoms were seen more often in teenagers. Some young children had no respiratory symptoms. Gastrointestinal symptoms, including diarrhea and nausea or vomiting, occurred in up to one third of cases. The clinical course of SARS-CoV infection varied with age. Adults were most severely affected, with initial onset of fever, cough, chills, myalgia, malaise, and headache. Following an initial improvement at the end of the 1st wk, fever recurred and respiratory distress developed, with dyspnea, hypoxemia, and diarrhea. These symptoms progressed in 20% of patients to acute respiratory distress syndrome and respiratory failure. Acute renal failure with histologic acute tubular necrosis was present in 6.9% of patients, likely a result of hypoxic kidney damage. Of SARS patients, 28.8% had abnormal urinalysis, with viral genome detectable by quantitative RT-PCR. In contrast, children younger than 12 yr of age had a relatively mild nonspecific illness, with only a minority experiencing significant lower respiratory tract disease and illness typically lasting less than 5 days. There were no deaths or acute respiratory distress syndrome in children younger than 12 yr of age from SARS-CoV infection. Adolescents manifested increasing severity in direct correlation to increasing age; respiratory distress and hypoxemia were observed in 10-20% of patients, one third of whom required ventilator support. The case fatality rate from SARS-CoV infection during the 2003 outbreak was 10-17%. No pediatric deaths were reported. The estimated case fatality rate according to age varied from <1% for those younger than 20 yr of age to >50% for those older than 65 yr of age.

Middle East Respiratory Syndrome Coronavirus
The incubation period of HCoV-EMC infection is thought to be approximately 10 days. Because most healthcare workers caring for patients with HCoV-EMC infection have not been infected, this virus is considered to be less transmissible from person to person than SARS-CoV. Two clusters of patients have been diagnosed with confirmed cases, although it is difficult to determine if their infections were spread from person to person or if they shared a common environmental exposure. A third cluster in the United Kingdom confirmed person-to-person transmission, as only 1 of the individuals had traveled to the Arabian Peninsula. Because the method of transmission is presently unknown, appropriate airborne and contact precautions are required when treating infected patients. Patients have presented with acute respiratory infection, a fever higher than 38°C (100.4°F), cough, and pulmonary parenchymal disease such as pneumonia or acute respiratory distress syndrome. Lymphopenia, neutropenia, and late thrombocytopenia occurred in the index-case patient. This patient also had progressive renal impairment, beginning on the ninth day of symptoms which continued to progress until the patient’s death at day 11. The case fatality rate is presently >65% for the limited number of confirmed cases. Most patients have been adults, although children as young as 1 yr of age have been infected. Approximately 63% of patients have severe disease requiring hospitalization; approximately 5% had mild disease, and the remainder may have been asymptomatic.

Diagnosis
In the past, specific diagnostic tests for coronavirus infections were not available in all clinical settings. The use of conserved PCR primers for coronaviruses in multiplex RT-PCR viral diagnostic panels now allows widely available and sensitive detection of the viruses. Virus culture of primary clinical specimens remains a challenge for HCoV’s HKU1, OC43, 229E, and NL63, even though both SARS-CoV and MERS-CoV can successfully be grown in culture from respiratory samples. Serodiagnosis with complement fixation, neutralization, hemagglutination inhibition, enzyme immunoassay, and Western blots have been used in the research setting. The diagnosis of SARS-CoV infection can be confirmed by serologic testing, detection of viral RNA using RT-PCR, or isolation of the virus in cell culture. Even though serology for SARS-CoV has sensitivity and specificity approaching 100%, antibodies are not detectable until 10 days after the onset of symptoms, and immunoglobulin G seroconversion may be delayed for up to 4 wk. In addition, the SARS epidemic resulted in the inclusion of coronavirus-conserved primers in many diagnostic PCR multiplex assays such that coronaviruses may be more readily detected. For emerging coronaviruses, such as HCoV-EMC, highly conserved primers were used for initial detection, with confirmatory assays using specific primers. Thus, the mainstay of early diagnosis is RT-PCR. For all known endemic and emerging HCoVs, respiratory specimens (nasopharyngeal swabs or aspirates) are most likely to be positive, but in a setting of a possible novel coronavirus, serum or stool may be positive. Two highly sensitive real-time RT-PCR assays are currently available for testing for MERS-CoV RNA in addition to utilizing immunofluorescence microscopy for the detection of antibody response.

Treatment and Prevention
Coronavirus infections of humans are acute and self-limited, although persistent infection and shedding may occur in multiple animal models in the setting of minimal or no symptomology. There are no available antiviral agents for clinical use against coronaviruses, although strategies targeting conserved coronavirus proteases have been shown to block replication of the virus in vitro. Challenges for development of effective vaccines targeted against OC43, 229E, HKU1, and NL63 include the fact that infections are rarely life-threatening and reinfection is the rule, even in the presence of natural immunity from previous infections. Treatment of SARS-CoV and MERS-CoV infections is primarily supportive. The role of antiviral and immune-modulating
agents remains inconclusive, largely because none of these therapies have been evaluated in properly conducted randomized controlled trials. Ribavirin was extensively used during the 2003 SARS-CoV outbreak, but is of questionable benefit given its poor in vitro activity against SARS-CoV at clinically relevant concentrations. The identification of the proofreading nsp14-exonuclease suggests that this activity may be important in resistance to antiviral nucleosides and RNA mutagens such as ribavirin. Systemic corticosteroid therapy was temporally associated with clinical improvement in some patients. In another small, open-label, nonrandomized pilot study, interferon-α was associated with more rapid resolution of oxygen requirements and radiographic abnormalities. Human monoclonal antibodies derived from SARS patients demonstrate broad neutralization against early and late epidemic strains of SARS-CoV and could potentially be therapeutic.

An effective vaccine for SARS-CoV and MERS-CoV is highly desirable but not yet available. A potential vaccine target is the viral spike protein, which could be delivered as a recombinant protein or via viral or DNA vectors. This approach appears to be effective against closely related strains of SARS-CoV but not necessarily early animal or human variants. A SARS-CoV vaccine approach that recently has shown success in animal models utilized a live-engineered SARS-CoV mutant with inactivated ExoN, demonstrating attenuation and protection in a variety of aged, immunocompromised mice. Approaches for rapid development of stably attenuated live viruses or broadly immunogenic and cross-protective protein immunogens continues to be a key area for future research. Although SARS-CoV demonstrated characteristics of symptomatic transmission that made it controllable by public health measures like quarantine, these characteristics cannot be assumed for future novel HCoVs. The recent outbreak of MERS-CoV serves as a reminder that coronavirus emergence is both likely and unpredictable, making it very important to continue studies of the coronavirus replication, emergence, and transmission of coronaviruses. Additionally, strategies for rapid recovery, testing, and development of vaccines and neutralizing human monoclonal antibodies may be essential to prevent the high morbidity and mortality associated with previous epidemics.

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Diarrhea is a leading cause of childhood mortality in the world, accounting for 5-10 million deaths/yr. In early childhood, the single most important cause of severe dehydrating diarrhea is rotavirus infection. Rotavirus and other gastroenteric viruses not only are major causes of pediatric mortality but also lead to significant morbidity. Children in the United States, before vaccine was available, were estimated to have a risk of hospitalization for rotavirus diarrhea of 1:43, corresponding to 80,000 hospitalizations annually.

**ETIOLOGY**

Rotaviruses, astroviruses, caliciviruses such as the Norwalk agent, and enteric adenoviruses are the medically important pathogens of human viral gastroenteritis (see Chapter 340).

Rotaviruses are in the Reoviridae family and cause disease in virtually all mammals and birds. These viruses are wheel-like, triple-shelled icosahedrons containing 11 segments of double-stranded RNA. The diameter of the particles on electron microscopy is approximately 80 nm. Rotaviruses are classified by serogroup (A, B, C, D, E, F, and G) and subgroup (I or II). Rotavirus strains are species specific and do not cause disease in heterologous hosts. Group A includes the common human pathogens as well as a variety of animal viruses. Group B rotavirus is reported as a cause of severe disease in infants and adults in China only. Occasional human outbreaks of group C rotavirus are reported. The other serogroups infect only nonhumans.

Subgrouping of rotaviruses is determined by the antigenic structure of the inner capsid protein, VP6. Serotyping of rotaviruses, described for group A only, is determined by classic cross-neutralization testing and depends on the outer capsid glycoproteins, VP7 and VP4. The VP7 serotype is referred to as the G type (for glycoprotein). There are 10 G serotypes, of which 4 cause most illness and vary in occurrence from year to year and region to region. The VP4 serotype is referred to as the P type. There are 11 P serotypes. Although both VP4 and VP7 elicit neutralizing immunoglobulin G antibodies, the relative role of these systemic antibodies compared with that of mucosal immunoglobulin A antibodies and cellular responses in protective immunity remains unclear.

Caliciviruses, which constitute the Caliciviridae family, are small 27-35 nm viruses that are the most common cause of gastroenteritis outbreaks in older children and adults. Caliciviruses also cause a rotavirus-like illness in young infants. They are positive-sense, single-stranded RNA viruses with a single structural protein. Human caliciviruses are divided into 2 genera, the noroviruses and sapoviruses. Caliciviruses have been named for locations of initial outbreaks: Norwalk, Snow Mountain, Montgomery County, Sapporo, and others. Caliciviruses and astroviruses are sometimes referred to as small, round viruses on the basis of appearance on electron microscopy.

Astroviruses, which constitute the Astroviridae family, are important agents of viral gastroenteritis in young children, with a high incidence in both the developing and developed worlds. Astroviruses are positive-sense, single-stranded RNA viruses. They are small particles, approximately 30 nm in diameter, with a characteristic central 5- or 6-pointed star when viewed on electron microscopy. The capsid consists of 3 structural proteins. There are 8 known human serotypes.

Enteric adenoviruses are a common cause of viral gastroenteritis in infants and children. Although many adenovirus serotypes exist and are found in human stool, especially during and after typical upper respiratory tract infections (see Chapter 262), only serotypes 40 and 41 cause gastroenteritis. These strains are very difficult to grow in tissue culture. The virus consists of an 80 nm-diameter icosahedral particle with a relatively complex double-stranded DNA genome.

Aichi virus is a picornavirus that is associated with gastroenteritis and was initially described in Asia. Several other viruses that may cause diarrheal disease in animals have been postulated but are not well established as human gastroenteritis viruses. These include coronaviruses, toroviruses, and pestiviruses. The picobirnaviruses are an unclassified group of small (30 nm), single-stranded RNA viruses that have been found in 10% of patients with HIV-associated diarrhea.

**EPIDEMIOLOGY**

Worldwide, rotavirus is estimated to cause more than 111 million cases of diarrhea annually in children younger than 5 yr of age. Of these, 18 million cases are considered at least moderately severe, with approximately 500,000 deaths per year. Rotavirus causes 3 million cases of diarrhea, 80,000 hospitalizations, and 20-40 deaths annually in the United States.

Rotavirus infection is most common in winter months in temperate climates. In the United States, the annual winter peak historically spread from west to east. Unlike the spread of other winter viruses, such as influenza, this wave of increased incidence was not caused by a single prevalent strain or serotype. Since widespread adoption of vaccine, this geographic phenomenon has vanished. Typically, several serotypes predominate in a given community for 1 or 2 seasons, while nearby locations may harbor unrelated strains. Disease tends to be most severe in patients 3-24 mo of age, although 25% of the cases of severe disease occur in children older than 2 yr of age, with serologic evidence of infection developing in virtually all children by 4-5 yr of age. Infants younger than 3 mo are relatively protected by transplacental antibody and possibly breastfeeding. Infections in neonates and in adults in close
contact with infected children are generally asymptomatic. Some rotavirus strains have stably colonized newborn nurseries for years, infecting virtually all newborns without causing any overt illness.

Rotavirus and the other gastrointestinal viruses spread efficiently via a fecal-oral route, and outbreaks are common in children's hospitals and childcare centers. The virus is shed in stool at very high concentration before and for days after the clinical illness. Very few infectious virosions are needed to cause disease in a susceptible host.

The epidemiology of astroviruses is not as thoroughly studied as that of rotavirus, but these viruses are a common cause of mild to moderate watery winter diarrhea in children and infants and an uncommon pathogen in adults. Hospital outbreaks are common. Enteric adenovirus gastroenteritis occurs year-round, mostly in children younger than 2 yr of age. Nosocomial outbreaks occur but are less common than with rotavirus and astrovirus. Calicivirus is best known for causing large, explosive outbreaks among older children and adults, particularly in settings such as schools, cruise ships, and hospitals. Often a single food, such as shellfish or water used in food preparation, is identified as a source. Like astrovirus and rotavirus, caliciviruses are also commonly found in winter infantile gastroenteritis.

**PATHOGENESIS**

Viruses that cause human diarrhea selectively infect and destroy villus tip cells in the small intestine. Biopsies of the small intestines show variable degrees of villus blunting and round cell infiltrate in the lamina propria. Pathologic changes may not correlate with the severity of clinical symptoms and usually resolve before the clinical resolution of diarrhea. The gastric mucosa is not affected despite the commonly used term gastroenteritis, although delayed gastric emptying has been documented during Norwalk virus infection.

In the small intestine, the upper villus enterocytes are differentiated cells, which have both digestive functions, such as hydrolysis of disaccharides, and absorptive functions, such as the transport of water and electrolytes via glucose and amino acid cotransporters. Crypt enterocytes are undifferentiated cells that lack the brush-border hydrolytic enzymes and are net secretors of water and electrolytes. Selective viral infection of intestinal villus tip cells thus leads to (1) decreased absorption of salt and water and an imbalance in the ratio of intestinal fluid absorption to secretion, and (2) diminished disaccharidase activity and malabsorption of complex carbohydrates, particularly lactose. Most evidence supports altered absorption as the more important factor in the genesis of viral diarrhea. It has been proposed that a rotavirus nonstructural protein (NSP4) functions as an enterotoxin.

Viremia may occur often in severe, primary infections, but symptomatic extraintestinal infection is extremely rare in immunocompetent persons—although immunocompromised patients may rarely experience hepatic and renal involvement. The increased vulnerability of infants (compared with older children and adults) to severe morbidity and mortality from gastroenteritis viruses may relate to a number of factors, including decreased intestinal reserve function, lack of specific immunity, and decreased nonspecific host defense mechanisms such as gastric acid and mucus. Viral enteritis greatly enhances intestinal permeability to luminal macromolecules and has been postulated to increase the risk for food allergies.

**CLINICAL MANIFESTATIONS**

Rotavirus infection typically begins after an incubation period of <48 hr (range: 1-7 days) with mild to moderate fever as well as vomiting, followed by the onset of frequent, watery stools. All 3 symptoms are present in about 50-60% of cases. Vomiting and fever typically abate during the 2nd day of illness, but diarrhea often continues for 5-7 days. The stool is without gross blood or white blood cells. Dehydration may develop and progress rapidly, particularly in infants. The most severe disease typically occurs among children 4-36 mo of age. Malnourished children and children with underlying intestinal disease, such as short-bowel syndrome, are particularly likely to acquire severe rotavirus diarrhea. Rarely, immunodeficient children experience severe and prolonged illness. Although most newborns infected with rotavirus are asymptomatic, some outbreaks of necrotizing enterocolitis have been associated with the appearance of a new rotavirus strain in the affected nurseries.

The clinical course of astrovirus infection appears to be similar to that of rotavirus gastroenteritis, with the notable exception that the disease tends to be milder, with less significant dehydration. Adenovirus enteritis tends to cause diarrhea of longer duration, often 10-14 days. The Norwalk virus has a short (12-hr) incubation period. Vomiting and nausea tend to predominate in illness associated with the Norwalk virus, and the duration is brief, usually consisting of 1-3 days of symptoms. The clinical and epidemiologic picture of Norwalk virus often closely resembles so-called food poisoning from preformed toxins such as Staphylococcus aureus and Bacillus cereus.

**DIAGNOSIS**

In most cases, a satisfactory diagnosis can be made on the basis of the clinical and epidemiologic features. Enzyme-linked immunosorbent assays, which offer >90% specificity and sensitivity, are available for detection of group A rotavirus, caliciviruses, and enteric adenovirus in stool samples. Latex agglutination assays are also available for group A rotavirus and are less sensitive than enzyme-linked immunosorbent assay. Research tools include electron microscopy of stools, RNA polymerase chain reaction analysis to identify G and P antigens, and culture. The diagnosis of viral gastroenteritis should always be questioned in patients with persistent or high fever, blood or white blood cells in the stool, or persistent severe or bilious vomiting, especially in the absence of diarrhea.

**LABORATORY FINDINGS**

Isotonic dehydration with acidosis is the most common finding in children with severe viral enteritis. The stools are free of blood and leukocytes. Although the white blood cell count may be moderately elevated secondary to stress, the marked left shift seen with invasive bacterial enteritis is absent.

**DIFFERENTIAL DIAGNOSIS**

The differential diagnosis includes other infectious causes of enteritis, such as bacteria and protozoa. Occasionally, surgical conditions such as appendicitis, bowel obstruction, and intussusception may initially mimic viral gastroenteritis.

**TREATMENT**

Avoiding and treating dehydration are the main goals in treatment of viral enteritis. A secondary goal is maintenance of the nutritional status of the patient (see Chapters 58 and 340).

There is no routine role for antiviral drug treatment of viral gastroenteritis. Controlled studies show no benefit from antiemetics or anti-diarrheal drugs, and there is a significant risk for serious side effects with both types of agents. Antibiotics are similarly of no benefit. Immunoglobulins have been administered orally to both normal and immunodeficient patients with severe rotavirus gastroenteritis, but this treatment is currently considered experimental. Therapy with probiotic organisms such as Lactobacillus species has been shown to be helpful only in mild cases and not in dehydrating disease.

**Supportive Treatment**

Rehydration via the oral route can be accomplished in most patients with mild to moderate dehydration (see Chapters 58 and 340). Severe rehydration requires immediate intravenous therapy followed by oral rehydration. Modern oral rehydration solutions containing appropriate quantities of sodium and glucose promote optimum absorption of fluid from the intestine. There is no evidence that a particular carbohydrate source (rice) or addition of amino acids improves the efficacy of these solutions for children with viral enteritis. Other clear liquids, such as flat soda, fruit juice, and sports drinks, are inappropriate for rehydration of young children with significant stool loss. Rehydration via the oral (or nasogastric) route should be done over 6-8 hr, and feedings should be initiated immediately thereafter. Providing the rehydration fluid at a slow, steady rate, typically 5 mL/min, reduces vomiting and improves the success of oral therapy. Rehydration
solution should be continued as a supplement to make up for ongoing excessive stool loss. Initial intravenous fluids are required for the infant in shock or the occasional child with intractable vomiting.

After rehydration has been achieved, resumption of a normal diet for age has been shown to result in a more rapid recovery from viral gastroenteritis. Prolonged (>12 hr) administration of exclusive clear liquids or dilute formula is without clinical benefit and actually prolongs the duration of diarrhea. Breastfeeding should be continued even during rehydration. Selected infants may benefit from lactose-free feedings (such as soy formula and lactose-free cow’s milk) for several days, although this step is not necessary for most children. Hypocaloric diets low in protein and fat such as BRAT (bananas, rice, cereal, applesauce, and toast) have not been shown to be superior to a regular diet.

**PROGNOSIS**

Most fatalities occur in infants with poor access to medical care and are attributed to dehydration. Children may be infected with rotavirus each year during the 1st 5 yr of life, but each subsequent infection decreases in severity. Primary infection results in a predominantly serotype-specific immune response, whereas reinfection, which is usually with a different serotype, induces a broad immune response with cross-reactive heterotypic antibody. After the initial natural infection, children have limited protection against subsequent asymptomatic infection (38%) and greater protection against mild diarrhea (73%) and moderate to severe diarrhea (87%). After the second natural infection, protection increases against subsequent asymptomatic infection (62%) and mild diarrhea (75%) and is complete (100%) against moderate to severe diarrhea. After the third natural infection, there is even higher protection against subsequent asymptomatic infection (74%) and near-complete protection against even mild diarrhea (99%).

**PREVENTION**

Good hygiene reduces the transmission of viral gastroenteritis, but even in the most hygienic societies, virtually all children become infected as a result of the efficiency of infection of the gastroenteritis viruses. Good handwashing and isolation procedures can help control nosocomial outbreaks. The role of breastfeeding in prevention or amelioration of rotavirus infection may be small, given the variable protection observed in a number of studies. Vaccines offer the best hope for control of these ubiquitous infections.

**Vaccines**

A trivalent rotavirus vaccine was licensed in the United States in 1998 and was subsequently linked to an increased risk for intussusception, especially during the 3-14 day period after the 1st dose and the 3-7 day period after the 2nd dose. The vaccine was withdrawn from the market in 1999. Subsequently 2 new live, oral rotavirus vaccines have been approved in the United States after extensive safety and efficacy testing.

A live, oral, pentavalent rotavirus vaccine was approved in 2006 for use in the United States. The vaccine contains 5 reassortant rotaviruses isolated from human and bovine hosts. Four of the reassortant rotaviruses express 1 serotype of the outer protein VP7 (G1, G2, G3, or G4), and the 5th expresses the protein P1A (genotype P[8]) from the human rotavirus parent strain. The pentavalent vaccine protects against rotavirus gastroenteritis when administered as a 3 dose series at 2, 4, and 6 mo of age. The 1st dose should be administered between 6 and 12 wk of age, with all 3 doses completed by 32 wk of age. The vaccine provides substantial protection against rotavirus gastroenteritis, with primary efficacy of 98% against severe rotavirus gastroenteritis caused by G1-G4 serotypes and 74% efficacy against rotavirus gastroenteritis of any severity through the first rotavirus season after vaccination. It provides a 96% reduction in hospitalizations for rotavirus gastroenteritis through the 1st 2 yr after the 3rd dose. In a study of more than 70,000 infants, the pentavalent vaccine did not increase the risk for intussusception, although other studies suggest a slight increased risk.

Another new monovalent rotavirus vaccine was licensed in the United States and also appears to be safe and effective. It is an attenuated monovalent human rotavirus and is administered as 2 oral doses at 2 and 4 mo of age. The vaccine has 85% efficacy against severe gastroenteritis and was found to reduce hospital admissions for all diarrhea by 42%. Despite being monovalent, the vaccine is effective in prevention of all 4 common serotypes of human rotavirus.

Preliminary surveillance data on rotavirus incidence from the U.S. Centers for Disease Control and Prevention suggest that rotavirus vaccination greatly reduced the disease burden in the United States during the 2007-2008 rotavirus season. Given the incomplete vaccine coverage during this period, the results suggest a degree of “herd immunity” from rotavirus immunization. Studies from several developed countries show greater than 90% protection against severe rotavirus disease. Studies from developing countries show 50-60% protection from severe disease. Vaccine-associated disease has been reported in vaccine recipients who have severe combined immunodeficiency disease (a contraindication). In addition, vaccine-derived virus may undergo reassortment and become more virulent, producing diarrhea in unvaccinated siblings.

*Bibliography is available at Expert Consult.*
Bibliography


Human papillomaviruses (HPVs) cause a variety of proliferative cutaneous and mucosal lesions, including common skin warts, benign and malignant anogenital tract lesions, oral pharyngeal cancers, and life-threatening respiratory papillomas. Most HPV-related infections in children and adolescents are benign.

**ETIOLOGY**

The papillomaviruses are small (55 nm), DNA-containing viruses that are ubiquitous in nature, infecting most mammalian and many non-mammalian animal species. Strains are almost always species specific. More than 100 different types of HPVs have been identified through comparison of sequence homologies. The different HPV types typically cause disease in specific anatomic sites; more than 30 HPV types have been identified from genital tract specimens.

**EPIDEMIOLOGY**

HPV infections of the skin are common, and most individuals are probably infected with 1 or more HPV types at some time. There are no animal reservoirs for HPV; all transmission is presumably from person to person. There is little evidence to suggest that HPV is transmitted by fomites. Common warts, including palmar and plantar warts, are frequently seen in children and adolescents and typically infect the hands and feet, common areas of frequent minor trauma.

Human papillomavirus is the most prevalent viral sexually transmitted infection in the United States. Up to 80% of sexually active women will acquire HPV through sexual transmission; most have their first infection within 3 yr of beginning sexual intercourse. The greatest risks for HPV in sexually active adolescents is exposure to new sexual partners or having more than 1 partner, underscoring the ease of transmission of this virus through sexual contact. It is estimated that after 11 acts of sexual intercourse 100% of all HPV types will be transmitted to the other sexual partner. Couple studies show that there is high concordance in the genital area as well as between the hand and the genital area in the other partner. Whether the DNA detected in the hand is capable of transmitting infectious particles is unknown. Unlike other sexually transmitted infections, female-to-male transmission appears greater than male-to-female transmission. This may be because males in general have superficial transient infections or deposition. In turn, males do not develop an adequate immune response, so reinfections
are quite common. The prevalence of HPV in women decreases with time, suggesting immune protection, whereas in men, the prevalence of HPV remains high across all ages.

As with many other genital pathogens, perinatal transmission to newborns also occurs, but infections appear transient. Transmission from caregiver to the child during the early childhood years has also been documented but is generally transient, as with perinatal detection. It remains unclear whether these HPV DNA detections are simply deposition of caregiver DNA or true infections. Detection of HPV DNA in older preadolescent children is rare. HPV DNA detection in nonsexually active adolescents has been reported, but the reports of no sexual activity in adolescent populations can be difficult to confirm. If lesions are detected in a child older than 3 yr of age, the possibility of sexual transmission should be raised.

In adolescents, HPV DNA is most commonly detected without evidence of any lesion. Some of these detections are thought to be the result of partner deposition and hence do not represent a true infection. In older women, detection of HPV DNA is more commonly associated with a lesion. This is because the HPV DNA detected in older women reflects those HPV infections that became established persistent infections. Persistence is now the known necessary prerequisite for the development of significant precancerous lesions and cervical cancer. Approximately 15-20% of sexually active adolescents have detectable HPV at any given time and have normal cytologic findings. External genital warts are much less common, occurring in <1% of adolescents. The most common clinically detected lesion in adolescent women is the cervical lesion termed low-grade squamous intraepithelial lesion (LSIL) (Table 266-1). LSILs can be found in 25-30% of adolescents infected with HPV. LSIL is a cytologic and histologic term to reflect the benign changes caused by an active viral infection and is likely present in most, if not all, women with HPV infection. The majority of women, however, have very minute or subtle lesions not easily detected by cytology. As with HPV DNA detection, most LSILs regress spontaneously in young women and do not require any intervention or therapy. Less commonly, HPV can induce more severe cellular changes, termed high-grade squamous intraepithelial lesions (HSILs) (see Chapter 553).

Although HSILs are considered precancerous lesions, they rarely progress to invasive cancer. HSILs occur in approximately 0.4-3% of sexually active women, whereas invasive cervical cancer occurs in 8 cases per 100,000 adult women. In true virginal populations, including children who are not sexually abused, rates of clinical disease are close to zero. In the United States, there are approximately 12,000 new cases and 3,700 deaths from cervical cancer each year. Worldwide, cervical cancer is the second most common cause of cancer deaths among women.

Some infants may acquire papillomaviruses during passage through an infected birth canal, leading to recurrent juvenile laryngeal papillomatosis (also referred to as respiratory papillomatosis). Cases also have been reported after cesarean section. The incubation period for emergence of clinically apparent lesions (genital warts or laryngeal papillomas) after perinatally acquired infection is unknown but is estimated to be around 3-6 mo (see Chapter 390.2). It may be that infections can also occur during hygienic care from an infected parent.

Genital warts appearing in childhood may result from sexual abuse, with HPV transmission during the abusive contact. Genital warts may represent a sexually transmitted infection even in some very young children. Their presence is cause to suspect that possibility. A child with genital warts should therefore be provided with a complete evaluation for evidence of possible abuse (see Chapter 40.1), including the presence of other sexually transmitted infections (see Chapter 120). Presence of genital warts in a child does not confirm sexual abuse, because perinatally transmitted genital warts may go undetected until the child is older. Typing for specific genital HPV types in children is not helpful in diagnosis or to confirm sexual abuse status, because the same genital types occur in both perinatal transmission and abuse.

### PATHOGENESIS

Initial HPV infection of the cervix is thought to begin by viral invasion of the basal cells of the epithelium, a process that is enhanced by disruption of the epithelium caused by trauma or inflammation. It is thought that the virus initially remains relatively dormant because virus is present without any evidence of clinical disease. The life cycle of HPV depends on the differentiation program of keratinocytes. The pattern of HPV transcription varies throughout the epithelial layer as well as through different stages of disease (LSIL, HSIL, invasive cancer). Understanding of HPV transcription enhances understanding of its ability to behave as an oncovirus. Early region proteins, E6 and E7, function as transactivating factors that regulate cellular transformation. Complex interactions between E6- and E7-transcribed proteins and host proteins result in the perturbation of normal processes that regulate cellular DNA synthesis. The perturbations caused by E6 and E7 are primarily disruption of the antioncoprotein p53 and retinoblastoma protein (Rb), respectively, contributing to the development of anogenital cancers. Disruption of these proteins results in continued cell proliferation, even under the circumstances of DNA damage, which leads to basal cell proliferation, chromosomal abnormalities,

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**Table 266-1** Terminology for Reporting Cervical Cytology and Histology

<table>
<thead>
<tr>
<th>SQUAMOUS CELL</th>
<th>EQUIVALENT TERMINOLOGY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atypical squamous cells of undetermined significance (ASC-US)</td>
<td>Squamous atypia</td>
</tr>
<tr>
<td>Atypical squamous cells, cannot exclude HSIL (ASC-H)</td>
<td>Mild dysplasia, condylomatous atypia, HPV-related changes, koilocytic atypia, cervical intraepithelial neoplasia (CIN) 1</td>
</tr>
<tr>
<td>Low-grade squamous intraepithelial lesion (LSIL)</td>
<td>Moderate dysplasia, CIN 2, severe dysplasia, CIN 3, carcinoma in situ</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>GLANDULAR CELL</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Endometrial cells, cytologically benign, in a postmenopausal woman</td>
<td></td>
</tr>
<tr>
<td>Atypical</td>
<td></td>
</tr>
<tr>
<td>• Endocervical cells, NOS</td>
<td></td>
</tr>
<tr>
<td>• Endometrial cells, NOS</td>
<td></td>
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<tr>
<td>• Glandular cells, NOS</td>
<td></td>
</tr>
<tr>
<td>• Endocervical cells, favor neoplastic</td>
<td></td>
</tr>
<tr>
<td>• Glandular cells, favor neoplastic</td>
<td></td>
</tr>
<tr>
<td>Endocervical adenocarcinoma in situ</td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td></td>
</tr>
<tr>
<td>• Endocervical</td>
<td></td>
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<tr>
<td>• Endometrial</td>
<td></td>
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<tr>
<td>• Exeauterine</td>
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<tr>
<td>• NOS</td>
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</tbody>
</table>

NOS, not otherwise specified.
and aneuploidy, hallmarks of squamous intraepithelial lesion (SIL) development.

Evidence of productive viral infection occurs in benign lesions such as external genital warts and LSILs, with the abundant expression of viral capsid proteins in the superficial keratinocytes. The appearance of the HPV-associated koilocyte is a result of the expression of E4, a structural protein that causes collapse of the cytoskeleton. Low-level expression of E6 and E7 proteins results in cell proliferation seen in the basal cell layer of LSILs. LSILs are a manifestation of active viral replication and protein expression. In HSILs, expression of E6 and E7 predominates throughout the epithelium with little expression of the structural proteins L1 and L2. This results in the chromosomal abnormalities and aneuploidy characteristic of the higher-grade lesions. The critical events that lead to cancer have not been verified; however, several mechanisms are thought to be critical, including viral integration into the host chromosome and activation of telomerase to lengthen chromosomes and avoid physiologic cell senescence. Over 150 HPV types have been documented and are classified by degree of their DNA homology into 5 genera, with the different types having different life-cycle and disease characteristics. The predominant group is α HPV types, which are associated with cutaneous and mucosal anogenital infections and cancers. β, γ, μ, and ν cause predominantly benign cutaneous lesions but can be difficult to manage in severely immunocompromised individuals. β Types are commonly detected on the skin without any apparent lesions but are associated with the development of skin cancers in those with epidermodysplasia verruciformis or other forms of immunodeficiency. Genital lesions caused by the α HPV types may be broadly grouped into those with little to no malignant potential (low risk) and those with greater malignant potential (high risk). Low-risk HPV types 6 and 11 are most commonly found in genital warts and are rarely found isolated in malignant lesions. High-risk HPV types are those that are associated with anogenital cancers, specifically cervical cancer. HPV 16 and 18 are thought to be more oncogenic than other HPV types because they comprise 70% of cervical cancers, whereas each of the other 13 high-risk types (31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, and 73) contributes less than 1-9%. HPV 16 appears to be even more important in anal and HPV-associated oropharyngeal cancers, comprising close to 90% of these cancers. HPV 16 is also commonly found in women without lesions or in those with LSILs, making the connection with cancer confusing. Genital warts and SIL are commonly associated with the detection of multiple HPV types, including a combination of low- and high-risk HPV types. Recent data show that it is likely that a single lesion arises from a single HPV type. Detection of multiple HPV types reflects the presence of cervical and anal coexisting lesions. Almost all (95%) incident low-risk and high-risk HPV DNA detection, with or without detectable SIL, will spontaneously resolve within 1-3 yr. Although HPV 16 has a slower rate of regression than some of the other high-risk types, the majority of incident HPV 16 detection also will resolve. Data suggest that clearance of an HPV type results in natural immune protection against reinfection with that same type. Redetections of the same type are not common and when found are often associated with a history of a new sexual partner, suggesting that these are not reactivated infections but are due to new exposures. These redetections rarely result in high-grade disease. Persistent high-risk–type infections are associated with increased risk for development of HSILs and invasive cancer. Progression of HSIL to invasive cancer is still rare, with only 5-15% showing progression. Approximately 50% of HPV 16–associated HSILs and 80% of non–HPV 16 HSILs will spontaneously regress in young women. Genital and common warts in general also resolve without therapy but may take years to do so. Genital warts in only extremely rare conditions can become malignant.

Most infants with recognized genital warts are infected with the low-risk types. In contrast, children with a history of sexual abuse have a clinical picture more like that of adult genital warts, consisting of mixed low- and high-risk types. There are rare reports of HPV–associated genital malignancies occurring in preadolescent children and adolescents. On the other hand, precancerous HSILs do occur in sexually active adolescents. There is a concern that younger age of sexual debut has contributed to the increase in invasive cervical cancers seen in women younger than 50 yr of age in the United States, specifically cervical adenocarcinomas. Persistent HPV infections are considered necessary but not sufficient for the development of invasive cancers. Other risk factors for which there is relatively strong suggestive evidence of association include smoking cigarettes, prolonged oral contraceptive use, greater parity, and Chlamydia trachomatis and herpes simplex virus infections.

**CLINICAL MANIFESTATIONS**

The clinical findings in HPV infection depend on the site of epithelial infection.

**Skin Lesions**

The typical HPV-induced lesions of the skin are proliferative, papular, and hyperkeratotic. Common warts are raised circinate lesions with a keratinized surface (Fig. 266-1). Plantar and palmar warts are practically flat. Multiple warts are common and may create a mosaic pattern. Flat warts appear as small (1-5 mm), flat, flesh-colored papules.

**Genital Warts**

Genital warts may be found throughout the perineum around the anus, vagina, and urethra, as well as in the cervical, intravaginal, and intraanal areas (Fig. 266-2). Intraanal warts occur predominantly in patients who have had receptive anal intercourse, in contrast with perianal warts, which may occur in men and women without a history of anal sex. Although rare, lesions caused by genital genotypes can also be found on other mucosal surfaces, such as the conjunctiva, tongue, gingivae, and nasal mucosa. They may be single or multiple lesions and are frequently found in multiple anatomic sites, including the cervix. External genital warts can be flat, dome shaped, keratotic, pedunculated, and cauliflower shaped and may occur singly, in clusters, or as plaques. On mucosal epithelium, the lesions are softer. Depending on the size and anatomic location, lesions may be pruritic and painful, may cause burning with urination, may be friable and bleed, or may become superinfected. Adolescents are frequently disturbed by the development of genital lesions. Other rarer lesions caused by HPV of the external genital area include Bowen disease, Bowenoid papulosis, squamous cell carcinomas, Buschke-Löwenstein tumors, and vulvar intraepithelial neoplasias.

**Squamous Intraepithelial Lesions and Cancers**

Squamous intraepithelial lesions detected with cytology are usually invisible to the naked eye and require the aid of colposcopic magnification and acetic acid. With aid, the lesions appear white and show evidence of neovascularity. SILs can occur on the cervix, vagina, vulva, penis, and intraanus. Invasive cancers tend to be more exophytic, with aberrant-appearing vasculature. These lesions are rarely found in non-sexually active individuals.

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*Figure 266-1 Common warts of the left hand and the chest wall. (From Meneghini CL, Bonifaz E: An atlas of pediatric dermatology, Chicago, 1986, Year Book Medical Publishers, p. 45.)*
Laryngeal Papillomatosis

The median age at diagnosis of recurrent laryngeal papillomatosis is 3 yr. Children present with hoarseness, an altered cry, and sometimes stridor. Rapid growth of respiratory papillomas can occlude the upper airway, causing respiratory compromise. These lesions may recur within weeks of removal, requiring frequent surgery. The lesions do not become malignant unless treated with irradiation.

DIAGNOSIS

The diagnosis of external genital warts and common warts may be reliably determined by visual inspection of a lesion by an experienced observer and does not require additional tests for confirmation. A biopsy should be considered if the diagnosis is uncertain, the lesions do not respond to therapy, or the lesions worsen during therapy.

Screening for cervical cancer in young women begins with cytology, which is either performed by Papanicolaou smear or liquid-based cytology. Screening guidelines, which were updated in 2012 by the American Cancer Society and the U.S. Preventive Services Task Force, recommend to start screening at age 21 yr. Screening earlier is more likely to result in unnecessary referrals for colposcopy, because most lesions, both LSILs and HSILs in this group, are likely to regress. Updated guidelines now recommend screening with cytology every 3 yr. At 30 yr of age, screening can also include cotesting with HPV DNA. This is not recommended earlier, because HPV infections are extremely common in young women, resulting in a very-low positive-predictive value in this age group. The recommended terminology used for cytologic evaluation is based on the Bethesda system (see Table 266-1). Recent updates to terminology used for histology use similar terms. Many clinicians still prefer the World Health Organization terminology using cervical intraepithelial neoplasia (CIN) 1, 2, and 3 (see Table 266-1). Although the purpose of screening is to identify CIN 3+ lesions, the majority of these lesions are found in women who were referred for atypical squamous cells of undetermined significance (ASC-US) or LSILs on cytology. On the other hand, few CIN 3 or cancers exist in women younger than 24 yr of age. For women 21-24 yr of age, ASC-US and LSILs are treated the same. The current preferred recommendation for young women with ASC-US or LSILs is to repeat cytology every 12 mo for up to 24 mo. For persistent ASC-US or LSILs at 2 yr of follow-up, referral for colposcopy is recommended. Women 21-24 yr of age with HSIL at any visit should be referred for colposcopy and biopsy. In adult women, HSIL can be treated without histologic confirmation. However, this approach should be avoided in those 21-24 yr of age, because HSIL is often misdiagnosed in this group or will resolve spontaneously.

In women older than 21 yr of age, high-risk HPV testing is acceptable to assist in ASC-US triage. This recommendation is based on the observations that adult women with ASC-US and a positive HPV test result for high-risk types are more likely to have CIN 2/3 than women with a negative HPV test result. However, in women with ASC-US and a positive HPV test for high-risk types, repeat cytology is recommended. In women 21-24 yr of age referred for colposcopy and found to have no lesion or biopsy-confirmed LSIL after ASC-US or LSIL cytology, repeat cytology is recommended at 12 mo intervals. If ASC-US or LSIL has persisted after 2 yr or if HSIL is present at any time, referral for colposcopy is recommended. In women with biopsy-confirmed LSIL after atypical squamous cells of high grade (ASC-H) or HSIL, observation with cytology and colposcopy is recommended at 6 mo intervals for up to 2 yr. For persistent ASC-H or HSIL at 2 yr or progression at any time, treatment is recommended. Any young woman with histology-confirmed HSIL can be followed by colposcopy and cytology at 6 mo intervals if the patient is compliant. If HSIL continues to persist after 2 yr of follow-up, treatment is recommended. When CIN 3 is specified, treatment is recommended. These guidelines and updates can be found at http://www.asccp.org.

Very sensitive tests for the presence of HPV DNA, RNA, and proteins are becoming generally available, although they are not required for the diagnosis of external genital warts or related conditions. There are no indications for HPV DNA testing in women younger than 21 yr of age or children. HPV DNA testing is not recommended in women 21-24 yr of age but is acceptable for ASC-US triage.

Diagnosis of juvenile laryngeal papillomatosis (JLP) is made based on laryngeal examination.

DIFFERENTIAL DIAGNOSIS

A number of other conditions should be considered in the differential diagnosis of genital warts, including condyloma lataum, seborrheic keratoses, dysplastic and benign nevi, molluscum contagiosum, pearly penile papules, neoplasms, Bowen disease, Bowenoid papulosis, Buschke-Löwenstein tumors, and vulvar intraepithelial neoplasias.

Condyloma lataum is caused by secondary syphilis and can be diagnosed with darkfield microscopy and standard serologic tests for syphilis. Seborrheic keratoses are common, localized, hyperpigmented lesions that are rarely associated with malignancy. Molluscum contagiosum is caused by a poxvirus, is highly infectious, and is often umbilicated. Pearly penile papules occur at the penile corona and are normal variants that require no treatment.

TREATMENT

Most common (plantar, palmar, skin) warts eventually resolve spontaneously (see Chapter 667). Symptomatic lesions should be removed. Removal includes a variety of self-applied therapies, including salicylic acid preparations and provider-applied therapies (cryotherapy, laser therapy, electrosurgery). Genital warts are benign and usually remit, but only over an extended period. It is recommended that genital lesions be treated if the patient or the parent requests therapy. Treatments for genital warts are categorized into self-applied and provider-applied. No one therapy has been shown to be more efficacious than any other. Recommended patient-applied treatment regimens for external genital warts include topical podofllox, imiquimod, and sinecatechins. Podofllox 0.5% solution (using a cotton swab) or gel (using a finger) is applied to visible wart 3 times daily for up to 16 wk; the treated area should be washed with mild soap and water 6-10 hr after treatment. Sinecatechins (15% ointment) is a topical product from green tea extract used for external genital wart treatment that can be used 3 times daily for up to 16 wk. Provider-applied therapies include surgical treatments (electrosurgery, surgical excision, laser surgery) and office-based treatment (cryotherapy with liquid nitrogen or a cryoprobe, podofllox resin 10-25%, and bichloroacetic or trichloroacetic acid). Office-based treatments are usually applied once a week for 3-6 wk. Podofllox resins have lost favor to other methods because of the variability in preparations. Intrareional interferon is associated with significant adverse effects and is reserved for treatment of recalcitrant cases.

Many therapies are painful, and children should not undergo painful genital treatments unless adequate pain control is provided. Parents and
patients should not be expected to apply painful therapies themselves. None of the patient-applied therapies are approved for use during pregnancy, and podophyllin resin is contraindicated in pregnancy. For any of the nonsurgical treatments, prescription is contraindicated in a patient with any history of hypersensitivity to any product constituents.

If HPV exposure as a result of sexual abuse is suspected or known, the clinician should ensure that the child's safety has been achieved and is maintained.

When indicated, the most common treatments for CIN 2/3 are ablative and excisional treatments, including cryotherapy, laser, and loop electrosurgical excisional procedures. Once confirmed by histology with CIN 1, LSILs can be observed indefinitely. The decision to treat a persistent CIN 1 rests between the provider and patient. Risks of treatment, including premature delivery in a future pregnancy, should be discussed prior to any treatment decision. Treatment in pregnancy is not recommended unless invasive cancer is present.

JRP is commonly treated with surgical removal of lesions, but laser and microdebriders are also used.

**COMPLICATIONS**

The presence of HPV lesions in the genital area may be a cause of profound embarrassment to a child or parent. Complications of therapy are uncommon; chronic pain (vulvodynia) or hypoesthesia may occur at the treatment site. Lesions may heal with hypopigmentation or hyperpigmentation and less commonly with depressed or hypertrophic scars. Surgical therapies can lead to infection and scarring. Premature delivery and low birthweight in future pregnancies are complications of excisional therapy for CIN.

It is estimated that 5-15% of untreated CIN 3 lesions will progress to cervical cancer. Most cancer is prevented by early detection and treatment of these lesions. Despite screening, cervical cancer develops rapidly in a few adolescents and young women. The reason for the rapid development of cancer in these rare cases remains unknown, but host genetic defects are likely underlying causes. Juvenile laryngeal papillomas rarely become malignant, unless they have been treated with irradiation. Vulvar condylomas rarely become cancerous. HPV-associated cancers of the vagina, vulva, anus, penis, and oral cavity are much rarer than cervical tumors, and therefore screening for them is not currently recommended. However, anal, vaginal, and vulvar cancers are more common in women with cervical cancer; hence, it is recommended to screen women with cervical cancer for these tumors with visual and/or digital inspection.

**PROGNOSIS**

With all forms of therapy, genital warts commonly recur, and approximately half of children and adolescents require a 2nd or 3rd treatment. Recurrence is also evident in patients with Juvenile laryngeal papillomatosis. Patients and parents should be warned of this likelihood. Combination therapy for genital warts (imiquimod and podofilox) does not improve response and may increase complications. Prognosis of cervical disease is better, with 85-90% cure rates after a single treatment with the loop electrosurgical excision procedure. Cryotherapy has a slightly lower cure rate. Recalcitrant disease should prompt an evaluation and is common in immunocompromised individuals, specifically men and women infected with HIV.

**PREVENTION**

The only means of preventing HPV infection is to avoid direct contact with lesions. Condoms may reduce the risk for HPV transmission; condoms also prevent other sexually transmitted infections, which are risk factors associated with SIL development. In addition, condoms appear to hasten the regression of LSILs in women. Avoiding smoking cigarettes is important in preventing cervical cancer. Prolonged oral contraceptive use and parity have been shown to be risks for cervical cancer. However, the mechanisms associated with these factors have not been identified, and consequently no change in counseling is recommended.

HPV vaccines show efficacy against type-specific persistence and development of type-specific disease, including the cervix, vagina, vulva, and anus. A quadrivalent HPV vaccine containing types 6, 11, 16, and 18 was licensed in the United States in 2006, and a bivalent HPV vaccine containing types 16 and 18 was licensed in the United States in 2009. A 9-valent vaccine containing types 6, 11, 16, 18, 31, 33, 45, 52, and 58 has recently been approved. The efficacy of these vaccines is mediated by the development of neutralizing antibodies. Data from Sweden and Australia show a decrease in national rates of genital warts within 4 yr of implementing vaccination programs. Vaccination in the United States is recommended routinely for all girls at 11-12 yr of age and is administered intramuscularly in the deltoid region in a 3 dose series at 0, 1-2, and 6 mo. It is important that vaccination take place in children before they become sexually active, because the rate of HPV acquisition is high shortly after the onset of sexual activity. Vaccine can be given to girls as young as 9 yr of age, and a catch-up vaccination is recommended in girls 13-26 yr. Individuals who are already infected with 1 or more vaccine-related HPV types prior to vaccination are protected from clinical disease caused by the remaining vaccine HPV types. However, the vaccines are not therapeutic. The quadrivalent vaccine is also licensed to be administered in a 3 dose series to males 9 through 26 yr of age to reduce their likelihood of acquiring genital warts and developing anal dysplasia and cancer. Two doses of the vaccines have shown similar levels of immunogenicity as 3 doses. A vaccine that will cover 9 HPV high-risk types has been approved.

*Bibliography is available at Expert Consult.*
Bibliography
The arthropod-borne viral infections in North America are a group of mosquito-transmitted pathogens of several taxa causing neurologic infections or acute viral exanthems. Neuroviruses are transmitted during warmer weather in overlapping regions across most the United States and much of southern Canada.

**ETIOLOGY**

The principal causes of the arthropod-borne infections (with or without encephalitis) of North America are West Nile encephalitis (WNE), St. Louis encephalitis (SLE), Powassan (POW), a complex of California encephalitis group viruses, and, less frequently, western equine encephalitis (WEE), eastern equine encephalitis (EEE), and Colorado tick fever. Chikungunya virus is an emerging pathogen in the Western Hemisphere including the United States. The etiologic agents belong to different viral taxa: alphaviruses of the family Togaviridae (chikungunya virus, EEE, and WEE), Flaviviridae (WNE, SLE, POW), the California complex of the family Bunyaviridae (California encephalitis), and Reoviridae (Colorado tick fever virus). Alphaviruses are 69 nm, enveloped, positive-sense RNA viruses that evolved from a common Venezuelan equine encephalitis–like viral ancestor in the Western hemisphere. Flaviviruses are 40-50 nm, enveloped, positive-sense RNA viruses that evolved from a common ancestor. They are mosquito-borne (WNE, SLE) and tick-borne (POW) agents, globally distributed, and responsible for many important human viral diseases. The California serogroup, 1 of 16 Bunyavirus groups, are 75-115 nm enveloped viruses possessing a 3-segment, negative-sense RNA genome. Reoviruses are 60-80 nm double-stranded RNA viruses.

**EPIDEMIOLOGY**

**Eastern Equine Encephalitis**

In the United States, EEE is a very low incidence disease, with a median of 8 cases occurring annually in the Atlantic and Gulf States from 1964-2007 (Fig. 267-1). Transmission occurs often in focal endemic
water impoundments, irrigated farmland, and naturally flooded land provide breeding sites for *Culex tarsalis*. The virus is transmitted in a cycle involving mosquitoes, birds, and other vertebrate hosts. Humans and horses are susceptible to encephalitis. The case:infection ratio varies by age, having been estimated at 1:58 in children younger than 4 yr of age and 1:1,150 in adults. Infections are most severe at the extremes of life; one third of cases occur in children younger than 1 yr of age. Recurrent human epidemics have been reported from the Yakima Valley in Washington State and the Central Valley of California; the largest outbreak on record resulted in 3,400 cases and occurred in Minnesota, North and South Dakota, Nebraska, and Montana as well as Alberta, Manitoba, and Saskatchewan, Canada. Epizootics in horses precede human epidemics by several weeks. For the past 20 yr, only 3 cases of WEE have been reported, presumably reflecting successful mosquito abatement.

**Western Equine Encephalitis**

WEE infections occur principally in the United States and Canada west of the Mississippi River (see Fig. 267-1), mainly in rural areas where

<table>
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<tr>
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<th>WEE Human Cases</th>
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</table>

**Figure 267-1** The distribution and incidence of reported cases of eastern equine encephalitis (A), western equine encephalitis (B), St. Louis encephalitis (C), California serogroup encephalitis (D), and Powassan encephalitis (E) reported by state to the Centers for Disease Control and Prevention, 1964–2010. (From Division of Vector-Borne Diseases, Centers for Disease Control and Prevention. Available at: http://www.cdc.gov/ncidod/dvbid/arbor/arbocase.htm)
**St. Louis Encephalitis**
Cases of STLE are reported from nearly all states; the highest attack rates occur in the Gulf and central states (see Fig. 267-1). Epidemics frequently occur in urban and suburban areas; the largest, in 1975, involved 1,800 persons living in Houston, Chicago, Memphis, and Denver. Cases often cluster in areas where there is ground water or septic systems, which support mosquito breeding. The principal vectors are *Culex pipiens* and *Culex quinquefasciatus* in the central Gulf States, *Culex nigripalpus* in Florida, and *C. tarsalis* in California. STLE virus is maintained in nature in a bird–mosquito cycle. Viral amplification occurs in bird species abundant in residential areas (e.g., sparrows, blue jays, and doves). Virus is transmitted in the late summer and early fall. The case infection ratio may be as high as 1:300. Age-specific attack rates are lowest in children and highest in individuals older than age 60 yr. The most recent small outbreaks were in Florida in 1990 and Louisiana in 2001. For the past 15 yr there have been a mean of 18 cases annually.

**West Nile Encephalitis**
West Nile (WN) virus has been implicated as the cause of sporadic summertime cases of human encephalitis and meningitis in Israel, India, Pakistan, Romania, Russia, and the United States. All American WN viruses are genetically similar and are related to a virus recovered from a goose in Israel in 1998. WN virus was imported into the United States in 1999 and now survives in a broad enzootic cycle across the United States. Every state in the continental United States plus 9 provinces in Canada have reported mosquito, bird, mammalian, or human WN virus infection, most frequently during the summer or fall months (Fig. 267-2). Through the end of 2012, 35,941 total cases had been reported, 40-50% of which were neuroinvasive, with 1,439 deaths. WN virus transmission cycles appear to resemble those of Japanese encephalitis with large epizootics and human cases every 5-10 yr. WN virus has entered the blood supply through asymptomatic viremic potential blood donors. Blood banks screen for WN virus RNA. In 2012, 597 viremic potential blood donors were identified and the donation was rejected (Fig. 267-2). WN virus has also been transmitted to humans via the placenta, breast milk, and organ transplantation. Throughout its range, the virus is maintained in nature by transmission between mosquitoes of the *Culex* genus and various species of birds. In the United States, human infections are largely acquired from *C. pipiens*. Horses are the nonavian vertebrates most likely to exhibit disease with WN virus infection. During the 2002 transmission season, 14,000 equine cases were reported, with a mortality rate of 30%. Disease occurs predominantly in individuals >30 yr of age.

**Powassan Encephalitis**
POW virus is transmitted by *Ixodes cookei* among small mammals in eastern Canada and the United States; it has been responsible for 39 deaths in the United States since 2008 (see Fig. 267-1). Other ticks may transmit the virus in a wider geographic area, and there is some concern that *Ixodes scapularis* (also called *Ixodes dammini*), a competent vector in the laboratory, may become involved as it becomes more prominent in the United States.

**La Crosse/California Encephalitis**
La Crosse viral infections are endemic in the United States, occurring annually from July to September, principally in the north-central and central states (see Fig. 267-1). Infections occur in peri-domestic environments as the result of bites from *Aedes triseriatus* mosquitoes, which often breed in tree holes. The virus is maintained vertically in nature by transovarial transmission and can be spread between mosquitoes by copulation and amplified in mosquito populations by viremic infections in various vertebrate hosts. Amplifying hosts include chipmunks, squirrels, foxes, and woodchucks. A case infection ratio of 1:22-300 has been surmised. La Crosse encephalitis is principally a disease of children, who may account for up to 75% of cases. A mean of 100 cases has been reported annually for the past 10 yr.

**Colorado Tick Fever**
Colorado tick fever virus is transmitted by the wood tick *Dermaentor andersoni*, which inhabits high-elevation areas of states extending from the central plains to the Pacific coast. The tick is infected with the virus at the larval stage and remains infected for life. Squirrels and chipmunks serve as primary reservoirs. Human infections typically occur in hikers and campers in indigenous areas during the spring and early summer.

**Chikungunya Virus**
Chikungunya virus is endemic in Africa and Asia as well as parts of Latin America. It is an emerging pathogen in areas of the United States inhabited by day biting mosquitoes (*Aedes aegyti, Aedes albopictus*).

**CLINICAL MANIFESTATIONS**
The arboviruses produce symptoms of viral meningitis or encephalitis. WN virus and Colorado tick fever illnesses more commonly manifest as flulike diseases and only occasionally as encephalitides.

**Eastern Equine Encephalitis**
EEE virus infections result in fulminant encephalitis with a rapid progression to coma and death in one third of cases. In infants and children, abrupt onset of fever, irritability, and headache are followed by lethargy, confusion, seizures, and coma. High temperature, bulging fontanel, stiff neck, and generalized flaccid or spastic paralysis are observed. There may be a brief prodrome of fever, headache, and dizziness. Unlike most other viral encephalitides, the peripheral white blood cell count usually demonstrates a marked leukocytosis, and the cerebrospinal fluid (CSF) may show marked pleocytosis. Pathologic changes are found in the cortical and gray matter, with viral antigens localized to neurons. There is necrosis of neurons, neutrophilic infiltration, and perivascular cuffing by lymphocytes.

**Western Equine Encephalitis**
In WEE, there may be a prodrome with symptoms of an upper respiratory tract infection. The onset is usually sudden with chills, fever, dizziness, drowsiness, increasing headache, malaise, nausea and vomiting, stiff neck, and disorientation. Infants typically present with the sudden cessation of feeding, fussiness, fever, and protracted vomiting. Convulsions and lethargy develop rapidly. On physical examination, patients are somnolent, exhibit meningeal signs, and have generalized motor weakness and reduced deep tendon reflexes. In infants, a bulging fontanel, spastic paralysis, and generalized convulsions may be observed. On pathologic examination, disseminated small focal abscesses, small focal hemorrhages, and patchy areas of demyelination are distinctive.
St. Louis Encephalitis
Clinical manifestations of STLE vary from a mild febrile illness to fatal encephalitis. There may be a prodrome of nonspecific symptoms with subtle changes in coordination or mentation of several days to 1 wk in duration. Early signs and symptoms include fever, photophobia, headache, malaise, nausea, vomiting, and neck stiffness. About half of patients exhibit abrupt onset of weakness, incoordination, disturbed sensorium, restlessness, confusion, lethargy, and delirium or coma. The peripheral white blood cell count is modestly elevated, with 100-200 cells/μL found in the CSF. On autopsy, the brain shows scattered foci of neuronal damage and perivascular inflammation.

West Nile Encephalitis
WNE may be asymptomatic, but when clinical features appear, they include an abrupt onset of high fever, headache, myalgias, and nonspecific signs of emesis, rash, abdominal pain, or diarrhea. Most infections manifest as a febrile febrile illness, whereas a minority of patients demonstrate meningitis or encephalitis, or both. Rarely there may be cardiac dysrhythmias, myocarditis, rhabdomyolysis, optic neuritis, uveitis, retinitis, orchitis, pancreatitis, or hepatitis. WN virus disease in the United States has been accompanied by prolonged lymphopenia and an acute asymmetric polio-like paralytic illness with CSF pleocytosis involving the anterior horn cells of the spinal cord. A striking but uncommon feature has been parkinsonism and movement disorders (with tremor and myoclonus). WN virus infections have been shown to lead to chronic kidney disease in a small group of patients.

Powassan Encephalitis
POW encephalitis has occurred mostly in adults living in enzootic areas with vocational or recreational exposure; it is associated with significant long-term morbidity and has a case-fatality rate of 10-15%.

Lacrosse/California Encephalitis
The clinical spectrum includes a mild febrile illness, aseptic meningitis, and fatal encephalitis. Children typically present with a prodrome of 2-3 days with fever, headache, malaise, and vomiting. The disease evolves with clouding of the sensorium, lethargy, and, in severe cases, focal or generalized seizures. On physical examination, children are lethargic but not disoriented. Focal neurologic signs, including weakness, aphasia, and focal or generalized seizures, have been reported in 16-25% of cases. CSF shows low to moderate leukocyte counts. On autopsy, the brain shows focal areas of neuronal degeneration, inflammation, and perivascular cuffing.

Colorado Tick Fever
Colorado tick fever begins with the abrupt onset of a febrile illness, including high temperature, malaise, arthralgia and myalgia, vomiting, headache, and decreased sensorium. Rash is uncommon. The symptoms rapidly disappear after 3 days of illness. However, in approximately half of patients, a second identical episode reoccurs 24-72 hr after the first, producing the typical “saddleback” temperature curve of Colorado tick fever. Complications, including encephalitis, meningoencephalitis, and a bleeding diathesis, develop in 3-7% of infected persons and may be more common in children younger than 12 yr of age.

Chikungunya Virus
Clinical manifestations begin 3-7 days after a mosquito bite and begin abruptly with high fever and severe joint symptoms (hands, feet, ankles, wrists) that include symmetric bilateral polyarthralgia or arthritis. Most patients are symptomatic, and all ages are vulnerable. In addition, there may be headache, myalgia, conjunctivitis, weakness, lymphopenia, and a maculopapular rash. Mortality is rare; some develop prolonged joint symptoms (tenosynovitis, arthritis) lasting over a year. The acute episode lasts 7-10 days. The differential diagnosis includes dengue, West Nile, enterovirus diseases, leptospirosis, rickettsial disease, measles, parvovirus disease, rheumatologic diseases, and other alphavirus diseases in endemic areas. Figure 267-3 lists the diagnostic criteria.

DIAGNOSIS
The etiologic diagnosis of a specific arboviral infection is established by testing an acute-phase serum ≥5 days after onset of illness for the presence of virus-specific immunoglobulin (Ig) M antibodies using an indirect immunofluorescence test or an enzyme-linked immunosorbent assay IgM capture test. Alternatively, acute and convalescent sera can be tested for a 4-fold or greater increase in enzyme-linked immunosorbent assay, hemagglutination inhibition, or neutralizing IgG antibody titers. Commercial serologic diagnostic kits are marketed, especially for WN viral infections. Serum and CSF should be tested for WN virus-specific IgM. However, IgM may reflect past infection, because it may be present up to 12 mo after infection. The diagnosis may also be established by isolation in cell cultures of virus in brain tissue, obtained by brain biopsy or at autopsy, or by identification of viral RNA reverse transcriptase polymerase chain reactions.

The diagnosis of encephalitis may be aided by CT or MRI and by electroencephalography. Focal seizures or focal findings on CT or MRI or electroencephalography should suggest the possibility of herpes simplex encephalitis, which should be treated with acyclovir (see Chapter 252).

Criteria Definition
1 Clinical criteria: Acute onset of fever >38.5°C and severe arthralgia or arthritis Possible case when not explained by other medical condition: dengue or alphavirus infection, arthritic disease, endemic malaria
2 Epidemiologic criteria: Residing in or visited epidemic area within 15 days before onset of symptoms Probable case if clinical and epidemiologic criteria are met: other pathogens with similar clinical manifestations can cocirculate within the same geographic region
3 Laboratory criteria: After acute phase
• Virus isolation
• Presence of viral RNA
• Specific IgM antibodies
• Four-fold increase in IgG titers in paired samples Confirmed case if a patient tests positive for 1 of the laboratory criteria, irrespective of clinical manifestations

Figure 267-3 Diagnostic criteria for chikungunya virus fever. (From Burt FJ, Rolph MS, Rulli NE, et al: Chikungunya: a re-emerging virus, Lancet 379:662–668, 2012, Fig. 6.)
**TREATMENT**
There is no specific treatment for arboviral encephalitides, although oral ribavirin may have been of benefit in a case of La Crosse encephalitis. The treatment of acute arboviral encephalitis is intensive supportive care (see Chapter 67), including control of seizures (see Chapter 593).

**PROGNOSIS**
Fatalities occur with all arboviral encephalitides. With the exception of EEE, most resolve without residua.

**Eastern Equine Encephalitis**
The prognosis in EEE is better for patients with a prolonged prodrome; the occurrence of convulsions conveys a poor prognosis. Patient fatality rates are 33-75% and are highest in the elderly. Residual neurologic defects are common, especially in children.

**Western Equine Encephalitis**
Patient fatality rates in WEE are 3-9% and highest in the elderly. Major neurologic sequelae have been reported in up to 13% of cases and may be as high as 30% in infants. Parkinsonian syndrome has been reported as a residual in adult survivors.

**St. Louis Encephalitis**
The principal risk factor for fatal outcome of STLE is advanced age, with patient fatality rates being as high as 80% in early outbreaks. In children, mortality rates are 2-5%. In adults, underlying hypertensive cardiovascular disease has been a risk factor for fatal outcome. Recovery from STLE is usually complete, but the rate of serious neurologic sequelae has been reported to as high as 10% in children.

**West Nile Encephalitis**
Cases and deaths caused by WNE occur mainly in the elderly, although many serologic surveys show that persons of all ages are infected. In 2012, among a total of 5,387 human cases, 2,734 were neuroinvasive disease, which resulted in 243 deaths, an 8.9% mortality rate (Fig. 267-4). Paralysis may result in permanent weakness.

**Powassan Encephalitis**
In a limited experience, POW encephalitis has occurred mainly in adults with vocational or recreational exposure and has a high fatality rate.

**La Crosse or California Encephalitis**
Recovery from California encephalitis is usually complete. The case fatality rate is approximately 1%.

**Colorado Tick Fever**
Recovery from Colorado tick fever is usually complete. Three deaths have been reported, all in persons with hemorrhagic signs.

**Chikungunya**
The incidence of febrile convulsions is high in infants. Prognosis is generally good, although in large outbreaks in Africa and India severe disease and deaths have been attributed to chikungunya infections, predominantly in adults.

**PREVENTION**
Killed EEE, WEE, and WNE vaccines are available for horses, and an experimental killed vaccine is administered to human laboratory workers who handle EEE virus. Flocks of sentinel chickens or pheasants have been stationed at various locations along the Atlantic coast during the late summer or early fall to obtain early warning of increased transmission of EEE virus. No human vaccine is licensed for arboviral encephalitides, although several WNE vaccines are in late-stage development. Killed WNE vaccines are licensed for veterinary use. Protection against CHIK is attained by avoiding bites by vector mosquitoes. These bite during daytime hours in and around human habitations (see Chapter 269).

**Bibilography** is available at Expert Consult.
Bibliography


Globally, the principal causes of arboviral encephalitis are Venezuelan equine encephalitis (VEE), Japanese encephalitis (JE), West Nile fever (WN), and tickborne encephalitis (TBE) (Table 268-1). Other widespread arboviral infections include chikungunya (CHIK) and dengue (DEN) (see Chapter 269).
### Table 268-1 Vectors and Geographic Distribution of Arboviral Encephalitis Outside North America

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<th>VECTOR</th>
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<td>Togavirus</td>
<td>Venezuelan equine encephalitis</td>
<td>Culex and others</td>
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### 268.1 Venezuelan Equine Encephalitis

Scott B. Halstead

The VEE virus was isolated from an epizootic in Venezuelan horses in 1938. Human cases were first identified in 1943. Hundreds of thousands of equine and human cases have occurred over the past 70 yr. During 1971, epizootics moved through Central America and Mexico to southern Texas. After 2 decades of quiescence, epizootic disease emerged again in Venezuela and Colombia in 1995.

### ETIOLOGY

VEE is an alphavirus of the family Togaviridae. VEE circulates in nature in 6 subtypes. Virus types I and III have multiple antigenic variants. Types IAB and IC have caused epizootics and human epidemics.

### EPIDEMIOLOGY

The majority of epizootics resulting from types IAB and IC have occurred in Venezuela and Colombia. The virus resides in ill-defined sylvatic reservoirs in the South American rain forests. Known hosts include rodents and aquatic birds with transmission by Culex melanoconion species. Vectors for horse-to-horse and horse-to-human transmission include Aedes taeniorhynchus and Psorophora confinis. Epizootics move rapidly, up to several miles per day. Human cases are proportional to and follow epizootic occurrences. Viremia levels in human blood are high enough to infect mosquitoes. Because virus can be recovered from human pharyngeal swabs, and household attack rates are often as high as 50%, it is widely believed that person-to-person transmission occurs, although direct evidence is lacking. Virus types II-VI are restricted to relatively small foci; each has a unique vector–host relationship and rarely results in human infections.

### CLINICAL MANIFESTATIONS

The incubation period is 2-5 days, followed by the abrupt onset of fever, chills, headache, sore throat, myalgia, malaise, prostration, photophobia, nausea, vomiting, and diarrhea. In 5-10% of cases, there is a biphasic illness; the 2nd phase is heralded by seizures, projectile vomiting, ataxia, confusion, agitation, and mild disturbances in consciousness. There is cervical lymphadenopathy and conjunctival suffusion. Cases of meningoencephalitis may demonstrate cranial nerve palsy, motor weakness, paralysis, seizures, and coma. Microscopic examination of tissues reveals inflammatory infiltrates in lymph nodes, spleen, lung, liver, and brain. Lymph nodes show cellular depletion, necrosis of germinal centers, and lymphphogocytosis. The liver shows patchy hepatocellular degeneration, the lungs demonstrate a diffuse interstitial pneumonia with intraalveolar hemorrhages, and the brain shows patchy cellular infiltrates.

### DIAGNOSIS

The etiologic diagnosis of VEE is established by testing an acute-phase serum collected early in the illness for the presence of virus-specific immunoglobulin (Ig) M antibodies or, alternatively, demonstrating a 4-fold or greater increase in IgG antibody titers by testing paired acute and convalescent sera. The virus can also be identified by isolation in tissue cultures or recovery of viral RNA by polymerase chain reaction.

### TREATMENT

There is no specific treatment for VEE. The treatment is intensive supportive care (see Chapter 67), including control of seizures (see Chapter 593).

### PROGNOSIS

In patients with VEE meningoencephalitis, the fatality rate ranges from 10-25%. Sequelae include nervousness, forgetfulness, recurrent headache, and easy fatigability.

### PREVENTION

Several veterinary vaccines are available to protect equines. VEE virus is highly infectious in laboratory settings, and biosafety level 3 containment should be used. An experimental vaccine is available for use in laboratory workers. Several vaccine constructs are in the pipeline for potential use in humans.

Bibliography is available at Expert Consult.

### 268.2 Japanese Encephalitis

Scott B. Halstead

Epidemics of encephalitis were reported in Japan from the late 1800s.

### ETIOLOGY

JE virus is a positive-sense, single-stranded RNA virus of the family Flaviviridae.

### EPIDEMIOLOGY

JE is a mosquito-borne viral disease of humans as well as horses, swine, and other domestic animals that causes human infections and acute disease in a vast area of Asia, northern Japan, Korea, China, Taiwan, the Philippines, and the Indonesian archipelago and from Indochina through the Indian subcontinent. Culex tritaeniorhynchus sumnarosus, a nightbiting mosquito that feeds preferentially on large domestic animals and birds but only infrequently on humans, is the principal vector of zoonotic and human JE in northern Asia. A more complex ecology prevails in southern Asia. From Taiwan to India, C. tritaeniorhynchus and members of the closely related Culex vishnui group are vectors. Before the introduction of JE vaccine, summer outbreaks of JE occurred regularly in Japan, Korea, China, Okinawa, and Taiwan. Over the past decade, there has been a pattern of steadily enlarging recurrent seasonal outbreaks in Vietnam, Thailand, Nepal, and India, with small outbreaks in the Philippines, Indonesia, and the northern tip of Queensland, Australia. Seasonal rains are accompanied by increases in mosquito populations and JE transmission. Pigs serve as an amplifying host.

The annual incidence in endemic areas ranges from 1-10 per 10,000 population. Children younger than 1.5 yr of age are principally affected, with nearly universal exposure by adulthood. The case:infection ratio for JE virus has been variously estimated at 1:25 to 1:1,000. Higher ratios have been estimated for populations indigenous to enzootic areas. JE occurs in travelers visiting Asia; therefore, a travel history in the diagnosis of encephalitis is critical.
Bibliography
CLINICAL MANIFESTATIONS

After a 4-14 day incubation period, cases typically progress through the following 4 stages: prodromal illness (2-3 days), acute stage (3-4 days), subacute stage (7-10 days), and convalescence (4-7 wk). Onset may be characterized by abrupt onset of fever, headache, respiratory symptoms, anorexia, nausea, abdominal pain, vomiting, and sensory changes, including psychotic episodes. Grand mal seizures are seen in 10-24% of children with JE; parkinsonian-like nonintention tremor and cogwheel rigidity are seen less frequently. Particularly characteristic are rapidly changing central nervous system signs (e.g., hyperreflexia followed by hyporeflexia or plantar responses that change). The sensory status of the patient may vary from confusion through disorientation and delirium to somnolence, progressing to coma. There is usually a mild pleocytosis (100-1,000 leukocytes/μL) in the cerebrospinal fluid, initially polymorphonuclear but in a few days predominantly lymphocytic. Albuminuria is common. Fatal cases usually progress rapidly to coma, and the patient dies within 10 days.

DIAGNOSIS

JE should be suspected in patients reporting exposure to night-biting mosquitoes in endemic areas during the transmission season. The etiologic diagnosis of JE is established by testing acute-phase serum collected early in the illness for the presence of virus-specific IgM antibodies or, alternatively, demonstrating a fourfold or greater increase in IgG antibody titers by testing paired acute and convalescent sera. The virus can also be identified by polymerase chain reaction.

TREATMENT

There is no specific treatment for JE. The treatment is intensive supportive care (see Chapter 67), including control of seizures (see Chapter 593).

PROGNOSIS

Patient fatality rates for JE are 24-42% and are highest in children 5-9 yr of age and in adults older than 65 yr of age. The frequency of sequelae is 5-70% and is directly related to the age of the patient and severity of disease. Sequelae are most common in patients younger than 10 yr at the onset of disease. The more common sequelae are mental deterioration, severe emotional instability, personality changes, motor abnormalities, and speech disturbances.

PREVENTION

Travelers to endemic countries who plan to be in rural areas of the endemic region during the expected period of seasonal transmission and travelers in rural areas experiencing endemic transmission should receive JE vaccine. An inactivated vaccine manufactured in Japan by intracerebral injection of young mice and available throughout the world has been taken off the market owing to a high incidence of adverse events. In 2008-2009, tissue culture–based JE vaccine (Ixiaro) was licensed in Europe, Australia, and the United States. In the United States, this vaccine (also called IC51) is licensed for use in children and adults and is distributed by Novartis (Basel). For this vaccine, JE virus is grown in Vero cells, then formalin inactivated and administered intramuscularly as 2 doses of 0.5 mL each, 28 days apart. The final dose should be completed at least 1 wk prior to the patient's expected arrival in a JE endemic area. This vaccine contains alum and protamine sulfate and has exhibited only mild adverse events. A highly efficacious live-attenuated single-dose JE vaccine developed in China for children is licensed and marketed in some Asian countries. This vaccine can be coadministered with live-attenuated measles vaccine without altering the immune responses to either vaccine. In humans, prior dengue virus infection provides partial protection from clinical JE.

Personal measures should be taken to reduce exposure to mosquito bites, especially for short-term residents in endemic areas. They consist of avoiding evening outdoor exposure, using insect repellents, covering the body with clothing, and using bed nets or house screening.

Commercial pesticides, widely used by rice farmers in Asia, are effective in reducing populations of C. tritaeniorhynchus. Fenitrothion, and phenthoate are effectively adulticidal and larvicidal. Insecticides may be applied from portable sprayers or from helicopters or light aircraft.

Bibliography is available at Expert Consult.

268.3 Tickborne Encephalitis

Scott B. Halstead

TBE is widespread in Europe, where it has also been identified as the cause of milkborne encephalitis.

ETIOLOGY

TBE virus is a positive-sense, single-stranded RNA virus of the family Flaviviridae.

EPIDEMIOLOGY

TBE refers to neurotropic tick-transmitted flaviviral infections occurring across the Eurasian land mass. In the Far East, the disease is called Russian spring-summer encephalitis; the milder, often biphasic form in Europe is simply called TBE. TBE is found in all countries of Europe except Portugal and the Benelux countries. The incidence is particularly high in Austria, Poland, Hungary, Czech Republic, Slovakia, former Yugoslavia, and Russia. The incidence tends to be very focal. Seroprevalence is as high as 50% in farm and forestry workers. The majority of cases occur in adults, but even young children may be infected while playing in the woods or on picnics or camping trips. The seasonal distribution of cases is midsummer in southern Europe, with a longer season in Scandinavia and the Russian Far East. TBE can be excreted from the milk of goats, sheep, or cows. Before World War II, when milk was consumed unpasteurized, milkborne cases of TBE were common.

Viruses are transmitted principally by hard ticks of Ixodes ricinus in Europe and Ixodes persulcatus in the Far East. Viral circulation is maintained by a combination of transmission from ticks to birds, rodents, and larger mammals and transtadial transmission from larval to nymphal and adult stages. In some parts of Europe and Russia, ticks feed actively during the spring and early fall, giving rise to the name “spring-summer encephalitis.”

CLINICAL MANIFESTATIONS

After an incubation period of 7-14 days, the European form begins as an acute nonspecific febrile illness that is followed in 5-30% of cases by meningoencephalitis. The Far Eastern variety more often results in encephalitis with higher case fatality and sequelae rates. The 1st phase of illness is characterized by fever, headache, myalgia, malaise, nausea, and vomiting for 2-7 days. Fever disappears and after 2-8 days may return accompanied by vomiting, photophobia, and signs of meningeal irritation in children and more severe encephalitic signs in adults. This phase rarely lasts more than 1 wk.

DIAGNOSIS

The diagnosis of TBE should be suspected in any patient reporting a tick bite in an endemic area during the transmission season. The etiologic diagnosis of TBE is established by testing acute-phase serum collected early in the illness for the presence of virus-specific IgM antibodies or, alternatively, demonstrating a 4-fold or greater increase in IgG antibody titers by testing paired acute and convalescent sera. The virus can also be identified by polymerase chain reaction. With widespread use of vaccines, an IgM titer of >500 arbitrary units in early convalescent serum has been recommended for the diagnosis of acute TBE.

TREATMENT

There is no specific treatment for TBE. The treatment is intensive supportive care (see Chapter 67), including control of seizures (see Chapter 593).

PROGNOSIS

The main risk for fatal outcome is advanced age; the fatality rate in adults is approximately 1%, but sequelae in children are rare. Transient
Bibliography


unilateral paralysis of an upper extremity is a common finding in adults. Common sequelae include chronic fatigue, headache, sleep disorders, and emotional disturbances.

**PREVENTION**
Specific immunoglobulin has been given to persons with seasonal tick bite exposure, although efficacy of this preventive therapy is not well studied. Effective inactivated vaccines for human use, made from virus grown in tissue culture, are licensed in Russia and Europe. They are administered in a 3 dose series.

Bibliography is available at Expert Consult.

**268.4 West Nile Encephalitis**
See Chapter 267.
Bibliography


Dengue fever is a benign syndrome caused by several arthropod-borne viruses and is characterized by biphasic fever, myalgia or arthralgia, rash, leukopenia, and lymphadenopathy. Dengue hemorrhagic fever (Philippine, Thai, or Singapore hemorrhagic fever; hemorrhagic dengue; acute infectious thrombocytopenic purpura) is a severe, often fatal, febrile disease caused by 1 of 4 dengue viruses. It is characterized by capillary permeability, abnormalities of hemostasis, and, in severe cases, a protein-losing shock syndrome (dengue shock syndrome), which is thought to have an immunopathologic basis.

ETIOLOGY
There are at least 4 distinct antigenic types of dengue virus (dengue 1, 2, 3, and 4), members of the family Flaviviridae. In addition, 3 other arthropod-borne viruses (arboviruses) cause similar or identical febrile diseases with rash (Table 269-1).

EPIDEMIOLOGY
Dengue viruses are transmitted by mosquitoes of the Stegomyia family. *Aedes aegypti,* a daytime biting mosquito, is the principal vector, and all 4 virus types have been recovered from it. In most tropical areas, *A. aegypti* is highly urbanized, breeding in water stored for drinking or bathing and in rainwater collected in any container. Dengue viruses have also been recovered from *Aedes albopictus,* as in the 2001 Hawaiian epidemic, whereas outbreaks in the Pacific area have been attributed to several other *Aedes* species. These species breed in water trapped in vegetation. In Southeast Asia and West Africa, dengue virus may be maintained in a cycle involving canopy-feeding jungle monkeys and *Aedes* species, which feed on monkeys.

Epidemics were common in temperate areas of the Americas, Europe, Australia, and Asia until early in the 20th century. Dengue fever and dengue-like disease are now endemic in tropical Asia, the South Pacific Islands, northern Australia, tropical Africa, the Arabian Peninsula, the Caribbean, and Central and South America. Dengue fever occurs frequently among travelers to these areas. Locally acquired disease has been reported in Florida and Texas, and imported cases in the United States occur in travelers to endemic areas. More than 390 million dengue infections occur annually; approximately 96 million have clinical disease.

Dengue outbreaks in urban areas infested with *A. aegypti* may be explosive; up to 70-80% of the population may be involved. Most overt disease occurs in older children and adults. Because *A. aegypti* has a limited flight range, spread of an epidemic occurs mainly through viremic human beings and follows the main lines of transportation. Sentinel cases may infect household mosquitoes; a large number of nearly simultaneous secondary infections give the appearance of a contagious disease. Where dengue is endemic, children and susceptible foreigners may be the only persons to acquire overt disease, as adults have become immune.

Dengue-like diseases may occur in epidemics. Epidemiologic features depend on the vectors and their geographic distribution (see Table 269-1). Chikungunya virus is enzootic throughout much of West, Central, and South Africa as well as Central America and recently the southern United States. Periodic introductions of virus into the urban transmission cycle have led to pandemics, resulting in widespread endemcity in the most populous areas of Asia. In Asia, *A. aegypti* is the principal vector; in Africa, other Stegomyia species may be important vectors. In Southeast Asia, dengue and chikungunya outbreaks occur concurrently. Outbreaks of o’nyong-nyong fever usually involve villages or small towns, in contrast to the urban outbreaks of dengue and chikungunya. West Nile virus is enzootic in Africa. Chikungunya is now endemic in urban cycles in tropical countries throughout the world. Intense transmission in Caribbean countries presages emergence of chikungunya into the United States.

Dengue Hemorrhagic Fever
Dengue hemorrhagic fever occurs where multiple types of dengue virus are simultaneously or sequentially transmitted. It is endemic in all of tropical America and Asia, where warm temperatures and the practices of water storage in homes plus outdoor breeding sites result in large, permanent populations of *A. aegypti* species, which feeds on monkeys. Under these conditions, infections with dengue viruses of all types are common. A first infection, referred to as a primary infection, may be followed by infection with a different dengue virus, referred to as a secondary infection. In areas of high endemicity secondary infections are frequent.

Secondary dengue infections are relatively mild in the majority of instances, ranging from an inapparent infection through an undifferentiated upper respiratory tract or dengue-like disease, but may also progress to dengue hemorrhagic fever. Nonimmune foreigners, both adults and children, who are exposed to dengue virus during outbreaks of hemorrhagic fever have classic dengue fever or even milder disease. The differences in clinical manifestations of dengue infections between natives and foreigners in Southeast Asia are related more to immunologic status than to racial susceptibility. Dengue hemorrhagic fever can occur during primary dengue infections, most frequently in infants whose mothers are immune to dengue. Dengue hemorrhagic fever or severe dengue occurs rarely in individuals of African ancestry because of an as yet
undiscovered resistance gene that would explain the low incidence of severe dengue throughout much of Africa and among African populations in the American tropics despite high rates of dengue infection.

**PATHOGENESIS**

Fatalities with chikungunya and West Nile fever infections are not common but have been ascribed to viral encephalitis.

The pathogenesis of dengue hemorrhagic fever is incompletely understood, but epidemiologic studies suggest that it is usually associated with second heterotypic infections with dengue types 1-4. Retrospective studies of sera from human mothers whose infants acquired dengue hemorrhagic fever and prospective studies in children acquiring sequential dengue infections have shown that the circulation of infection-enhancing antibodies at the time of infection is the strongest risk factor for development of severe disease. Absence of cross-reactive neutralizing antibodies and presence of enhancing antibodies from passive transfer or active production are the best correlates of risk for dengue hemorrhagic fever. Monkeys that are infected sequentially or are receiving small quantities of enhancing antibodies have enhanced viremias. In humans studied early during the course of secondary dengue infections, viremia levels directly predicted disease severity. When dengue virus immune complexes attach to macrophage Fc receptors, a signal is sent that suppresses innate immunity, resulting in enhanced viral production. In the Americas, dengue hemorrhagic fever and dengue shock syndrome have been associated with dengue types 1-4 strains of recent Southeast Asian origin. Recent occurrences of sizable dengue hemorrhagic fever outbreaks in India, Pakistan, and Bangladesh also appear to be related to imported dengue strains.

Early in the acute stage of secondary dengue infections, there is rapid activation of the complement system. Shortly before or during shock, blood levels of soluble tumor necrosis factor receptor, interferon-γ, and interleukin-2 are elevated. C1q, C3, C4, C5-C8, and C3 proactivators are depressed, and C3 catabolic rates are elevated. These factors, the virus itself, or viral nonstructural protein 1 (NS1) may interact with endothelial cells, blood clotting factors, and platelets to produce increased vascular permeability. The blood clotting and fibrinolytic systems are activated, and levels of factor XII (Hageman factor) are depressed. The mechanism of bleeding in dengue hemorrhagic fever is not known, but a mild degree of disseminated intravascular coagulopathy, liver damage, and thrombocytopenia may operate synergistically. Capillary damage allows fluid, electrolytes, small proteins, and, in some instances, red blood cells to leak into extravascular spaces. This internal redistribution of fluid, together with deficits caused by fasting, thirsting, and vomiting, results in hemoconcentration, hypovolemia, increased cardiac work, tissue hypoxia, metabolic acidosis, and hypotension.

Usually no pathologic lesions are found to account for death. In rare instances, death may be a result of gastrointestinal or intracranial hemorrhages. Minimal to moderate hemorrhages are seen in the upper gastrointestinal tract, and petechial hemorrhages are common in the interventricular septum of the heart, on the pericardium, and on the suberosal surfaces of major viscera. Focal hemorrhages are occasionally seen in the lungs, liver, adrenals, and subarachnoid space. The liver is usually enlarged, often with fatty changes. Yellow, watery, and at times blood-tinged effusions are present in serous cavities in approximately 75% of patients at autopsy.

Dengue virus is frequently absent in tissues at the time of death; viral antigens or RNA have been localized to hepatocytes and macrophages in liver, spleen, lung, and lymphatic tissues.

**CLINICAL MANIFESTATIONS**

**Dengue Fever**

The incubation period is 1-7 days. The clinical manifestations are variable and are influenced by the age of the patient. In infants and young children, the disease may be undifferentiated or characterized by fever for 1-5 days, pharyngeal inflammation, rinitis, and mild cough. A majority of infected older children and adults experience sudden onset of fever, with temperature rapidly increasing to 39.4-41.1°C (103-106°F), usually accompanied by frontal or retroorbital pain, particularly when pressure is applied to the eyes. Occasionally, severe back pain precedes the fever (back-break fever). A transient, macular, generalized rash that blanches under pressure may be seen during the 1st 24-48 hr of fever. The pulse rate may be slow relative to the degree of fever. Myalgia and arthralgia occur soon after the onset of fevers and increase in severity over time. Joint symptoms may be particularly severe in patients with chikungunya or o’nyong-nyong infection. From the 2nd-6th day of fever, nausea and vomiting are apt to occur, and generalized lymphadenopathy, cutaneous hyperesthesia or hyperalgesia, taste aberrations, and pronounced anorexia may develop.

Approximately 1-2 days after defervescence, a generalized, morbilliform, maculopapular rash appears that spares the palms and soles. It disappears in 1-5 days; desquamation may occur. Rarely there is edema of the palms and soles. About the time this second rash appears, the body temperature, which has previously decreased to normal, may become slightly elevated and demonstrate the characteristic biphasic temperature pattern.

**Dengue Hemorrhagic Fever**

Differences between dengue fever and dengue hemorrhagic fever is difficult early in the course of illness. A relatively mild 1st phase with abrupt onset of fever, malaise, vomiting, headache, anorexia, and cough may be followed after 2-5 days by rapid clinical deterioration and collapse. In this 2nd phase, the patient usually has cold, clammy extremities, a warm trunk, flushed face, diaphoresis, restlessness, irritability, midepigastic pain, and decreased urinary output. Frequently, there are scattered petechiae on the forehead and extremities; spontaneous ecchymoses may appear, and easy bruising and bleeding at sites of venipuncture are common. A macular or maculopapular rash may appear, and there may be circumoral and peripheral cyanosis. Respirations are rapid and often labored. The pulse is weak, rapid, and thready, and the heart sounds are faint. The liver may enlarge to 4-6 cm below the costal margin and is usually firm and somewhat tender. Approximately 20-30% of cases of dengue hemorrhagic fever are complicated by shock (dengue shock syndrome). Dengue shock can be subtle, arising in patients who are fully alert, and is accompanied by increased peripheral vascular resistance and raised diastolic blood pressure. Shock is not from congestive heart failure but from venous pooling. With increasing cardiovascular compromise, diastolic pressure rises toward the systolic level and the pulse pressure narrows. Fewer than 10% of patients have gross ecchymosis or gastrointestinal bleeding, usually after a period of uncorrected shock. After a 24-36 hr period of crisis, convalescence is fairly rapid in the children who recover. The temperature may return to normal before or during the stage of shock. Bradycardia and ventricular extrasystoles are common during convalescence.

**DIAGNOSIS**

A clinical diagnosis of dengue fever derives from a high index of suspicion and knowledge of the geographic distribution and environmental cycles of causal viruses. Because clinical findings vary and there are many possible causative agents, the term dengue-like disease should be used until a specific diagnosis is established. A case is confirmed by isolation of the virus, viral antigen, or genome by polymerase chain reaction analysis, as well as demonstration of a 4-fold or greater increase in antibody titers. A probable case is a typical acute febrile illness with supportive serology and occurrence at a location where there are confirmed cases.

The World Health Organization criteria for dengue hemorrhagic fever are fever (2-7 days in duration or biphasic), minor or major hemorrhagic manifestations, thrombocytopenia (≤100,000/µL), and objective evidence of increased capillary permeability (hematocrit increased by ≥20%), pleural effusion or ascites (by chest radiography or ultrasonography), or hypoalbuminemia. Dengue shock syndrome criteria include those for dengue hemorrhagic fever as well as hypotension, tachycardia, narrow pulse pressure (<20 mm Hg), and signs of poor perfusion (cold extremities).

In 2009, the World Health Organization promulgated new guidelines for the diagnosis of probable dengue, dengue with warning signs, and a category called “severe dengue.” Occurrence of warning signs in an individual with probable dengue should alert the physician to the need for hospitalization. Severe dengue is a mixture of syndromes associated
with dengue infection. This includes classical dengue hemorrhagic fever and dengue shock syndrome, but also rare instances of encephalitis or encephalopathy associated with dengue infection. Severe dengue also includes respiratory distress that may be a harbinger of pulmonary edema caused by overhydration, an all too common outcome of inept treatment (see “Treatment” and “Complications” sections).

Virologic diagnosis can be established by serologic tests, by detection of viral proteins or viral RNA, or by the isolation of the virus from blood leukocytes or acute-phase serum. Following primary and secondary dengue infections, there is a relatively transient appearance of antidengue (immunoglobulin [Ig] M) antibodies. These disappear after 6-12 wk, a feature that can be used to time a dengue infection. In secondary dengue infections, most antibody is of the IgG class. Serologic diagnosis depends on a 4-fold or greater increase in IgG antibody titer in paired sera by hemagglutination inhibition, complement fixation, enzyme immunoassay, or neutralization test. Carefully standardized IgM and IgG capture enzyme commercial immunoassays are now widely used to identify acute-phase antibodies from patients with primary or secondary dengue infections in single-serum samples. Usually such samples should be collected not earlier than 5 days and not later than 6 wk after onset. It may not be possible to distinguish the infecting virus by serologic methods alone, particularly when there has been prior infection with another member of the same arbovirus group. Virus can be recovered from acute-phase serum after inoculating tissue culture or living mosquitoes. Viral RNA can be detected in blood or tissues by specific complementary RNA probes or amplified first by polymerase chain reaction or by real-time polymerase chain reaction. A viral nonstructural protein, NS1, is released by infected cells into the circulation and can be detected in acute-stage blood samples using monoclonal or polyclonal antibodies. The detection of NS1 is the basis of commercial tests, including rapid lateral flow tests. These tests offer reliable point of care diagnosis of acute dengue infection.

**DIFFERENTIAL DIAGNOSIS**

The differential diagnosis of dengue fever includes dengue-like diseases, viral respiratory and influenza-like diseases, the early stages of malaria, mild yellow fever, scrub typhus, viral hepatitis, and leptospirosis.

Four arboviral diseases have dengue-like courses but without rash: Colorado tick fever, sandfly fever, Rift Valley fever, and Ross River fever. Colorado tick fever occurs sporadically among campers and hunters in the western United States; sandfly fever in the Mediterranean region, the Middle East, southern Russia, and parts of the Indian subcontinent; and Rift Valley fever in North, East, Central, and South Africa. Ross River fever is endemic in much of eastern Australia, with epidemic extension to Fiji. In adults, Ross River fever often produces protracted and crippling arthralgia involving weight-bearing joints.

Because meningococcemia, yellow fever (see Chapter 270), other viral hemorrhagic fevers (see Chapter 271), many rickettsial diseases, and other severe illnesses caused by a variety of agents may produce a clinical picture similar to dengue hemorrhagic fever, the etiologic diagnosis should be made only when epidemiologic or serologic evidence suggests the possibility of a dengue infection.

**LABORATORY FINDINGS**

In dengue fever, pancytopenia may develop after the 3-4 days of illness. Neutropenia may persist or reappear during the latter stage of the disease and may continue into convalescence, with white blood cell counts <2,000/µL. Platelet counts rarely fall below 100,000/µL. Venous clotting, bleeding and prothrombin times, and plasma fibrinogen values are within normal ranges. The tourniquet test result may be positive. Mild acidosis, hemoconcentration, increased transaminase values, and hypoprothrombinemia may occur during some primary dengue virus infections. The electrocardiogram may show sinus bradycardia, ectopic ventricular foci, flattened T waves, and prolongation of the P-R interval.

The most common hematologic abnormalities during dengue hemorrhagic fever and dengue shock syndrome are hemoconcentration with an increase of >20% in hematocrit, thrombocytopenia, prolonged bleeding time, and a moderately decreased prothrombin level that is seldom <40% of control. Fibrinogen levels may be subnormal, and fibrin split-product values are elevated. Other abnormalities include moderate elevations of serum transaminase levels, consumption of complement, mild metabolic acidosis with hyponatremia, occasionally hypochloremia, slight elevation of serum urea nitrogen, and hypoalbuminemia. Roentgenograms of the chest reveal pleural effusions (right > left) in nearly all patients with dengue shock syndrome. Ultrasonography can be used to detect serosal effusions of the thorax or abdomen. Thickening of gallbladder wall and presence of perivascular fluid are characteristic signs of increased vascular permeability.

**TREATMENT**

Treatment of uncomplicated dengue fever is supportive. Bed rest is advised during the febrile period. Antipyretics should be used to keep body temperature <40°C (104°F). Analgesics or mild sedation should not be used because of its effects on hemostasis. Fluid and electrolyte replacement is required for deficits caused by sweating, fasting, thirsting, vomiting, and diarrhea.

**Dengue Hemorrhagic Fever and Dengue Shock Syndrome**

Dengue shock syndrome is a medical emergency that may occur in any child with a recent travel history to a tropical destination. Management begins with diagnostic suspicion and the understanding that shock often occurs during defervescence. Detailed instructions for case management are available at the Geneva or New Delhi World Health Organization websites: http://www.who.int/csr/don/archive/disease/dengue_fever/dengue.pdf. Management of dengue hemorrhagic fever and dengue shock syndrome includes immediate evaluation of vital signs and degrees of hemoconcentration, dehydration, and electrolyte imbalance. Close monitoring is essential for at least 48 hr, because shock may occur or recur precipitously early in the disease. Patients who are cyanotic or have labored breathing should be given oxygen. Rapid intravenous replacement of fluids and electrolytes can frequently sustain patients until spontaneous recovery occurs. Normal saline is more effective than the more expensive Ringer lactated saline in treating shock. When pulse pressure is <10 mm Hg or when elevation of the hematocrit persists after replacement of fluids, plasma or colloid preparations are indicated.

Care must be taken to avoid overhydration, which may contribute to cardiac failure. Transfusions of fresh blood or platelets suspended in plasma may be required to control bleeding; they should not be given during hemoconcentration but only after evaluation of hemoglobin or hematocrit values. Salicylates are contraindicated because of their effect on blood clotting.

Sedation may be required for children who are markedly agitated. Use of vasopressors has not resulted in a significant reduction of mortality over that observed with simple supportive therapy. Disseminated intravascular coagulation may require treatment (see Chapter 483). Corticosteroids do not shorten the duration of disease or improve prognosis in children receiving careful supportive therapy.

**COMPLICATIONS**

Hypervolemia during the fluid reabsorptive phase may be life-threatening and is heralded by a decrease in hematocrit with wide pulse pressure. Diuretics and digitalization may be necessary.

Primary infections with dengue fever and dengue-like diseases are usually self-limited and benign. Fluid and electrolyte losses, hyperpyrexia, and febrile convulsions are the most frequent complications in infants and young children. Epistaxis, petechiae, and purpuric lesions are uncommon but may occur at any stage. Blood from epis-taxis that is swallowed, vomited, or passed by rectum may be erroneously interpreted as gastrointestinal bleeding. In adults and possibly in children, underlying conditions may lead to clinically significant bleeding. Convulsions may occur during high temperature, especially with chikungunya fever. Infrequently, after the febrile stage, prolonged asthenia, mental depression, bradycardia, and ventricular extrasystoles may occur in children.

In endemic areas, dengue hemorrhagic fever should be suspected in children with a febrile illness suggestive of dengue fever who experience hemoconcentration and thrombocytopenia.
PROGNOSIS

Dengue Fever
The prognosis is good. Care should be taken to avoid use of drugs that suppress platelet activity.

Dengue Hemorrhagic Fever
The prognosis of dengue hemorrhagic fever is adversely affected by late diagnosis and delayed or improper treatment. Death has occurred in 40-50% of patients with shock, but with adequate intensive care, deaths should occur in <1% of cases. Infrequently, there is residual brain damage as a consequence of prolonged shock or occasionally of intracranial hemorrhage. Many fatalities are caused by overhydration.

PREVENTION
Several types of dengue type 1-4 vaccines are under development, and a killed vaccine for chikungunya is efficacious but not licensed. Large-scale Phase III clinical evaluations of a chimeric yellow fever/dengue tetravalent vaccine manufactured by Sanofi Pasteur reveal only moderate protection against individual dengue viruses but a reduction in hospitalization and severe disease. Other major vaccine manufacturers, GlaxoSmithKline, Takeda and Merck, have other tetravalent dengue vaccines in human clinical trials. Sanofi plans to license their vaccine first in dengue-endemic countries. The possibility exists that incomplete dengue immunization may sensitize recipients, with the potential that ensuing dengue infections could result in dengue hemorrhagic fever. Prophylaxis consists of avoiding daytime household-based mosquito bites through the use of insecticides, repellents, body covering with clothing, screening of houses, and destruction of A. aegypti breeding sites. If water storage is mandatory, a tight-fitting lid or a thin layer of oil may prevent egg laying or hatching. A larvicide, such as Abate (O,O′-[thiodi-p-phenylene] O,O,O,O′-tetramethyl phosphorothioate), available as a 1% sand-granule formation and effective at a concentration of 1 ppm, may be added safely to drinking water. Ultra-low-volume spray equipment effectively dispenses the adulticide malathion from truck or airplane for rapid intervention during an epidemic. Only mosquito repellants and other personal antimosquito measures are effective against mosquitoes in the field, forest, or jungle.

Bibliography is available at Expert Consult.
Bibliography


Yellow fever is an acute infection characterized in its most severe form by fever, jaundice, proteinuria, and hemorrhage. The virus is mosquito-borne and occurs in epidemic or endemic form in South America and Africa. Seasonal epidemics occurred in cities located in temperate areas of Europe and the Americas until 1900, and epidemics continue in West, Central, and East Africa.

ETIOLOGY
Yellow fever is the prototype of the Flavivirus genus of the family Flaviviridae, which are enveloped single-stranded RNA viruses 35-50 nm in diameter.

Yellow fever circulates zoonotically as 5 genotypes: type IA in West Central Africa, type IB in South America, type II in West Africa, type III in East Central Africa, and type IV in East Africa. Types IA and IB virus are capable of urban transmission between human beings by Aedes aegypti. Sometime in the 1600s yellow fever virus was brought to the American tropics through the African slave trade. Subsequently, yellow fever caused enormous coastal and riverine epidemics in the Atlantic and Caribbean basins until the 20th century, when the virus and its urban and sylvan mosquito cycles were identified, mosquito control methods were perfected, and a vaccine was developed. The East and East/Central African genotypes have not fully entered the urban cycle and have not spread to the East Coast of Africa or to the countries of Asia.

EPIDEMIOLOGY
Human and nonhuman primate hosts acquire the yellow fever infection by the bite of infected mosquitoes. After an incubation period of 3-6 days, virus appears in the blood and may serve as a source of infection for other mosquitoes. The virus must replicate in the gut of the mosquito and pass to the salivary gland before the mosquito can transmit the virus. Yellow fever virus is transmitted in an urban cycle—human to A. aegypti to human—and a jungle cycle—monkey to jungle mosquitoes to monkey. Classic yellow fever epidemics in the United States, South America, the Caribbean, and parts of Europe were of the urban variety. Since 2000, West Africa has experienced 5 urban epidemics, including in the capital cities of Abidjan (Cote d’Ivoire), Conakry (Guinea), and Dakar (Senegal). In 2012-2013, large outbreaks of East and East/Central yellow fever occurred across a large, predominantly rural area of war-ravaged Darfur in southwestern Sudan and in adjacent areas of northern Uganda. Most of the approximately 200 cases reported each year in South America are jungle yellow fever. In colonial times, urban yellow fever attack rates in white adults were very high, suggesting that subclinical infections are uncommon in this age group. Yellow fever may be less severe in children, with subclinical infection:clinical case ratios ≥ 2:1. In areas where outbreaks of urban yellow fever are common, most cases involve children because many adults are immune. Transmission in West Africa is highest during the rainy season, from July to November. The migration of nonimmune laborers into endemic regions is a significant factor in some outbreaks.

In tropical forests, yellow fever virus is maintained in a transmission cycle involving monkeys and tree hole-breeding mosquitoes (Haemagogus in Central and South America; the Aedes africanus complex in Africa). In the Americas, most cases involve tourists, campers, and men who work in forested areas and are exposed to infected mosquitoes. In Africa, the virus is prevalent in moist savanna and savanna transition areas, where other tree hole-breeding Aedes vectors transmit the virus between monkeys and humans and between humans.

PATHOGENESIS
Pathologic changes seen in the liver include: (1) coagulative necrosis of hepatocytes in the midzone of the liver lobule, with sparring of cells around the portal areas and central veins; (2) eosinophilic degeneration of hepatocytes (Councilman bodies); (3) microvacuolar fatty change; and (4) minimal inflammation. The kidneys show acute tubular necrosis. In the heart, myocardial fiber degeneration and fatty infiltration are seen. The brain may show edema and petechial hemorrhages. Direct viral injury to the liver results in impaired ability to perform functions of biosynthesis and detoxification; this is the central pathogenic event of yellow fever. Hemorrhage is postulated to result from decreased synthesis of vitamin K–dependent clotting factors and, in some cases, disseminated intravascular clotting. However, because the pathogenesis of shock in patients with yellow fever appears similar to that described for dengue shock syndrome and the other viral hemorrhagic fevers, viral damage to platelets and endothelial cells resulting in release of prohemorrhagic factors may be the central mechanism of hemorrhage in yellow fever.

Renal dysfunction has been attributed to hemodynamic factors (pre-renal failure progressing to acute tubular necrosis).

CLINICAL MANIFESTATIONS
In Africa, inapparent, abortive, or clinically mild infections are frequent; some studies suggest that children experience a milder disease than adults do. Abortive infections, characterized by fever and headache, may be unrecognized except during epidemics.

In its classic form, yellow fever begins with sudden onset of fever, headache, myalgia, lumbar sacral pain, anorexia, nausea, and vomiting. Physical findings during the early phase of illness, when virus is present in the blood, include prostration, conjunctival injection, flushing of
face and neck, reddening of the tongue at the tip and edges, and relative bradycardia. After 2-3 days, there may be a brief period of remission, followed in 6-24 hr by reappearance of fever with vomiting, epigastric pain, jaundice, dehydration, gastrointestinal and other hemorrhages, albuminuria, hyponatremia, renal failure, delirium, convulsions, and coma. Death may occur after 7-10 days, with the fatality rate in severe cases approaching 50%. Some patients who survive the acute phase of illness later succumb to renal failure or myocardial damage. Laboratory abnormalities include leukopenia; prolonged clotting, prothrombin, and partial thromboplastin times; thrombocytopenia; hyperbilirubinemia; elevated serum transaminase values; albuminuria; and azotemia. Hypoglycemia may be present in severe cases. Electrocardiogram abnormalities such as bradycardia and ST-T changes are described.

**DIAGNOSIS**

Yellow fever should be suspected when fever, headache, vomiting, myalgia, and jaundice appear in residents of enzootic areas or in unimmunized visitors who have recently traveled (within 2 wk before onset of symptoms) to endemic areas. Clinically, yellow fever is quite similar to dengue hemorrhagic fever. In contrast to the gradual onset of acute viral hepatitis resulting from hepatitis A, B, C, D, or E virus, jaundice and fever in yellow fever appear after 3-5 days of high temperature and is often accompanied by severe prostration. Mild yellow fever is dengue-like and cannot be distinguished from a wide variety of other infections. Jaundice and fever may occur in any of several other tropical diseases, including malaria, viral hepatitis, house-borne relapsing fever, leptospirosis, typhoid fever, rickettsial infections, certain systemic bacterial infections, sickle cell crisis, Rift Valley fever, Crimean-Congo hemorrhagic fever, and other viral hemorrhagic fevers. Outbreaks of yellow fever always include cases with severe gastrointestinal hemorrhage. Specific diagnosis depends on detection of virus or viral antigen in acute-phase blood samples or antibody assays. The immunoglobulin M enzyme immunoassay is particularly useful. Sera obtained during the 1st 10 days after onset of symptoms should be kept in an ultra-low-temperature freezer (−70°C [−94°F]) and shipped on dry ice for virus testing. Convalescent-phase samples for antibody tests are managed by conventional means. In handling acute-phase blood specimens, medical personnel must take care to avoid contaminating themselves or others on the evacuation trail (laboratory personnel and others). Postmortem diagnosis is based on virus isolation from liver or blood, identification of Councilman bodies in liver tissue, or detection of antigen or viral genome in liver tissue.

**TREATMENT**

It is customary to keep patients with yellow fever in a mosquito-free area, with use of mosquito nets if necessary. Patients are viremic during the febrile phase of the illness. Although there is no specific treatment for yellow fever, medical care is directed at maintaining physiologic status with the following measures: (1) sponging and acetaminophen to reduce high temperature, (2) vigorous fluid replacement of losses resulting from fasting, thirsting, vomiting, or plasma leakage, (3) correcting acid–base imbalance, (4) maintaining nutritional intake to lessen the severity of hypoglycemia, and (5) avoiding drugs that are either metabolized by the liver or toxic to the liver, kidney, or central nervous system.

**COMPLICATIONS**

Complications of acute yellow fever include severe hemorrhage, liver failure, and acute renal failure. Bleeding should be managed by transfusion of fresh whole blood or fresh plasma with platelet concentrates if necessary. Renal failure may require peritoneal dialysis or hemodialysis.

**PREVENTION**

Yellow fever 17D is a live-attenuated vaccine with a long record of safety and efficacy. It is administered as a single 0.5 mL subcutaneous injection at least 10 days before arrival in a yellow fever–endemic area. With the exceptions noted later, individuals traveling to endemic areas in South America and Africa should be considered for vaccination, but length of stay, exact locations to be visited, and environmental or occupational exposure may determine the specific risk and individual need for vaccination. Persons traveling from yellow fever–endemic to yellow fever–receptive countries may be required by national authorities to obtain a yellow fever vaccine (e.g., from South America or Africa to India). Usually countries that require travelers to obtain a yellow fever immunization do not issue a visa without a valid immunization certificate. Vaccination is valid for 10 yr for international travel certification, although immunity lasts at least 40 yr and probably for life. Immunoglobulin M antibodies circulate for years after administration of yellow fever vaccine. Since 1996, there have been a number of reports of yellow fever vaccine–associated viscerotropic disease with higher risk in elderly vaccine recipients and in persons with previous thymectomies. Yellow fever vaccine should not be administered to persons who have symptomatic immunodeficiency diseases, are taking immunosuppressant drugs, or have a history of thymectomy. A recent study has shown that individuals on maintenance corticosteroids may be successfully vaccinated. Although the vaccine is not known to harm fetuses, its administration during pregnancy is not advised. The vaccine virus may be rarely transmitted through breastfeeding. In very young children, there is a small risk of encephalitis and death after yellow fever 17D vaccination. The 17D vaccine should not be administered to infants younger than 4 mo. Residence in or travel to areas of known or anticipated yellow fever activity (e.g., forested areas in the Amazon basin), which puts an individual at high risk, warrants immunization of infants 4-9 mo of age. Immunization of children 9 mo of age and older is routinely recommended before entry into endemic areas. Immunization of persons older than 60 yr of age should be weighed against their risk for sylvatic yellow fever in the American tropics and for urban or sylvatic yellow fever in Africa. Vaccination should be avoided in persons with a history of egg allergy. Alternatively, a skin test can be performed to determine whether a serious allergy exists that would preclude vaccination.

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Bibliography

Ebola and Other Viral Hemorrhagic Fevers

Scott B. Halstead

Viral hemorrhagic fevers are a loosely defined group of clinical syndromes in which hemorrhagic manifestations are either common or especially notable in severe illness. Both the etiologic agents and clinical features of the syndromes differ, but disseminated intravascular coagulopathy may be a common pathogenetic feature.

ETIOLOGY

Six of the viral hemorrhagic fevers are caused by arthropod-borne viruses (arboviruses) (Table 271-1). Four are caused by togaviruses of the family Flaviviridae: Kyasanur Forest disease, Omsk hemorrhagic fever, dengue (see Chapter 269), and yellow fever (see Chapter 270) viruses. Three are caused by viruses of the family Bunyaviridae: Congo fever, Hantaan fever, and Rift Valley fever (RVF) viruses. Four are caused by viruses of the family Arenaviridae: Junin fever, Machupo fever, Guanarito fever, and Lassa fever. Two are caused by viruses of the family Filoviridae: Ebola and Marburg disease. The Filoviridae are enveloped, filamentous RNA viruses that are sometimes branched, unlike any other known virus.

EPIDEMIOLOGY AND CLINICAL MANIFESTATIONS

With some exceptions, the viruses causing viral hemorrhagic fevers are transmitted to humans via a nonhuman entity. The specific ecosystem...
Severe hemorrhagic manifestations have been reported in some cases. The virus causing RVF is responsible for epizootics involving sheep, Rift Valley Fever in northern Romania. Vectors may include Omsk Hemorrhagic Fever area of Mysore State, India. The main vectors are 2 Ixodidae ticks, Kyasanur Forest Disease species Africa in 1984. In the Russian Federation, the vectors are ticks of the Afghanistan in 1976, in the Arabian Peninsula in 1983, and in South in Bulgaria, western Crimea, and the Rostov-on-Don and Astrakhan Sporadic human infection with Crimean-Congo hemorrhagic fever in Crimea-Congo Hemorrhagic Fever required for viral survival determines the geographic distribution of disease. Although it is commonly thought that all viral hemorrhagic fevers are arthropod borne, 7 may be contracted from environmental contamination caused by animals or animal cells or from infected humans (see Table 271-1). Laboratory and hospital infections have occurred with many of these agents. Lassa fever and Argentine and Bolivian hemorrhagic fevers are reportedly milder in children than in adults.

Crimean-Congo Hemorrhagic Fever Sporadic human infection with Crimean-Congo hemorrhagic fever in Africa provided the original virus isolation. Natural foci are recognized in Bulgaria, western Crimea, and the Rostov-on-Don and Astrakhan regions; disease occurs in Central Asia from Kazakhstan to Pakistan. Index cases were followed by nosocomial transmission in Pakistan and Afghanistan in 1976, in the Arabian Peninsula in 1983, and in South Africa in 1984. In the Russian Federation, the vectors are ticks of the species *Hyalomma marginatum* and *Hyalomma anatolicum*, which, along with hares and birds, may serve as viral reservoirs. Disease occurs from June to September, largely among farmers and dairy workers.

Kyasanur Forest Disease Human cases of Kyasanur Forest disease occur chiefly in adults in an area of Mysore State, India. The main vectors are 2 Ixodidae ticks, *Haemaphysalis turturis* and *Haemaphysalis spinigera*. Monkeys and forest rodents may be amplifying hosts. Laboratory infections are common.

Omsk Hemorrhagic Fever Omsk hemorrhagic fever occurs throughout south-central Russia and northern Romania. Vectors may include *Dermacentor pictus* and *Dermacentor marginatus*, but direct transmission from moles and muskrats to humans seems well established. Human disease occurs in a spring-summer-autumn pattern, paralleling the activity of vectors. This infection occurs most frequently in persons with outdoor occupational exposure. Laboratory infections are common.

Rift Valley Fever The virus causing RVF is responsible for epizootics involving sheep, cattle, buffalo, certain antelopes, and rodents in North, Central, East, and South Africa. The virus is transmitted to domestic animals by *Culex theileri* and several *Aedes* species. Mosquitoes may serve as reservoirs by transovarial transmission. An epizootic in Egypt in 1977-1978 was accompanied by thousands of human infections, principally among veterinarians, farmers, and farm laborers. Smaller outbreaks occurred in Senegal in 1987, Madagascar in 1990, and Saudi Arabia and Yemen in 2000-2001. Humans are most often infected during the slaughter or skinning of sick or dead animals. Laboratory infection is common.

**Table 271-1 Viral Hemorrhagic Fevers**

<table>
<thead>
<tr>
<th>MODE OF TRANSMISSION</th>
<th>DISEASE</th>
<th>VIRUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tick-borne</td>
<td>Crimean-Congo hemorrhagic fever (HF)*</td>
<td>Congo</td>
</tr>
<tr>
<td></td>
<td>Kyasanur Forest disease</td>
<td>Omsk</td>
</tr>
<tr>
<td></td>
<td>Omsk HF</td>
<td></td>
</tr>
<tr>
<td>Mosquito-borne†</td>
<td>Dengue HF</td>
<td>Dengue (4 types)</td>
</tr>
<tr>
<td></td>
<td>Rift Valley fever</td>
<td>Rift Valley fever</td>
</tr>
<tr>
<td></td>
<td>Yellow fever</td>
<td>Yellow fever</td>
</tr>
<tr>
<td>Infected animals or materials to humans</td>
<td>Argentine HF</td>
<td>Junin</td>
</tr>
<tr>
<td></td>
<td>Bolivian HF</td>
<td>Machupo</td>
</tr>
<tr>
<td></td>
<td>Lassa fever*</td>
<td>Lassa</td>
</tr>
<tr>
<td></td>
<td>Marburg disease*</td>
<td>Marburg</td>
</tr>
<tr>
<td></td>
<td>Ebola HF*</td>
<td>Ebola</td>
</tr>
<tr>
<td></td>
<td>HF with renal syndrome</td>
<td>Hantaan</td>
</tr>
</tbody>
</table>

*Patients may be contagious; nosocomial infections are common.†Chikungunya virus is associated infrequently with petechiae and epistaxis. Severe hemorrhagic manifestations have been reported in some cases.

**Argentine Hemorrhagic Fever**

Before introduction of vaccine, hundreds to thousands of cases of Argentine hemorrhagic fever occurred annually from April through July in the maize-producing area northwest of Buenos Aires that reaches to the eastern margin of the Province of Cordoba. Junin virus has been isolated from the rodents *Mus musculus*, *Akodon arenicola*, and *Calomys laucha laucha*. It infects migrant laborers who harvest the maize and who inhabit rodent-contaminated shelters.

**Bolivian Hemorrhagic Fever**

The recognized endemic area of Bolivian hemorrhagic fever consists of the sparsely populated province of Beni in Amazonian Bolivia. Sporadic cases occur in farm families who raise maize, rice, yucca, and beans. In the town of San Joaquin, a disturbance in the domestic rodent ecosystem may have led to an outbreak of household infection caused by Machupo virus transmitted by chronically infected *Calomys callosus*, ordinarily a field rodent. Mortality rates are high in young children.

**Venezuelan Hemorrhagic Fever**

In 1989, an outbreak of hemorrhagic illness occurred in the farming community of Guanarito, Venezuela, 200 miles south of Caracas. Subsequently, in 1990-1991, there were 104 cases reported with 26 deaths caused by Guanarito virus. Cotton rats (*Sigmodon alstoni*) and cane rats (*Zygodontomys brevicauda*) have been implicated as likely reservoirs of Venezuelan hemorrhagic fever.

**Lassa Fever**

Lassa virus has an unusual potential for human-to-human spread, which has resulted in many small epidemics in Nigeria, Sierra Leone, and Liberia. In 2012, an outbreak of more than 1,000 cases of Lassa fever occurred in east-central Nigeria. Medical workers in Africa and the United States have also contracted the disease. Patients with acute Lassa fever have been transported by international aircraft, necessitating extensive surveillance among passengers and crew. The virus is probably maintained in nature in a species of African peridomestic rodent, *Mus musculus*. Rodent-to-rat transmission and infection of humans probably occur via mechanisms established for other arenaviruses.

**Marburg Disease**

Until recently, the world experience of Marburg disease had been limited to 26 primary and 5 secondary cases in Germany and Yugoslavia in 1967, and to small outbreaks in Zimbabwe in 1975, Kenya in 1980 and 1988, and South Africa in 1983. However, in 1999 a large outbreak occurred in Congo Republic and in 2005 a still larger outbreak occurred in Uganda Province, Angola, with 252 cases and 227 deaths. In laboratory and clinical settings, transmission occurs by direct contact with tissues of the African green monkey or with infected human blood or semen. A reservoir in bats has been demonstrated. It appears that the virus is transmitted by close contact between fructivorous bats and from bats by aerosol to humans.

**Ebola Hemorrhagic Fever**

Ebola virus was isolated in 1976 from a devastating epidemic involving small villages in northern Zaire and southern Sudan; smaller outbreaks have occurred subsequently. Outbreaks have initially been nosocomial. Attack rates have been highest in the birth-1 yr old and 15-50 yr old age groups. The virus is closely related to Marburg virus. Ebola virus epidemics have occurred in Kikwit, Zaire, in 1995, followed by scattered outbreaks in Uganda and Central and West Africa. The virus has been recovered from chimpanzees, and antibodies have been found in other subhuman primates, which apparently acquire infection from a zoonotic reservoir in bats. The mode of transmission to humans is unknown. Reston virus, related to Ebola virus, has been recovered from Philippine monkeys and pigs and has caused subclinical infections in workers in monkey colonies in the United States.

West Africa in 2014 has experienced the largest number of cases of Ebola virus disease (EVD), with more than 17,900 cases reported as of December 2014 (Fig. 271-1). Countries primarily affected are Liberia, Sierra Leone, and Guinea, with imported cases reported in Nigeria,
Mali, and Senegal as well as Europe and the United States. Of the 3 strains of EVD (Zaire, Sudan, Bundibugyo), the new strain in Zaire has a mortality rate of approximately 55-65%.

EVD may occur following exposure to fruit bats or bushmeat but most often occurs through exposure to body fluids (blood, sweat, saliva, vomitus, diarrhea, and less often human milk or semen). Patients are infectious once they are symptomatic; the incubation period is 2-21 days (mean: 11 days). The age range in the West African epidemic is broad but most patients are between 15 and 44 yr old.

Manifestations of EVD may come in stages, but most EVD begins with the sudden onset of fever accompanied by fatigue, weakness, myalgias, headache, and sore throat. This is followed by gastrointestinal involvement including anorexia, nausea, abdominal pain, vomiting, and diarrhea. Hemorrhage (defined by any evidence of bleeding) is seen in more than 50% and is a serious later phase often accompanied by vascular leakage, multiorgan failure, and death. Those who survive improve on approximately days 6-11 of EVD.

The diagnosis is confirmed by enzyme-linked immunosorbent assay immunoglobulin M and polymerase chain reaction (which may need to be repeated if initially negative). The differential diagnosis includes malaria, typhoid, Lassa fever, influenza, and meningococcemia. Criteria to aid in the diagnosis of EVD include temperature >38.6°C (101.5°F) plus symptoms: contact with an affected patient, the patient’s body fluids, or the funeral; residence in or travel to an endemic region; or a history of handling rodents, bats, or primates from an endemic area.

Treatment of EVD often requires an intensive care unit and management of multiorgan system dysfunction, including fluid replacement and ventilation support. Convalescent serum and monoclonal antibodies have been employed on an experimental basis. Strict isolation and appropriate barrier protection of healthcare workers is mandatory. There is no vaccine, and epidemic measures, isolation, and quarantine have been used to attempt to decrease the spread of the West African epidemic.

**Hemorrhagic Fever with Renal Syndrome**

The endemic area of hemorrhagic fever with renal syndrome (HFRS), also known as *epidemic hemorrhagic fever* and *Korean hemorrhagic fever*, includes Japan, Korea, far eastern Siberia, China, European and Asian Russia, Scandinavia, Czechoslovakia, Romania, Bulgaria, Yugoslavia, and Greece. Although the incidence and severity of hemorrhagic manifestations and the mortality are lower in Europe than in northeastern Asia, the renal lesions are the same. Disease in Scandinavia, *nephropathia epidemica*, is caused by a different although antigenically related virus, Puumala virus, associated with the bank vole, *Clethrionomys glareolus*. Cases occur predominantly in the spring and summer. There appears to be no age factor in susceptibility, but because of occupational hazards, young adult men are most frequently attacked. Rodent plagues and evidence of rodent infestation have accompanied endemic and epidemic occurrences. Hantaan virus has been detected in lung tissue and excreta of *Apodemus agrarius coreae*. Antigenically related agents have been detected in laboratory rats and in urban rat populations around the world, including Prospect Hill virus in the wild rodent *Microtus pennsylvanicus* in North America and *sin nombre* virus in the deer mouse in the southern and southwestern United States; these viruses are causes of hantavirus pulmonary syndrome (see Chapter 273). Rodent-to-rodent and rodent-to-human transmission presumably occurs via the respiratory route.

**Clinical Manifestations**

Dengue hemorrhagic fever (see Chapter 269) and yellow fever (see Chapter 270) cause similar syndromes in children in endemic areas.

**Crimean-Congo Hemorrhagic Fever**

The incubation period of 3-12 days is followed by a febrile period of 5-12 days and a prolonged convalescence. Illness begins suddenly with fever, severe headache, myalgia, abdominal pain, anorexia, nausea, and vomiting. After 1-2 days, fever may subside until the patient experiences an erythematous facial or truncal flush and injected conjunctivae. A second febrile period of 2-6 days then develops, with a hemorrhagic enanthem on the soft palate and a fine petechial rash on the chest and abdomen. Less frequently, there are large areas of purpura and bleeding from the gums, nose, intestines, lungs, or uterus. Hematuria and proteinuria are relatively rare. During the hemorrhagic stage, there is usually tachycardia with diminished heart sounds and occasionally hypotension. The liver is usually enlarged, but there is no icterus. In protracted cases, central nervous system signs include delirium, somnolence, and progressive clouding of consciousness. Early in the disease, leukopenia with relative lymphocytosis, progressively worsening thrombocytopenia, and gradually increasing anemia occur. In convalescence there may be hearing and memory loss. The mortality rate is 2-50%.

**Kyasanur Forest Disease and Omsk Hemorrhagic Fever**

After an incubation period of 3-8 days, both Kyasanur Forest disease and Omsk hemorrhagic fever begin with sudden onset of fever and headache. Kyasanur Forest disease is characterized by severe myalgia, prostration, and bronchiolar involvement; it often manifests without hemorrhage but occasionally with severe gastrointestinal bleeding. In Omsk hemorrhagic fever, there is moderate epistaxis, hematemesi,
and a hemorrhagic enanthem but no profuse hemorrhage; bronchopneumonia is common. In both diseases, severe leukopenia and thrombocytopenia, vascular dilation, increased vascular permeability, gastrointestinal hemorrhages, and suberosal and interstitial petechial hemorrhages occur. Kyanarur Forest disease may be complicated by acute degeneration of renal tubules and focal liver damage. In many patients, recurrent febrile illness may follow an afibrile period of 7-15 days. This 2nd phase takes the form of a meningoencephalitis.

**Rift Valley Fever**
Most RVF infections have occurred in adults with signs and symptoms resembling those of dengue fever (see Chapter 269). Onset is acute, with fever, headache, prostration, myalgia, anorexia, nausea, vomiting, conjunctivitis, and lymphadenopathy. The fever lasts 3-6 days and is often biphasic. Convalescence is often prolonged. In the 1977-1978 outbreak many patients died after showing signs that included purpura, epistaxis, hematemesis, and melena. RVF affects the uvea and posterior chorioretina; macular scarring, vascular occlusion, and optic atrophy occur, resulting in permanent visual loss in a high proportion of patients with mild to severe RVF. At autopsy extensive eosinophilic degeneration of the parenchymal cells of the liver has been observed.

**Argentine, Venezuelan, and Bolivian Hemorraghic Fevers and Lassa Fever**
The incubation period in Argentine, Venezuelan, and Bolivian hemorrhagic fevers and Lassa fever is commonly 7-14 days; the acute illness lasts for 2-4 wk. Clinical illnesses range from undifferentiated fever to the characteristic severe illness. **Lassa fever** is most often clinically severe in white persons. Onset is usually gradual, with increasing fever, headache, diffuse myalgia, and anorexia (Table 271-2). During the 1st wk, signs frequently include a sore throat, dysphagia, cough, oropharyngeal ulcers, nausea, vomiting, diarrhea, and pains in the chest and abdomen. Pleuritic chest pain may persist for 2-3 wk. In Argentine and Bolivian hemorrhagic fevers and less frequently in Lassa fever, a petechial enanthem appears on the soft palate 3-5 days after onset and at about the same time on the trunk. The tourniquet test may be positive. The clinical course of Venezuelan hemorrhagic fever has not been well described.

In 35-50% of all patients, these diseases may become severe, with persistent high temperature, increasing toxicity, swelling of the face or neck, microscopic hematuria, and frank hemorrhages from the stomach, intestines, nose, gums, and uterus. A syndrome of **hypovolemic shock** is accompanied by pleural effusion and renal failure. **Respiratory distress** resulting from airway obstruction, pleural effusion, or congestive heart failure may occur. A total of 10-20% of patients experience late neurologic involvement, characterized by intention tremor of the tongue and associated speech abnormalities. In severe cases, there may be intention tremors of the extremities, seizures, and delirium. The cerebrospinal fluid is normal. In Lassa fever, nerve deafness occurs in early convalescence in 25% of cases. Prolonged convalescence is accompanied by alopecia and, in Argentine and Bolivian hemorrhagic fevers, by signs of autonomic nervous system lability, such as postural hypotension, spontaneous flushing or blanching of the skin, and intermittent diaphoreisis.

**Laboratory studies** reveal marked leukopenia, mild to moderate thrombocytopenia, proteinuria, and, in Argentine hemorrhagic fever, moderate abnormalities in blood clotting, decreased fibrinogen, increased fibrinogen split products, and elevated serum transaminases. There is focal, often extensive eosinophilic necrosis of liver parenchyma, focal interstitial pneumonitis, focal necrosis of the distal and collecting tubules, and partial replacement of splenic follicles by amorphous eosinophilic material. Usually bleeding occurs by diapedesis with little inflammatory reaction. The mortality rate is 10-40%.

**Marburg Disease and Ebola Hemorrhagic Fever**
After an incubation period of 4-7 days, illness begins abruptly with severe frontal headache, malaise, drowsiness, lumbar myalgia, vomiting, nausea, and diarrhea. A **maculopapular** eruption begins 5-7 days later on the trunk and upper arms. It becomes generalized and often hemorrhagic and exfoliates during convalescence. The exanthem is accompanied by a dark red enanthem on the hard palate, conjunctivitis, and scrotal or labial edema. Gastrointestinal hemorrhage occurs as the severity of illness increases. Late in the illness, the patient may become tearfully depressed with marked hyperalgesia to tactile stimuli. In fatal cases, patients become hypotensive, restless, and confused and lapse into coma. Convalescent patients may experience alopecia and may have paresthesias of the back and trunk. There is a marked leukopenia with necrosis of granulocytes. **Disseminated intravascular coagulopathy** and thrombocytopenia are universal and correlate with severity of disease; there are moderate abnormalities in concentrations of clotting proteins and elevations of serum transaminases and amylose.

Pregnant women and young children are at high risk of severe disease with fatal outcome. The mortality rate of Marburg disease is 25-85%, and the mortality rate of Ebola hemorrhagic fever 50-90%. High viral loads in acute-phase blood samples convey a poor prognosis.

**Hemorrhagic Fever with Renal Syndrome**
In most cases, HFRS is characterized by fever, petechiae, mild hemorrhagic phenomena, and mild proteinuria, followed by relatively uneventful recovery. In 20% of recognized cases, the disease may progress through 4 distinct phases. The febrile phase is ushered in with fever, malaise, and facial and truncal flushing. It lasts 3-8 days and ends with thrombocytopenia, petechiae, and proteinuria. The hypotensive phase, of 1-3 days, follows defervescence. Loss of fluid from the intravascular compartment may result in marked hemoconcentration. Proteinuria and ecchymoses increase. The oliguric phase, usually 3-5 days in duration, is characterized by a low output of protein-rich urine, increasing nitrogen retention, nausea, vomiting, and dehydration. Confusion, extreme restlessness, and hypertension are common. The diuretic phase, which may last for days or weeks, usually initiates clinical improvement. The kidneys show little concentrating ability, and rapid loss of fluid may result in severe dehydration and shock. Potassium and sodium depletion may be severe. Fatal cases manifest as abundant protein-rich retroperitoneal edema and marked hemorrhagic necrosis of the renal medulla. The mortality rate is 5-10%.

**DIAGNOSIS**
Diagnosis of these viral hemorrhagic fevers depends on a high index of suspicion in endemic areas. In nonendemic areas, histories of recent travel, recent laboratory exposure, or exposure to an earlier case should evoke suspicion of a viral hemorrhagic fever.

In all viral hemorrhagic fevers, the viral agent circulates in the blood at least transiently during the early febrile stage. Togaviruses and bunyaviruses can be recovered from acute-phase serum samples by inoculation into tissue culture or living mosquitoes. Argentine, Bolivian, and Venezuelan hemorrhagic fever viruses can be isolated from acute-phase blood or throat washings by intracerebral inoculation into guinea pigs, infant hamsters, or infant mice. Lassa virus may be isolated from acute-phase blood or throat washings by inoculation into tissue cultures. For Marburg disease and Ebola hemorrhagic fever,
acute-phase throat washings, blood, and urine may be inoculated into tissue culture, guinea pigs, or monkeys. The viruses are readily identified on electron microscopy, with a filamentous structure differentiating them from all other known agents. Specific complement-fixing and immunofluorescent antibodies appear during convalescence. The virus of HFRS is recovered from acute-phase serum or urine by inoculation into tissue culture. A variety of antibody tests using viral subunits is becoming available. Serologic diagnosis depends on demonstration of seroconversion or a 4-fold or greater increase in immunoglobulin G antibody titer in acute and convalescent serum specimens collected 3-4 wk apart. Viral RNA may also be detected in blood or tissues with use of reverse transcriptase polymerase chain reaction analysis.

Handling blood and other biologic specimens is hazardous and must be performed by specially trained personnel. Blood and autopsy specimens should be placed in tightly sealed metal containers, wrapped in absorbent material inside a sealed plastic bag, and shipped on dry ice to laboratories with biocontainment safety level 4 facilities. Even routine hematologic and biochemical tests should be done with extreme caution.

Differential Diagnosis
Mild cases of hemorrhagic fever may be confused with almost any self-limited systemic bacterial or viral infection. More severe cases may suggest typhoid fever; epidemic, murine, or scrub typhus; leptospirosis; or a rickettsial spotted fever, for which effective chemotherapeutic agents are available. Many of these disorders may be acquired in geographic or ecologic locations endemic for a viral hemorrhagic fever.

TREATMENT
Ribavirin administered intravenously is effective in reducing mortality rates in Lassa fever and HFRS. Further information and advice about management, control measures, diagnosis, and collection of biohazardous specimens can be obtained from the Centers for Disease Control and Prevention, National Center for Infectious Diseases, Special Pathogens Branch, Atlanta, Georgia 30333 (404-639-1115).

The therapeutic principle involved in all of these diseases, especially HFRS, is the reversal of dehydration, hemoconcentration, renal failure, and protein, electrolyte, or blood losses. The contribution of disseminated intravascular coagulopathy to the hemorrhagic manifestations is unknown, and the management of hemorrhage should be individualized. Transfusions of fresh blood and platelets are frequently given. Good results have been reported in a few patients after the administration of clotting factor concentrates. The efficacy of corticosteroids, α-aminoacaproic acid, pressor amines, and α-adrenergic blocking agents has not been established. Sedatives should be selected with regard to the possibility of kidney or liver damage. The successful management of HFRS may require renal dialysis.

Although whole-blood transfusions from Ebola virus–immune donors are thought to be therapeutic, studies in a monkey model were unable to confirm this outcome.

Patients suspected of having Lassa fever, Ebola fever, Marburg fever, or Congo Crimean hemorrhagic fever should be placed in a private room on standard contact and droplet precautions. Caretakers should use barrier precautions to prevent skin or mucous membrane exposure. All persons entering the patient's room should wear gloves and gowns and face shields. Before exiting the patient's room, caretakers should safely remove and dispose of all protective gear and should clean and disinfect shoes. Protocols require two-person clinical care teams, one observer and one caregiver. (see CDC website: www.cdc.gov/vhf/ebola/hcp).

PREVENTION
A live-attenuated vaccine (Candid-I) for Argentine hemorrhagic fever (Junin virus) is highly efficacious. A form of inactivated mouse brain vaccine is reported to be effective in preventing Omsk hemorrhagic fever. Inactivated RVF vaccines are widely used to protect domestic animals and laboratory workers. HFRS inactivated vaccine is licensed in Korea, and killed and live-attenuated vaccines are widely used in China. A vaccinia-vector glycoprotein vaccine provides protection against Lassa fever in monkeys. A single dose of a recombinant vesicular stomatitis virus vaccine containing surface glycoproteins from Ebola and Marburg viruses is effective in preventing virus hemorrhagic fevers due to several strains of filovirus in a monkey model.

Prevention of mosquito-borne and tick-borne infections includes use of repellents, wearing of tight-fitting clothing that fully covers the extremities, and careful examination of the skin after exposure, with removal of any vectors found. Diseases transmitted from a rodent-infected environment can be prevented through methods of rodent control; elimination of refuse and breeding sites is particularly successful in urban and suburban areas.

Patients should be isolated until they are virus-free or for 3 wk after illness. Patient urine, sputum, blood, clothing, and bedding should be disinfected. Disposable syringes and needles should be used. Prompt and strict enforcement of barrier nursing may be lifesaving. The mortality rate among medical workers contracting these diseases is 50%. A few entirely asymptomatic Ebola infections result in strong antibody production.

Bibliography is available at Expert Consult.
Bibliography


Lymphocytic choriomeningitis virus (LCMV) is a prevalent human pathogen and an important cause of meningitis in children and adults. Capable of crossing the placenta and infecting the fetus, LCMV is also an important cause of neurologic birth defects and encephalopathy in the newborn.

**ETIOLOGY**

LCMV is a member of the family Arenaviridae, which are enveloped, negative-sense single-stranded RNA viruses. The name of the arenaviruses is derived from *arenosus*, the Latin word for “sandy,” because of the fine granularities observed within the virion on ultrathin electron microscopic sections.

**EPIDEMIOLOGY**

Like all arenaviruses, LCMV utilizes rodents as its reservoir. The common house mouse, *Mus musculus*, is both the natural host and primary reservoir for the virus, which is transferred vertically from 1 generation of mice to the next via intrauterine infection. Hamsters and guinea pigs are also potential reservoirs. Although heavily infected with LCMV, rodents that acquire the virus transplacentally often remain asymptomatic because congenital infection provides rodents with immunologic tolerance for the virus. Infected rodents shed the virus in large quantities in nasal secretions, urine, feces, saliva, and milk throughout their lives.

Humans typically acquire LCMV by contacting fomites contaminated with infectious virus or by inhaling aerosolized virus. Most human infections occur during the fall and early winter, when mice move into human habitations. Humans can also acquire the virus via organ transplantation. Congenital LCMV infection occurs when a woman acquires a primary LCMV infection during pregnancy. The virus passes through the placenta to the fetus during maternal viremia. The fetus may also acquire the virus during passage through the birth canal from exposure to infected vaginal secretions. Outside of organ transplantation and vertical transmission during pregnancy, there have been no cases of human-to-human transmission of LCMV.

LCMV is prevalent in the environment, has a great geographic range, and infects large numbers of humans. The virus is found throughout the world’s temperate regions and probably occurs wherever the genus *Mus* has been introduced (which is every continent but...
Antarctica). An epidemiologic study found that 9% of house mice are infected and that substantial clustering occurs, where the prevalence is higher. Serologic studies demonstrate that approximately 5% of adult humans possess antibodies to LCMV, indicating prior exposure and infection.

**PATHOGENESIS**

LCMV is not a cytopathic virus. Thus, unlike many other nervous system pathogens that directly damage the brain by killing host brain cells, LCMV pathogenesis involves other underlying mechanisms. Furthermore, the pathogenic mechanisms are different in postnatal (acquired) infection than in prenatal (congenital) infection. A critical difference in the pathogenesis of postnatal vs prenatal infection is that the virus infects brain parenchyma in the case of prenatal infection, but is restricted to the meninges and choroid plexus in postnatal cases.

In postnatal infections, LCMV replicates to high titers in the choroid plexus and meninges. Viral antigen within these tissues becomes the target of an acute mononuclear cell infiltration driven by CD8+ T lymphocytes. The presence of lymphocytes in large numbers within the meninges and cerebrospinal fluid leads to the symptoms of meningoencephalitis that mark acquired LCMV infection. As the lymphocytes clear the virus from the meninges and cerebrospinal fluid, the density of lymphocytes declines, and the symptoms of meningoencephalitis resolve. Thus, symptoms of acquired (postnatal) LCMV infection are immune mediated and are a result of the presence of large numbers of lymphocytes.

Prenatal infection likewise inflames the tissues surrounding the brain parenchyma, and this inflammation leads to some of the signs of congenital LCMV. In particular, within the ventricular system, congenital LCMV infection often leads to ependymitis, inflammation, which may block the egress of cerebrospinal fluid (CSF) at the cerebral aqueduct and lead to hydrocephalus. However, unlike postnatal cases, prenatal infection with LCMV includes infection of the substance of the brain rather than just the meninges or ependyma. This infection of brain parenchyma leads to the substantial neuropathologic changes typically accompanying congenital LCMV infection. In particular, LCMV infects the mitotically active neuroblasts, located at periventricular sites. Through an unknown mechanism, presence of the virus kills these periventricular cells, leading to periventricular calcifications, a radiographic hallmark of this disorder. Within the fetal brain, LCMV infection of neurons and glial cells also disrupts neuronal migration, leading to abnormal gyral patterns, and interferes with neuronal mitosis, leading to microcephaly and cerebellar hypoplasia.

**CLINICAL MANIFESTATIONS**

The clinical manifestations of LCMV infection depend on whether the infection occurs prenatally or postnatally. Congenital infection with LCMV is unique, as it involves both the postnatal infection of a pregnant woman and the prenatal infection of a fetus.

**Acquired (Postnatal) Lymphocytic Choriomeningitis Virus Infection**

LCMV infection during postnatal life (during childhood or adulthood) typically consists of a brief febrile illness, from which the patient fully recovers. The illness classically consists of 2 clinical phases. In the 1st phase, the symptoms are those of a nonspecific viral syndrome and include fever, myalgia, malaise, nausea, anorexia, and vomiting. These symptoms usually resolve after several days but are followed by a 2nd phase, consisting of central nervous system disease. The symptoms of this 2nd phase are those of aseptic meningitis, including headache, fever, nuchal rigidity, photophobia, and vomiting. The entire course of the biphasic disease is typically 1-3 wk.

The clinical spectrum of LCMV infection is broad. One third of postnatal infections are asymptomatic. Other patients develop extraneural disease that extends beyond the usual symptoms and may include orchitis, pneumonitis, myocarditis, parotitis, dermatitis, alopecia, and pharyngitis. In others, the neurologic disease may be considerably more severe than usual and may include transverse myelitis, Guillain-Barré syndrome, hydrocephalus, and encephalitis. Recovery from acquired LCMV infection is usually complete, but fatalities occasionally occur.

LCMV infections acquired via solid organ transplantation always induce severe disease. Several weeks posttransplantation, recipients of infected organs develop fever, leukopenia, and lethargy. Following these nonspecific symptoms, the course of disease rapidly progresses to multiorgan system failure and shock. These cases are almost always fatal.

**Congenital Lymphocytic Choriomeningitis Virus Infection**

LCMV infection during pregnancy can kill the fetus and induce spontaneous abortion. Among surviving fetuses, the 2 clinical hallmarks of congenital LCMV infection are vision impairment and brain dysfunction.

The vision impairment in congenital LCMV infection is a result of chorioretinitis and the formation of choriotinal scars. The scarring is usually bilateral and most commonly located in the periphery of the fundus, but involvement of the macula also occurs.

Although the retinal injuries from congenital LCMV infection are often severe, it is the brain effects that cause the greatest disability. Prenatal infection with LCMV commonly induces either macrocephaly or microcephaly. Macrocephaly following LCMV infection is almost invariably caused by noncommunicating hydrocephalus, stemming from inflammation within the ventricular system. Microcephaly is a result of virus-induced failure of brain growth. In addition to disturbances of head size, periventricular calcifications are also cardinal features of congenital LCMV infection.

Although hydrocephalus, microencephaly, and periventricular calcifications are by far the most commonly observed abnormalities of the brain in congenital LCMV, other forms of neuropathology, alone or in combination, can also occur. These include periventricular cysts, porencephalic cysts, encephalomalacia, intraparenchymal calcifications, cerebellar hypoplasia, and neuronal migration disturbances.

Infants with congenital LCMV infection typically present during the newborn period with evidence of brain dysfunction. The most common signs are lethargy, seizures, irritability, and jitteriness.

Within the fetus, LCMV has a specific tropism for the brain. Thus, unlike many other congenital infections, LCMV usually does not induce systemic manifestations. Birthweight is typically appropriate for gestational age. Skin rashes and thrombocytopenia, which are common in several other prominent congenital infections, are unusual in congenital LCMV infection. Hepatosplenomegaly is only rarely observed, and serum liver enzyme levels are usually normal. Auditory deficits are unusual.

**LABORATORY FINDINGS**

In acquired (postnatal) LCMV infection, the hallmark laboratory abnormality occurs during the 2nd (central nervous system) phase of the disease and is CSF pleocytosis. The CSF typically contains hundreds to thousands of white blood cells, almost all of which are lymphocytes. However, CSF eosinophilia may also occur. Mild elevations of CSF protein and hypoglycorrhachia are common.

In congenital LCMV infection, laboratory findings in the newborn depend on whether the infant is still infected or not. If the infant still harbors the infection, then examination of the CSF may reveal a lymphocytic pleocytosis. Unlike many other congenital infections, LCMV does not typically induce elevations in liver enzymes, thrombocytopenia, or anemia. In many cases, the most reliably abnormal test is the head CT scan, which typically reveals a combination of microencephaly, hydrocephalus, and periventricular calcifications (Fig. 272-1).

**DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS**

Acute LCMV infections can be diagnosed by isolating the virus from CSF. Polymerase chain reaction has also been used to detect LCMV RNA in patients with active infections. However, by the time of birth, a baby prenatally infected with LCMV may no longer harbor the virus. Thus, congenital LCMV infection is more commonly diagnosed by serologic testing. The immunofluorescent antibody test detects both immunoglobulin (Ig) M and IgG and has greater sensitivity than the more widely available complement fixation method. The immunofluorescent antibody test is commercially available, and its specificity and sensitivity make it an acceptable diagnostic tool. A more sensitive test for detecting congenital LCMV infection is the enzyme-linked
Children with hydrocephalus from congenital LCMV infection often require placement of a ventriculoperitoneal shunt during infancy for treatment of hydrocephalus. Seizures often begin during early postnatal life, are often difficult to control, and require administration of multiple antiepileptic medications. The mental retardation induced by congenital LCMV infection is often profound. In most cases, affected children should be referred for educational intervention during early life. The spasticity accompanying congenital LCMV infection is often severe. Although physical therapy can help to maintain range of motion and minimize painful spasms and contractures, implantation of a baclofen pump is often helpful.

**PROGNOSIS**

The great majority of patients with postnatally acquired LCMV infection have a full recovery with no permanent sequelae. Rarely, postnatal infections induce hydrocephalus and require shunting. Rarer yet, postnatal LCMV infection is fatal.

In contrast to the usual benign outcome of postnatal infections, prenatal infections typically lead to severe and permanent disability. In children with congenital LCMV infection, brain function is nearly always impaired and chorioretinitis is invariably present. Mental retardation, cerebral palsy, ataxia, epilepsy, and blindness are common neurologic sequelae. However, children with congenital LCMV infection have diverse outcomes. All children with the combination of microencephaly and periventricular calcifications are profoundly neurologically impaired. Blindness, medically refractory epilepsy, spastic quadriaparesis, and mental retardation are typical of this group. However, other children with congenital LCMV infection who do not have the combination of microencephaly and periventricular calcifications often have a more favorable outcome, with less severe motor, mental, and vision impairments. Children with isolated hypoplasia may be ataxic but have only mild or moderate mental retardation and vision loss.

**PREVENTION**

No vaccine exists to prevent LCMV infection. However, measures can be taken to reduce the risk of infection. Because rodents, especially house mice, are the principal reservoir of LCMV, people can reduce their risk of contracting LCMV by minimizing their exposure to the secretions and excretions of mice. This can be accomplished most effectively by eliminating cohabitation with mice. Congenital LCMV infection will not occur unless a woman contracts a primary infection with LCMV during pregnancy. Thus, women should be especially careful to avoid contact or cohabitation with mice during pregnancy. Pregnant women should also avoid contact with pet rodents, especially mice and hamsters. These facts should be stressed during prenatal visits.

Acquisition of LCMV from solid organ transplantation represents a substantial risk to organ recipients. Prospective donors with LCMV meningitis or encephalitis pose a clear risk for transmitting a fatal infection to recipients. Healthcare providers, transplantation centers, and organ procurement organizations should be aware of the risks posed by LCMV and should consider LCMV in any potential donor with signs of aseptic meningitis but no identified infectious agent. The risks and benefits of offering and receiving organs from donors with LCMV infection should be carefully considered.

*Bibliography is available at Expert Consult.*
**Bibliography**


The hantavirus pulmonary syndrome (HPS) is caused by multiple closely related hantaviruses that have been identified from the western United States, with sporadic cases reported from the eastern United States (Fig. 273-1) and Canada and important foci of disease in several countries in South America. HPS is characterized by a febrile
Hantavirus Pulmonary Syndrome Cases, by State of Exposure

<table>
<thead>
<tr>
<th>State</th>
<th>Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>CA (60)</td>
<td>1-15</td>
</tr>
<tr>
<td>TX (35)</td>
<td>16-50</td>
</tr>
<tr>
<td>VT (1)</td>
<td>&gt;50</td>
</tr>
<tr>
<td>ME (1)</td>
<td>Zero cases</td>
</tr>
</tbody>
</table>

Total Cases: (N = 639 in 34 states)
28 cases with an unknown state of exposure. Cumulative case count per state valid as of April 21, 2014.

Source: Viral Special Pathogens Branch, CDC

Figure 273-1 Total number of confirmed cases of Hantavirus pulmonary syndrome, by state of exposure—United States, 1993-2014. N = 639 as of April 21, 2014. (From Viral Special Pathogens Branch, Centers for Disease Control and Prevention. Available at: http://www.cdc.gov/hantavirus/surveillance/reporting-state.html).

Hantavirus pulmonary syndrome (HPS), one of the most serious exotic infections, is a major public health threat. The disease is caused by a group of viruses that are currently classified as Hantaviruses. These viruses are transmitted to humans through rodent bites, inhalation, or ingestion of contaminated food or water. Hantaviruses are found worldwide, with HPS cases occurring in both the Western and Eastern hemispheres.

**ETIOLOGY**
Hantaviruses are a genus in the family Bunyaviridae, which are lipid-enveloped viruses. The rodent host is the primary reservoir for these viruses. The virus is transmitted to humans through contact with infected rodents or their excretions. Several species of hantaviruses exist, each with its own specific reservoir host and geographic distribution. For example, the Sin Nombre virus is primarily found in the United States, while the Dobrava virus is prevalent in Europe and Asia.

**PATHOGENESIS**
HPS is characterized by sudden and catastrophic pulmonary edema, resulting in anoxia and acute heart failure. The virus is detected in pulmonary capillaries, suggesting that pulmonary edema is the consequence of T-cell attack on virus-infected capillaries. Disease severity is predicted by the level of acute-phase viremia titer. A useful hamster model of HPS is available.

**CLINICAL MANIFESTATIONS**
HPS is characterized by a prodrome and a cardiopulmonary phase. The mean duration after the onset of prodromal symptoms to hospitalization is 5.4 days. The mean duration of symptoms to death is 8 days (median: 7 days; range: 2-16 days). The most common prodromal symptoms are fever and myalgia (100%); cough or dyspnea (76%); gastrointestinal symptoms, including vomiting, diarrhea, and midabdominal pain (76%); and headache (71%). The cardiopulmonary phase is heralded by progressive cough and shortness of breath. The most common initial physical findings are tachypnea (100%), tachycardia (94%), and hypotension (50%). Rapidly progressive acute pulmonary edema, hypoxia, and shock develop in most severely ill patients. Pulmonary vascular permeability is complicated by cardiogenic shock associated with increased vascular resistance. The clinical course of the illness is variable, and the course of HPS is dependent on the level of acute-phase viremia titer. A useful hamster model of HPS is available.

**DIAGNOSIS**
The diagnosis of HPS should be considered in a previously healthy patient presenting with a febrile prodrome and acute respiratory distress. Occurrence of thrombocytopenia with the febrile prodrome and outdoor exposure in the spring and summer months are strongly suggestive of HPS. Specific diagnosis of HPS is made by serologic tests that detect hantavirus immunoglobulin M antibodies. Early appearance of immunoglobulin G antibodies signals probable recovery. Hantavirus antigen can be detected in tissue by immunohistochemistry and amplification of hantavirus nucleotide sequences detected by reverse transcriptase polymerase chain reaction. The state health department or the Centers for Disease Control and Prevention should be consulted to assist in diagnosis, epidemiologic investigations, and outbreak control.

**Laboratory Findings**
Laboratory findings include leukocytosis (median: 26,000 cells/µL), elevated hematocrit resulting from hemocentration, thrombocytopenia (median: 64,000 cells/µL), prolonged prothrombin and partial
thromboplastin times, elevated serum lactate dehydrogenase concentration, decreased serum protein concentrations, proteinuria, and microscopic hematuria. Patients who die often experience disseminated intravascular coagulopathy including frank hemorrhage and exceptionally high leukocyte counts.

**Differential Diagnosis**
The differential diagnosis includes adult respiratory distress syndrome, pneumonic plague, psittacosis, severe mycoplasmal pneumonia, influenza, leptospirosis, inhalation anthrax, rickettsial infections, pulmonary tularemia, atypical bacterial and viral pneumonial diseases, legionellosis, meningococcemia, and other sepsis syndromes. The key determinant in the diagnosis of HPS is thrombocytopenia.

**TREATMENT**
Management of patients with hantavirus infection requires maintenance of adequate oxygenation and careful monitoring and support of cardiovascular function. The pathophysiology of HPS somewhat resembles that of dengue shock syndrome (see Chapter 269). Pressor or inotropic agents, such as dobutamine, should be administered in combination with judicious volume replacement to treat symptomatic hypotension or shock while avoiding exacerbation of the pulmonary edema. Intravenous ribavirin, which is lifesaving if given early in the course of HFRS and is effective in preventing death in the hamster model, has not yet been demonstrated to be of value in HPS.

Further information and advice about management, control measures, diagnosis, and collection of biohazardous specimens can be obtained from the Centers for Disease Control and Prevention, National Center for Infectious Diseases, Special Pathogens Branch, Atlanta, Georgia 30333 (404-639-1115).

**PROGNOSIS**
In some geographic areas fatality rates for HPS have been 50%. Severe abnormalities in hematocrit, white blood cell count, lactate dehydrogenase value, and partial thromboplastin time, and a high viral load predict death with high specificity and sensitivity. Early appearance of immunoglobulin G antibodies may signal a hopeful prognosis.

**PREVENTION**
Avoiding contact with rodents is the only preventive strategy against HPS. Rodent control in and around the home is important. Barrier nursing is advised, and biosafety level 3 facilities and practices are recommended for laboratory handling of blood, body fluids, and tissues from suspect patients or rodents, because the virus may be aerosolized.

*Bibliography is available at Expert Consult.*
**Bibliography**

Centers for Disease Control and Prevention: Hantavirus pulmonary syndrome (HPS) [http://www.cdc.gov/hantavirus/hps/].


Rabies virus is a bullet-shaped, negative-sense, single-stranded, enveloped RNA virus from the family Rhabdoviridae, genus *Lyssavirus*. There are currently 12 known genotypes of *Lyssavirus*, and more are under taxonomic consideration. The classic rabies virus (genotype 1) is distributed worldwide and naturally infects a large variety of animals. The other 6 genotypes are more geographically confined, with none found in the Americas. Seven *Lyssavirus* genotypes are associated with rabies in humans, although genotype 1 accounts for the great majority of cases. Within genotype 1, a number of genetic variants have been defined. Each variant is specific to a particular animal reservoir, although cross-species transmission can occur.

**Rabies**

Rabies virus is present on all continents except Antarctica. Rabies predominantly afflicts underaged, poor, and geographically isolated populations. Approximately 50,000 cases of human rabies occur in Africa and Asia annually. Theoretically, rabies virus can infect any mammal (which then can transmit disease to humans), but true animal reservoirs that maintain the presence of rabies virus in the population are limited to terrestrial carnivores and bats. Worldwide, transmission from dogs accounts for >90% of human cases. In Africa and Asia, other animals serve as prominent reservoirs, such as jackals, mongooses, and raccoon dogs. In industrialized nations, canine rabies has been largely controlled through the routine immunization of pets. In the United States, raccoons are the most commonly infected wild animal along the eastern seaboard. Three phylogenies of skunk rabies are endemic in the Midwest (north and south) and California, and gray foxes harbor rabies in Arizona and Texas and mongooses in Puerto Rico. Rabies occurs infrequently in livestock. Among American domestic pets, infected cats outnumber infected dogs, probably because cats frequently prowl unsupervised and are not uniformly subject to vaccine laws. Rabies is rare in small mammals, including mice, squirrels, and rabbits; to date, no animal-to-human transmission from these animals has been documented.

The epidemiology of human rabies in the United States is dominated by cryptocogenic bat rabies. Bats are migratory in the spring and fall; rabid bats are identified in every state of the union except Hawaii. In 1 study, the largest proportion of cases of human rabies were infected with a bat variant, and in almost all cases of bat-associated human rabies there was no history of a bat bite. Among inhabitants of the Peruvian Amazon region who have exposure to rabies infected vampire bats, there are some who have rabies virus neutralizing antibodies and have survived. Antibody-positive patients remember bat bites but do not recall symptoms of rabies.

In the United States, 30,000 episodes of rabies postexposure prophylaxis (PEP) occur annually. Between 1 and 3 endemic human cases are diagnosed annually, half postmortem. There have been 3 outbreaks of rabies associated with solid-organ and corneal transplantations.

**Transmission**

Rabies virus is found in large quantities in the saliva of infected animals, and transmission occurs almost exclusively through inoculation of the infected saliva through a bite or scratch from a rabid mammal. Approximately 35-50% of people bitten by a known rabies-infected animal and receiving no PEP contract rabies. The transmission rate is increased if the victim has suffered multiple bites and if the inoculation occurs in highly innervated parts of the body such as the face and the hands. Infection does not occur after exposure of intact skin to infected secretions, but virus may enter the body through intact mucous membranes. Claims that spelunkers may experience rabies after inhaling bat excreta have come under doubt, although inhalational exposure can occur during laboratory accidents.

No case of nosocomial transmission to a healthcare worker has been documented to date, but caregivers of a patient with rabies are advised to use full barrier precautions. The virus is rapidly inactivated in the environment, and contamination of fomites is not a mechanism of spread.

**Pathogenesis**

After inoculation, rabies virus replicates slowly and at low levels in muscle or skin. This slow initial step likely accounts for the disease’s long incubation period. Virus then enters the peripheral motor nerve, utilizing the nicotinic acetylcholine receptor and possibly several other receptors for entry. Once in the nerve, the virus travels by fast axonal transport, crossing synapses roughly every 12 hr. Rapid dissemination occurs throughout the brain and spinal cord before symptoms appear. Infection of the dorsal root ganglia is apparently futile but causes characteristic radiculitis. Infection concentrates in the brainstem, accounting for autonomic dysfunction and relative sparing of cognition. Despite severe neurologic dysfunction with rabies, histopathology reveals limited damage, inflammation, or apoptosis. The pathologic
hallmark of rabies, the Negri body, is composed of clumped viral nucleocapsids that create cytoplasmic inclusions on routine histology. Negri bodies can be absent in documented rabies virus infection. Rabies may be a metabolic disorder of neurotransmission; tetrahydrobiopterin deficiency in human rabies causes severe deficiencies in dopamine, norepinephrine, and serotonin metabolism.

After infection of the central nervous system, the virus travels anterogradely through the peripheral nervous system to virtually all innervated organs. It is through this route that the virus infects the salivary glands. Many victims of rabies die from uncontrolled cardiac dysrhythmia. Deficiency of tetrahydrobiopterin, an essential cofactor for neuronal nitric oxide synthase, is predicted to lead to spasm of the basilar arteries. Onset of vasospasm has been confirmed in a few patients within 5–8 days of first hospitalization, at about the time coma supervenes in the natural history. Increased intracranial pressure is regularly measured early in rabies in association with elevated N-acetylaspartate in cerebrospinal fluid (CSF), but is rarely radiologically apparent. Metabolites in CSF consistent with ketogenesis are associated with demise.

**CLINICAL MANIFESTATIONS**

The incubation period for rabies is 1-2 months, but is variable. In severe wounds to the head, symptoms may occur within 5 days after exposure, and occasionally the incubation period can extend to longer than 6 months. Rabies has 2 principal clinical forms. **Encephalitic** or **“furious”** rabies begins with nonspecific symptoms, including fever, sore throat, malaise, headache, nausea and vomiting, and weakness. These symptoms are often accompanied by paresthesia and pruritus at or near the site of the bite that then extend along the affected limb. Soon thereafter the patient begins to demonstrate symptoms of encephalitis, with agitation, depressed mentation, and, occasionally, seizures. Characteristically, patients with rabies encephalitis initially have periods of lucidity alternating with periods of profound encephalopathy. Hydrophobia and aerophobia are the cardinal signs of rabies; they are unique to humans and are not universal or specific. Phobic spasms are manifested by agitation and fear created by being offered a drink or fanning of air in the face, which in turn produce choking and aspiration through spasms of the pharynx, neck, and diaphragm. The illness is relentlessly progressive. There is a dissociation of electrophysiologic or encephalographic activity with findings of brainstem coma caused by anterograde denervation. Death almost always occurs within 1-2 days of hospitalization in developing countries and by 18 days of hospitalization with intensive care.

A second form of rabies known as **paralytic** or **“dumb”** rabies is seen much less frequently and is characterized principally by fever and ascending motor weakness affecting both the limbs and the cranial nerves. Most patients with paralytic rabies also have some element of encephalopathy as the disease progresses subacutely.

Case reports suggest that milder forms of rabies encephalitis may exist, and 16 rabies survivors are known. Rabies should be considered earlier and more frequently in the diagnosis than current practice.

**DIAGNOSTIC FEATURES**

The differential diagnosis of rabies encephalitis includes all forms of severe cerebral infections, tetanus, and some intoxications and envenomations. Rabies can be confused with autoimmune (anti-N-methyl-D-aspartate receptor) encephalitis, other infectious encephalitis, psychiatric illness, drug abuse, and conversion disorders. Paralytic rabies is most frequently confused with Guillain-Barré syndrome. The diagnosis of rabies is frequently delayed in Western countries because of its rarity and the unfamiliarity of the medical staff with the infection. These considerations highlight the need to pursue a history of contact with an animal belonging to 1 of the known reservoirs for rabies or to establish a travel history to a rabies-endemic region.

**DIAGNOSIS**

The Centers for Disease Control and Prevention (CDC) require a number of tests to confirm a clinically suspected case of rabies. Reverse transcription polymerase chain reaction is the most sensitive available assay for the diagnosis of rabies when done iteratively. Rabies virus RNA has been detected in saliva, skin, and brain by the reverse transcription polymerase chain reaction. The virus can be grown both in cell culture and after animal injection, but identification of rabies by these methods is slow. Rabies antigen is detected through immunofluorescence of saliva or biopsies of hairy skin or brain. Corneal impressions are not recommended. Rabies-specific antibody can be detected in serum or CSF samples, but most patients die while seronegative. Antirabies antibodies are present in the sera of patients who have received an incomplete course of the rabies vaccine, precluding a meaningful interpretation in this setting. Antibody in CSF is rarely detected after vaccination and is considered diagnostic of rabies regardless of immunization status. CSF abnormalities in cell count, glucose, and protein content are minimal and are not diagnostic. MRI findings in the brain are late.

**TREATMENT AND PROGNOSIS**

Rabies is generally fatal. Conventional critical care yielded 1 survivor from 74 attempts since 1990. Five of 16 patients survived without use of critical care (including 3 milder cases) and 7 with use of the Milwaukee Protocol (http://www.mch.edu/rabies). Survival using the Milwaukee Protocol is estimated at 20%; neurologic outcomes are poor in one third of patients. Neither rabies immunoglobulin (RIG) nor rabies vaccine provides benefit once symptoms have appeared. Among 11 survivors of rabies after use of biologics, 6 had poor neurologic outcomes. Among 5 vaccine-naïve survivors, 1 had a poor outcome. Antiviral treatments have not been effective. Ribavirin delays the immune response and should be avoided during early management. In contrast, appearance of the normal antibody response by 7 days is associated with clearance of salivary viral load and survival.

**PREVENTION**

Primary prevention of rabies infection includes vaccination of domestic animals and education to avoid wild animals, stray animals, and animals with unusual behavior.

**Immunization and Fertility Control of Animal Reservoirs**

The introduction of routine rabies immunization for domestic pets in the United States and Europe during the middle of the 20th century virtually eliminated infection in dogs, which prior to that time had been the principal transmitter of rabies to humans in developed, as well as nonindustrialized, countries. In the 1990s, control efforts in Europe and North America shifted to immunization of wildlife reservoirs of rabies, where rabies was newly emerging. These programs employed bait laced with either an attenuated rabies vaccine or a recombinant rabies surface glycoprotein inserted into vaccinia, distributed by air or hand into areas inhabited by rabid animals. Human contact with vaccine-laden bait has been infrequent. Adverse events after such contact have been rare, but the vaccinia vector poses a threat to the same population at risk for vaccinia itself, namely, pregnant women, immunocompromised patients, and people with atopic dermatitis. Mass culling of endemic reservoirs has never worked; vaccination and fertility control stop outbreaks. Bats are ubiquitous and very important for insect control. Less than 1% of free-flying bats but >8% of downed bats and bats found in dwellings are rabid.

**Postexposure Prophylaxis**

The relevance of rabies for most pediatricians centers on evaluating whether an animal exposure warrants PEP (Table 274-1). No case of rabies has been documented in a person receiving the recommended schedule of PEP since introduction of modern cellular vaccines in the 1970s.

Given the incubation period for rabies, PEP is a medical urgency, not emergency. Algorithms have been devised to aid practitioners in deciding when to initiate rabies PEP (Fig. 274-1). The decision to proceed ultimately depends on the local epidemiology of animal rabies.
as determined by active surveillance programs, information that can be obtained from local and state health departments. In general, bats, raccoons, skunks, coyotes, and foxes should be considered rabid unless proven otherwise through euthanasia and testing of brain tissue, whereas bites from small herbivorous animals (squirrels, hamsters, gerbils, chipmunks, rats, mice, and rabbits) can be discounted. The response to bites from a pet, particularly a dog, cat, or ferret, depends on local surveillance statistics and on whether the animal is available for observation.

The approach to nonbite bat exposures is controversial. In response to the observation that most cases of rabies in the United States have been caused by bat variants and that the majority of affected patients had no recollection of a bat bite, the CDC has recommended that rabies PEP be considered after any physical contact with bats and when a bat is found in the same room as persons who may not be able to accurately report a bite, assuming that the animal is unavailable for testing. Such people include young children, the mentally disabled, and intoxicated individuals. Other nonbite contacts (e.g., handling a carcass, exposure to an animal playing with a carcass, or coming into contact with blood or excreta from a potentially rabid animal) usually do not require PEP.

In all instances of a legitimate exposure, effort should be made to recover the animal for quarantine and observation or brain examination after euthanasia. Testing obviates the need for PEP more than half the time. In most instances, PEP can be deferred until the results of observation or brain histology are known. In dogs, cats, and ferrets, symptoms of rabies always occur within several days of viral shedding; therefore, in these animals a 10-day observation period is sufficient to eliminate the possibility of rabies.

No duration of time between exposure and onset of symptoms should preclude rabies prophylaxis. Rabies PEP is most effective when applied expeditiously. Nevertheless, the series should be initiated in the asymptomatic person as soon as possible, regardless of the length of time since the bite. The vaccine and RIG are contraindicated once symptoms develop.

The first step in rabies PEP is to cleanse the wound thoroughly. Soapy water is sufficient to inactivate an enveloped virus, and its effectiveness is supported by broad experience. Other commonly used

### Table 274-1 Rabies Postexposure Prophylaxis Guide

<table>
<thead>
<tr>
<th>ANIMAL TYPE</th>
<th>EVALUATION AND DISPOSITION OF ANIMAL</th>
<th>POSTEXPOSURE PROPHYLAXIS RECOMMENDATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dogs, cats, and ferrets</td>
<td>Healthy and available for 10 days of observation</td>
<td>Prophylaxis only if animal shows signs of rabies†</td>
</tr>
<tr>
<td></td>
<td>Rabid or suspected of being rabid‡</td>
<td>Immediate immunization and RIG</td>
</tr>
<tr>
<td></td>
<td>Unknown (escaped)</td>
<td>Consult public health officials for advice</td>
</tr>
<tr>
<td>Bats, skunks, raccoons,</td>
<td>Regarded as rabid unless geographic area is known to be free of rabies or until</td>
<td>Immediate immunization and RIG</td>
</tr>
<tr>
<td>foxes, and most other</td>
<td>animal proven negative by laboratory tests†</td>
<td></td>
</tr>
<tr>
<td>carnivores; woodchucks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Livestock, rodents, and</td>
<td>Consider individually</td>
<td>Consult public health officials. Bites of squirrels, hamsters,</td>
</tr>
<tr>
<td>lagomorphs (rabbits,</td>
<td></td>
<td>guinea pigs, gerbils, chipmunks, rats, mice and other rodents,</td>
</tr>
<tr>
<td>hares, and pikas)</td>
<td></td>
<td>rabbits, hares, and pikas almost never require antirabies</td>
</tr>
<tr>
<td></td>
<td></td>
<td>treatment</td>
</tr>
</tbody>
</table>

*During the 10-day observation period, at the first sign of rabies in the biting dog, cat, or ferret, treatment of the exposed person with RIG (human) and vaccine should be initiated. The animal should be euthanized and tested.
†The animal should be euthanized and tested as soon as possible. Holding for observation is not recommended. Immunization is discontinued if immunofluorescent test result for the animal is negative.
‡RIG, rabies immunoglobulin.


![Figure 274-1](image-url) Algorithm for evaluating a child for rabies postexposure prophylaxis. This and any other algorithm should be used in concert with local epidemiologic information regarding the incidence of animal rabies in any given location.
disinfectants, such as iodine-containing preparations, are virucidal and should be used in addition to soap when available. Probably the most important aspect of this component is that the wound is cleansed with copious volumes of disinfectant. Primary closure is avoided; wounds may be bacterially infected as well, so cosmetic repair should follow. Antibiotics and tetanus prophylaxis (see Chapter 211) should be applied with the use of usual wound care criteria.

The second component of rabies PEP consists of passive immunization with RIG. Most failures of PEP are attributed to not using RIG. Human RIG, the formulation used in industrialized countries, is administered at a dose of 20 IU/kg. As much of the dose is infused around the wound as possible, and the remainder is injected intramuscularly in a limb distant from the 1 injected with the killed vaccine. Like other immunoglobulin preparations, RIG interferes with the take of live viral vaccines for at least 4 mo after administration of the RIG dose. Human RIG is not available in many parts of the developing world. Equine RIG serves as a substitute for the human immunoglobulin preparation in some areas. Modern preparations of equine RIG are associated with fewer side effects than prior products composed of crude horse serum. Regrettably, for a large segment of the world’s population, no passive immunization product is available at all. Monoclonal antibody products are in clinical trials and may alleviate this deficiency.

The third component of rabies PEP is immunization with inactivated vaccine. In most of the world, cell-based vaccines have replaced previous preparations. Two formulations currently are available in the United States, namely, RabAvert (Chiron Behring Vaccines, Maharashtra, India), a purified chick-embryo cell cultivated vaccine, and Imovax Rabies (Aventis Pasteur, Bridgewater, NJ), cultivated in human diploid cell cultures. In both children and adults, both vaccines are administered intramuscularly in a 1 mL volume in the deltoid or anterolateral thigh on days 0, 3, 7, and 14 after presentation. Injection into the gluteal area is associated with a blunted antibody response, so this area should not be used. The rabies vaccines can be safely administered during pregnancy. In most persons the vaccine is well tolerated; most adverse effects are related to booster doses. Pain and erythema at the injection site occur commonly, and local adenopathy, headache, and myalgias occur in 10-20% of patients. Approximately 5% of patients who receive the human diploid cell vaccine experience an immune complex–mediated allergic reaction, including rash, edema, and arthralgias, several days after a booster dose. The World Health Organization has approved schedules using smaller amounts of vaccine, administered intradermally, that are immunogenic and protective (http://www.who.int/rabies/human/postexp/en/), but none is approved for use in the United States. Other cell culture–derived rabies virus vaccines are available in the developing world. A few countries still produce nerve tissue–derived vaccines; these preparations are poorly immunogenic, and cross reactivity with human nervous tissue may occur in their use, producing severe neurologic symptoms even in the absence of rabies infection.

**Preexposure Prophylaxis**

The killed rabies vaccine can be given to prevent rabies in persons at high risk for exposure to wild-type virus, including laboratory personnel working with rabies virus, veterinarians, and others likely to be exposed to rabid animals as part of their occupation. Preexposure prophylaxis should be considered for persons traveling to a rabies-endemic region where there is a credible risk for a bite or scratch from a rabies-infected animal, particularly if there is likely to be a shortage of RIG or cell culture–based vaccine (see Chapter 175). Rabies vaccine as part of the routine vaccine series is under investigation in some countries. The schedule for preexposure prophylaxis consists of 3 intramuscular injections on days 0, 7, and 21 or 28. PEP in the patient who has received preexposure prophylaxis or a prior full schedule of PEP consists of 2 doses of vaccine (1 each on days 0 and 3) and does not require RIG. Immunity from preexposure prophylaxis wanes after several years and requires boosting if the potential for exposure to rabid animals recurs.

Bibliography is available at Expert Consult.
Bibliography

The polyomaviruses are small (45 nm), nonenveloped, circular, double-stranded DNA viruses with genomes of approximately 5,000 bp. Because of the association of animal polyomaviruses with tumors in the animals they infect, there has also been concern for a relationship to neoplasia in humans; however, the only virus for which there is strong evidence for an etiologic role in neoplasia is Merkel cell polyomavirus (see below). Among the polyomaviruses, the traditional human pathogens are JC virus and BK viruses. In recent years the number of human polyomaviruses has expanded dramatically, with discovery in humans of 10 additional viruses. Two of the newer polyomaviruses, designated KI virus and WU virus, can be detected in respiratory samples from children; however, a pathogenic role for these viruses has not been proven to date. Merkel cell polyomavirus is associated with Merkel cell carcinoma, an unusual neuroectodermal tumor of the skin that occurs primarily in elderly and immunocompromised individuals. Clonal integration of Merkel cell polyomavirus DNA is present in Merkel cell carcinoma cells, supporting an etiologic role for the virus in the development of the tumor. Another human polyomavirus has been isolated from patients with the dermatologic condition trichodysplasia spinulosa and has been named trichodysplasia spinulosa-associated polyomavirus. Trichodysplasia spinulosa is a condition of the skin that occurs in immunocompromised individuals and involves the development of follicular papules and keratin spines, usually involving the face. Two other viruses, designated human polyomaviruses 6 and 7, have also been found in human skin samples, but are not presently known to cause disease. Human polyomavirus 9 was detected in serum from a renal transplant recipient. The most recently discovered viruses, named Malawi virus and St. Louis virus, were first detected in stool samples, but a role in gastrointestinal or other disease has not been established at this time.

JC and BK viruses are tropic for renal epithelium; JC virus also infects brain oligodendrocytes and is the etiologic agent of progressive multifocal leukoencephalopathy, a rare and fatal demyelinating disease of immunocompromised persons, especially those with AIDS. Progressive multifocal leukoencephalopathy is now known to occur in individuals receiving the immunomodulatory agents natalizumab (Tysabri), used to treat multiple sclerosis and Crohn disease, and efalizumab (Raptiva), used to treat psoriasis. It has also been reported in individuals receiving the anti-CD20 monoclonal antibody rituximab (Rituxan) and the anti-CD52 monoclonal antibody alemtuzumab (Campath). BK virus is the cause of transplant nephropathy in renal transplant recipients and of hemorrhagic cystitis in hematopoietic stem cell and bone marrow transplant recipients. Several million persons in the United States were exposed to simian virus 40 (SV40), an oncogenic polyomavirus of Asian macaques, from contaminated poliovirus vaccines administered during 1955-1963. There were no recognized sequelae and no demonstrable increased risk for cancer.

Seroepidemiologic studies have shown that infection with all of the human polyomaviruses appears to be widespread, often occurring during childhood. Primary infection with these viruses is not recognized clinically. Approximately half of children in the United States are infected with BK virus by 3-4 yr of age and with JC virus by 10-14 yr of age, and approximately 60-80% of adults are seropositive for 1 or both viruses. Infection with polyomaviruses is thought to persist throughout life, with JC and BK viruses remaining latent in renal epithelium, oligodendrocytes, and peripheral blood mononuclear cells. The site of latency of the other human polyomaviruses is not currently known. Approximately 30-50% of healthy persons have detectable BK or JC virus in renal tissue at autopsy. Reactivation and viruria occur...
with increased frequency with advancing age and are more common in immunocompromised persons. On the basis of polymerase chain reaction results, BK and JC viruria occur in 2.6% and 13.2%, respectively, of persons younger than 30 yr of age and in approximately 9% and 50%, respectively, of persons older than 60 yr of age.

Reactivation of BK and JC viruses with asymptomatic viruria occurs in 10-50% of hematopoietic stem cell and bone marrow transplant recipients and in 30% of renal transplant recipients. Of those renal transplant recipients who demonstrate BK viruria, approximately one third also have plasma viremia. Recipients with plasma viremia are at risk for development of nephropathy, which can clinically mimic allograft rejection and can result in failure of the allograft. Reduction of immunosuppression has been effective in preventing progression from viremia to nephropathy, and thus posttransplantation monitoring of either urine or plasma by polymerase chain reaction is important. It is particularly important to distinguish BK nephropathy from rejection because the treatments are different—increase in immunosuppression for rejection but decrease in immunosuppression for BK nephropathy.

Polymerase chain reaction is the preferred means to detect the BK and JC viruses. The high seroprevalence in the general population and lack of clear relationship to clinical illness limit the usefulness of serologic testing. There are no proven antiviral treatments for BK or JC virus infection, although cidofovir may be effective in some cases of BK-related transplant nephropathy. Effective treatment of AIDS with antiretroviral therapy can prevent the progression of progressive multifocal leukoencephalopathy.

*Bibliography is available at Expert Consult.*
Bibliography
Advances in research and major improvements in the treatment and management of HIV infection have brought about a substantial decrease in the incidence of new HIV infections and AIDS in children. Globally, there has been an estimated 58% decline in newly infected children since 2001, largely the result of antiretroviral treatment of HIV-infected pregnant women for the prevention of mother-to-child transmission. More than 90% of adults and children with HIV infection live in sub-Saharan Africa, where the disease continues to have a devastating impact (Fig. 276-1). Children experience more rapid disease progression than adults, with up to half of untreated children dying within the 1st 2 yr of life. This rapid progression is correlated with a higher viral burden and faster depletion of infected CD4 lymphocytes in infants and children than in adults. Accurate diagnostic tests and the early initiation of potent drugs to inhibit HIV replication have dramatically increased the ability to prevent and control this disease.

Etiology
HIV-1 and HIV-2 are members of the Retroviridae family and belong to the Lentivirus genus, which includes cytopathic viruses causing diverse diseases in several animal species. The HIV-1 genome contains 2 copies of single-stranded RNA that is 9.2 kb in size. At both ends of the genome there are identical regions, called long terminal repeats, which contain the regulation and expression genes of HIV. The remainder of the genome includes 3 major sections: the GAG region, which encodes the viral core proteins (p24 [capsid protein: CA], p17 [matrix protein: MA], p9, and p6, which are derived from the precursor p55); the POL region, which encodes the viral enzymes (i.e., reverse transcriptase [p51], protease [p10], and integrase [p32]); and the ENV region, which encodes the viral envelope proteins (gp120 and gp41, which are derived from the precursor gp160). Other regulatory proteins, such as transactivator of transcription (tat: p14), regulator of virion (rev: p19), negative regulatory factor (nef: p27), viral protein r (vpr: p15), viral infectivity factor (vif: p23), viral protein u (vpu in HIV-1: P16), and viral protein x (vpx in HIV-2: P15) are involved in transactivation, viral messenger RNA expression, viral replication, induction of cell cycle arrest, promotion of nuclear import of viral reverse transcription complexes, downregulation of CD4 receptors and class I major histocompatibility complex, proviral DNA synthesis, and virus release and infectivity (Fig. 276-2).

The HIV tropism to the target cell is determined by its envelope glycoprotein (Env). Env consists of 2 components, namely the surface heavily glycosylated subunit gp120 protein and the associated transmembrane subunit glycoprotein gp41. Both gp120 and gp41 are produced from the precursor protein gp160. The glycoprotein gp41 is very immunogenic and is used to detect HIV-1 antibodies in diagnostic assays; gp120 is a complex molecule that includes the highly variable V3 loop. This region is immunodominant for neutralizing antibodies. The heterogeneity of gp120 presents major obstacles in establishing an effective HIV vaccine. The gp120 glycoprotein also carries the binding site for the CD4 molecule, the most common host cell surface receptor of T lymphocytes. This tropism for CD4+ T cells is beneficial to the virus because of the resulting reduction in the effectiveness of the host immune system. Other CD4-bearing cells include macrophages and microglial cells. The observations that CD4+ cells are also infected by HIV and that some CD4+ T cells are resistant to such infections suggests that other cellular attachment sites are needed for the interaction between HIV and human cells. Several chemokines serve as coreceptors for the envelope glycoproteins, permitting membrane fusion and entry into the cell. Most HIV strains have a specific tropism for 1 of the chemokines, including the fusion-inducing molecule CXCR4, which acts as a coreceptor for HIV attachment to lymphocytes, and CCR5, a β chemokine receptor that facilitates HIV entry into macrophages. Several other chemokine receptors (CCR-3) have also been shown in vitro to serve as virus co-receptors. Other mechanisms of attachment of HIV to cells use nonneutralizing antiviral antibodies and complement receptors. The Fab portion of these antibodies attaches to the virus surface, and the Fc portion binds to cells that express Fc receptors (macrophages, fibroblasts), thus facilitating virus transfer into the cell. Other cell-surface receptors, such as mannose-binding protein on macrophages or DC-specific C-type lectin (DC-SIGN) on dendritic cells, also bind to the HIV-1 envelope glycoprotein and increase the efficiency of viral infectivity. Cell-to-cell transfer of HIV without formation of fully formed particles is a more rapid mechanism of spreading the infection to new cells than is direct infection by the virus.

Following viral attachment, gp120 and the CD4 molecule undergo conformational changes, and gp41 interacts with the fusion receptor on the cell surface (Fig. 276-3). Viral fusion with the cell membrane allows entry of viral RNA into the cell cytoplasm. This process involves accessory viral proteins (nef, vif) and binding of cyclophilin A (a host cellular protein) to the capsid protein (p24). The p24 protein is involved in virus uncoating, recognition by restriction factors, and nuclear importation and integration of the newly created viral DNA. Viral DNA copies are then transcribed from the virion RNA through viral reverse transcriptase enzyme activity, which builds the 1st DNA strand from the viral RNA and then destroys the viral RNA and builds a 2nd DNA strand to produce double-stranded circular DNA. The HIV-1 reverse transcriptase is error prone and lacks error-correcting mechanisms. Thus, many mutations arise, creating wide genetic variation in
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HIV-1 isolates even within an individual patient. Many of the drugs used to fight HIV infection were designed to block the reverse transcriptase action. The circular DNA is transported into the cell nucleus, using viral accessory proteins like vpr, where it is integrated (with the help of the virus integrase) into the host chromosomal DNA and referred to as the provirus. The provirus has the advantage of latency, as it can remain dormant for extended periods, making it extremely difficult to eradicate. The infected CD4+ T cells that survive long enough to revert to resting memory state become the HIV latent reservoir where the virus persists indefinitely even in patients who respond favorably to potent antiretroviral therapy. The molecular mechanisms of this latency are complex and involve unique biologic properties of the latent provirus (e.g., absence of tat, epigenetic changes inhibiting HIV gene expression) and the nature of the cellular host (e.g., absence of transcription factors like nuclear factor κB). Integration usually occurs near active genes, which allow a high level of viral production in response to various external factors such as an increase in inflammatory cytokines (by infection with other pathogens) and cellular activation. Anti-HIV drugs that block the integrase enzyme activity have been developed. Depending on the relative expression of the viral regulatory genes (tat, rev, nef), the proviral DNA may encode production of the viral RNA genome, which, in turn, leads to production of viral proteins necessary for viral assembly.

HIV-1 transcription is followed by translation. A capsid polyprotein is cleaved to produce, the virus-specific protease (p10), among other products. This enzyme is critical for HIV-1 assembly because it cleaves the long polyproteins into the proper functional pieces. Several HIV-1 antiprotease drugs have been developed, targeting the increased sensitivity of the viral protease, which differs from the cellular proteases. The regulatory protein vif is active in virus assembly and Gag processing. The RNA genome is then incorporated into the newly formed viral capsid that requires zinc finger domains (p7) and the matrix protein (MA: p17). The matrix protein forms a coat on the inner surface of the viral membrane, which is essential for the budding of the new virus from the host cell's surface. As new virus is formed, it buds through specialized membrane areas, known as lipid rafts, and is released. The virus release is facilitated by the viroporin vpu, which induces rapid degradation of newly synthesized CD4 molecules that impede viral budding. In addition, vpu counteracts host innate immunity (e.g., hampering natural killer T-cell activity).

Full-length sequencing of the HIV-1 genome demonstrated 3 different groups (M [main], O [outlier], and N [non-M, non-O]), probably occurring from multiple zoonotic infections from primates in different geographic regions. The same technique identified 8 groups of HIV-2 isolates. Group M diversified to 9 subtypes (or clades A to D, F to H, J and K). In each region of the world, certain clades predominate, for example, clade A in Central Africa, clade B in the United States and South America, clade C in South Africa, clade E in Thailand, and clade F in Brazil. Although some subtypes were identified within group O, none was found in any of the HIV-2 groups. Clades are mixed in some patients as a result of HIV recombination, and some crossing between groups (i.e., M and O) has been reported.

HIV-2 has a similar life cycle to HIV-1 and is known to cause infection in several monkey species. Subtypes A and B are the major causes of infection in humans, but rarely cause infection in children. HIV-2 differs from HIV-1 in its accessory genes (e.g., it has no vpu gene but contains the vpx gene, which is not found in HIV-1). It is most prevalent in western Africa, but increasing numbers of cases are reported from Europe and southern Asia. The diagnosis of HIV-2 infection is more difficult because of major differences in the genetic sequences between HIV-1 and HIV-2. Thus, several of the standard confirmatory assays (immunoblot), which are HIV-1 specific, may give indeterminate results with HIV-2 infection. If HIV-2 infection is suspected, a combination screening test that detects antibody to HIV-1 and HIV-2 peptides should be used. In addition, the rapid HIV detection tests have been less reliable in patients suspected to be dually infected with HIV-1 and HIV-2, because of lower antibody concentrations against HIV-2.

**EPIDEMIOLOGY**

The World Health Organization (WHO) estimated that in 2013, 3.2 million children younger than 15 yr of age worldwide were living with
HIV-1 infection, 90% of whom were from sub-Saharan Africa. Although the number of children born with HIV in this region decreased by 43% between 2009 and 2013, still 199,000 children were newly infected with HIV in 2013 alone. These trends reflect the slow but steady expansion of services to prevent perinatal transmission of HIV to infants. Unfortunately, through 2011, an estimated 16.6 million children have been orphaned by AIDS, defined as having 1 or both parents die from AIDS.

The vast majority of HIV infections in childhood are the result of vertical transmission from an HIV-infected mother. In the United States, approximately 10,800 children, adolescents, or young adults were reported to be living with perinatally acquired HIV infection in 2010. The number of U.S. children with AIDS diagnosed each year increased from 1984-1992 but then declined by more than 95% to <100 cases annually by 2003, largely from the success of prenatal screening and perinatal antiretroviral treatment of HIV-infected mothers and infants. Children of racial and ethnic minority groups are disproportionately overrepresented, particularly non-Hispanic African-Americans and Hispanics. Race and ethnicity are not risk factors for HIV infection but more likely reflect other social factors that may be predictive of increased risk for HIV infection, such as lack of educational and economic opportunities. New York, Florida, Texas, and California are the states with the highest number of cases of HIV in children in the United States.

Although adolescents (13-24 yr of age) represent a minority of U.S. AIDS cases (approximately 4%), they constitute a growing population of newly infected individuals; in 2011, almost 10,500 new cases of HIV were diagnosed in this age group, representing 21% of all new HIV infections in the United States. In 2009, 69% of all new youth infections occurred in young males who have sex with males (MSM), with a 48% increase in new infections in black MSM between 2006 and 2009. More than 50% of HIV-positive youth report being unaware of their diagnosis. Considering the long latency period between the time of infection and the development of clinical symptoms, reliance on AIDS case definition surveillance data significantly underrepresents the impact of the disease in adolescents. Based on a median incubation period of 8-12 yr, it is estimated that 15-20% of all AIDS cases were acquired between 13 and 19 yr of age.

Risk factors for HIV infection vary by gender in adolescents. For example, 91-93% of males between the ages of 13 and 24 yr with HIV acquire infection through sex with males. In contrast, 91-93% of adolescent females with HIV are infected through heterosexual contact. As in the pediatric population, adolescent racial and ethnic minority populations are overrepresented, especially among females.

**Transmission**

Transmission of HIV-1 occurs via sexual contact, parenteral exposure to blood, or vertical transmission from mother to child. The primary route of infection in the pediatric population is vertical transmission. Rates of transmission of HIV from mother to child have varied in high- and low-resource countries; the United States and Europe have documented transmission rates in untreated women between 12% and 30%, whereas transmission rates in Africa and Haiti have been higher (25-52%), likely because of more advanced maternal disease and the presence of coinfections. Perinatal treatment of HIV-infected pregnant women with antiretroviral drugs has dramatically decreased the rate to <2%.
Vertical transmission of HIV can occur before (intrauterine), during (intrapartum), or after delivery (through breast feeding). Although intrauterine transmission has been suggested by identification of HIV by culture or polymerase chain reaction (PCR) in fetal tissue as early as 10 wk, statistical modeling data suggest that the majority of in utero transmissions likely occur in late gestation, when the vascular integrity of the placenta weakens and microtransfusions across the maternal–fetal circulation occur. It is generally accepted that 20-30% of infected newborns are infected in utero, because this percentage of infants has laboratory evidence of infection (possible maternal culture or PCR) within the 1st wk of life. Some studies have found that viral detection soon after birth also correlates with early onset of symptoms and rapid progression to AIDS, consistent with more longstanding infection during gestation.

A higher percentage of HIV-infected children acquire the virus intrapartum, evidenced by the fact that 70-80% of infected infants do not demonstrate detectable virus until after 1 wk of age. The mechanism of transmission appears to be mucosal exposure to infected blood and cervicovaginal secretions in the birth canal, and intrauterine contractions during active labor/delivery could also increase the risk of late microtransfusions. Breastfeeding is the least-common route of vertical transmission in industrialized nations, but is responsible for as much as 40% of perinatal infections in resource-limited countries. Both free and cell-associated viruses have been detected in breast milk from HIV-infected mothers. The risk for transmission through breastfeeding is approximately 9-16% in women with established infection, but is 29-53% in women who acquire HIV postnatally, suggesting that the viremia experienced by the mother during primary infection at least triples the risk for transmission. Where replacement feeding is readily available and safe, it seems reasonable for women to substitute infant formula for breast milk if they are known to be HIV infected or are at risk for ongoing sexual or parenteral exposure to HIV. However, the WHO recommends that in low-resource countries where other diseases (diarrhea, pneumonia, malnutrition) substantially contribute to a high infant mortality rate, the benefit of breastfeeding outweighs the risk for HIV transmission, and HIV-infected women in developing countries should breastfeed their infants for at least the 1st 6 mo of life (see "Prevention" below).

Several risk factors influence the rate of vertical transmission: maternal viral load at delivery, perterm delivery (<34 wk gestation), and low maternal antenatal CD4 count. The most important variable appears to be the level of maternal viremia; the odds of transmission may be (see "Prevention" below). When the mucosa serves as the portal of entry for HIV, the 1st cells to be affected are the dendritic cells. These cells collect and process antigens introduced from the periphery and transport them to the lymphoid tissue. HIV does not infect the dendritic cell but binds to its DC-SIGN surface molecule, allowing the virus to survive until it reaches the lymphatic tissue. In the lymphatic tissue (e.g., lamina propria, lymph nodes), the virus selectively binds to cells expressing CD4 molecules on their surface, primarily helper T lymphocytes (CD4+ T cells) and cells of the monocyte-macrophage lineage. Other cells bearing CD4, such as microglia, astrocytes, oligodendroglia, and placental tissue containing villous Hofbauer cells, may also be infected by HIV. Additional factors (coreceptors) are necessary for HIV fusion and entry into cells. These factors include the chemokines CXCR4 (fusin) and CCR5. Other chemokines (CCR1, CCR3) may be necessary for the fusion of certain HIV strains. Several host genetic determinants affect the susceptibility to HIV infection, the progression of disease, and the response to treatment. These genetic variants vary in different populations. A deletion in the CCR5 gene that is protective against HIV infection (CCR5Δ32) is relatively common in whites but is rare in blacks. Several other genes that regulate chemokine receptors, ligands, the histocompatibility complex, and cytokines also influence the outcome of HIV infection. Usually, CD4+ lymphocytes migrate to the lymphatic tissue in response to viral antigens and then become activated and proliferate, making them highly susceptible to HIV infection. This antigen-driven migration and accumulation of CD4 cells within the lymphoid tissue may contribute to the generalized lymphadenopathy characteristic of the acute retroviral syndrome in adults and adolescents. HIV preferentially infects the very cells that respond to it (HIV-specific memory CD4 cells), accounting for the progressive loss of these cells and the subsequent loss of control of HIV replication. The continued destruction of memory CD4+ cells in the gastrointestinal tract leads to reduced integrity of the gastrointestinal epithelium followed by leakage of bacterial particles into the blood and increased inflammatory response, which cause further CD4+ cell loss. When HIV replication reaches a threshold (usually within 3-6 wk from the time of infection), a burst of plasma viremia occurs. This intense viremia causes flu or mononucleosis-like symptoms (fever, rash, lymphadenopathy, arthralgia) in 50-70% of infected adults. With establishment of a cellular and humoral immune response within 2-4 mo, the viral load in the blood declines substantially, and patients enter a phase characterized by a lack of symptoms and a return of CD4 cells to only moderately decreased levels.

The HIV rapidly responds to the immune system pressure by developing a genetically complex population (quasispecies) that successfully evade it. In addition, inappropriate use of antiretroviral treatment increases the ability of the virus to diverge even further. Early HIV-1 replication in children has no apparent clinical manifestations. Whether tested by virus isolation or by PCR for viral nucleic acid sequences, fewer than 40% of HIV–1-infected infants demonstrate evidence of the virus at birth. The virus load increases by 1-4 mo, and almost all HIV-infected infants have detectable HIV-1 in peripheral blood by 4 mo of age.

In adults, the long period of clinical latency (8-12 yr) is not indicative of viral latency. In fact, there is a very high turnover of virus and CD4 lymphocytes (more than a billion cells per day), gradually causing deterioration of the immune system, marked by depletion of CD4 cells.
Several mechanisms for the depletion of CD4 cells in adults and children have been suggested, including HIV-mediated single cell killing, formation of multinucleated giant cells of infected and uninfected CD4 cells (syncytia formation), virus-specific immune responses (natural killer cells, antibody-dependent cellular cytotoxicity), superantigen-mediated activation of T cells (rendering them more susceptible to infection with HIV), autoimmunity, and programmed cell death (apoptosis). The viral burden is greater in the lymphoid organs than in the peripheral blood during the asymptomatic period. As HIV virions and their immune complexes migrate through the lymph nodes, they are trapped in the network of dendritic follicular cells. Because the ability of HIV to replicate in T cells depends on the state of activation of the cells, the immune activation that takes place within the microenvironment of the lymph nodes in HIV disease serves to promote infection of new CD4 cells as well as subsequent viral replication within these cells. Monocytes and macrophages can be productively infected by HIV yet resist the cytopathic effect of the virus and, with their long lifespan, explain their role as reservoirs of HIV and as effectors of tissue damage in organs such as the brain. In addition, they reside in anatomic viral sanctuaries where current treatment agents are less effective.

The innate immune system responds almost immediately following HIV infection by recognizing the viral nucleic acids, once the virus fuses into the infected cell, by the toll-like receptor 7. This engagement leads to activation of proinflammatory cytokines and interferon (IFN-α), which blocks virus replication and spread. The virus uses its Nef protein to downregulate the expression of major histocompatibility complex (MHC) and non-MHC ligands to reduce the natural killing (NK) cell–mediated anti-HIV activity. It also modulates NK cell differentiation and maturation, dysregulates cytokine production, and increases apoptosis. While the mechanism by which the innate system triggers the adaptive immune responses is not yet fully understood, cell-mediated and humoral responses occur early in the infection. CD8 T cells play an important role in containing the infection. These cells produce various ligands (macrophage inflammatory proteins 1α and 1β, RANTES), which suppress HIV replication by blocking the binding of the virus to the coreceptors (CCR5). HIV-specific cytotoxic T lymphocytes (CTLs) develop against both the structural (ENV, POL, GAG) and regulatory (tat) viral proteins. The CTLs appear at the end of the acute infection, as viral replication is controlled by killing HIV-infected cells before new viruses are produced and by secreting potent antiviral factors that compete with the virus for its receptors (CCR5). Neutralizing antibodies appear later in the infection and seem to help in the continued suppression of viral replication during clinical latency. There are at least 2 possible mechanisms that control the steady-state viral load level during the chronic clinical latency. One mechanism may be the limited availability of activated CD4 cells, which prevent further increase in viral load. The other mechanism is development of an active immune response, which is influenced by the amount of viral antigen and limits viral replication at a steady state. There is no general consensus about which of these 2 mechanisms is more important. The CD4 cell limitation mechanism accounts for the effect of antiretroviral therapy, whereas the immune response mechanism emphasizes the importance of immune modulation treatment (cytokines, vaccines) to increase the efficiency of immune-mediated control. A group of cytokines that includes tumor necrosis factor TNF-α, TNF-β, interleukin IL-1, IL-2, IL-3, IL-6, IL-8, IL-12, IL-15, granulocyte-macrophage colony-stimulating factor, and macrophage colony-stimulating factor plays an integral role in upregulating HIV expression from a state of quiescent infection to active viral replication. Other cytokines such as IFN-γ, IFN-β, and IL-13 exert a suppressive effect on HIV replication. Certain cytokines (IL-4, IL-10, IFN-γ, transforming growth factor-β) reduce or enhance viral replication depending on the infected cell type. The interactions among these cytokines influence the concentration of viral particles in the tissues. Plasma concentrations of cytokines need not be elevated for them to exert their effect, because they are produced and act locally in the tissues. The activation of virtually all the cellular components of the immune system (i.e., T and B cells, natural killer cells, and monocytes) plays a significant role in the pathologic aspects of HIV infection. Further understanding of their interactions during the infection will expand our treatment options. Commonly, HIV isolated during the clinical latency period grows slowly in culture and produces low titers of reverse transcriptase. These isolates use CCR5 as their coreceptor. By the late stages of clinical latency, the isolated virus is phenotypically different. It grows rapidly and to high titers in culture and uses CXCR4 as its coreceptor. The switch from CCR5 receptor to CXCR4 receptor increases the capacity of the virus to replicate, to infect a broader range of target cells (CXCR4 is more widely expressed on resting and activated immune cells), and to kill T cells more rapidly and efficiently. As a result, the clinical latency phase is over and progression toward AIDS is noted. The progression of disease is related temporally to the gradual disruption of lymph node architecture and degeneration of the follicular dendritic cell network with loss of its ability to trap HIV particles. The virus is freed to recirculate, producing high levels of viremia and an increased disappearance of CD4 T cells during the later stages of disease.

The clinical course of the HIV infection shows a substantial heterogeneity. This variation is determined by both viral and host factors. HIV viruses that use coreceptor CXCR4 in the course of the infection are associated with an accelerated deterioration of the immune system and more rapid progression to AIDS. In addition, several host genetic determinants (e.g., variants in the human leukocyte antigen region, polymorphisms in the CCR5 region like CCR5Δ32) were already identified as affecting the disease course. Three distinct patterns of disease were described in children. Approximately 15-25% of HIV-infected newborns in developed countries present with a rapid disease course, with onset of AIDS and symptoms during the 1st few months of life and a median survival time of 6-9 mo if untreated. In resource-poor countries, the majority of HIV-infected newborns will have this rapidly progressing disease. It has been suggested that if intrauterine infection coincides with the period of rapid expansion of CD4 cells in the fetus, the virus could effectively infect the majority of the body's immunocompetent cells. The normal migration of these cells to the marrow, spleen, and thymus would result in efficient systemic delivery of HIV, unchecked by the immature immune system of the fetus. Thus, infection would be established before the normal ontogenic development of the immune system, causing more-severe impairment of immunity. Most children in this group have a positive HIV-1 culture and/or detectable virus in the plasma (median level: 11,000 copies/mL) in the 1st 48 hr of life. This early evidence of viral presence suggests that the newborn was infected in utero. The viral load rapidly increases, peaking by 2-3 mo of age (median: 750,000 copies/mL) and staying high for at least the 1st 2 yr of life.

From 60-80% of perinatally infected newborns in developed countries present with a much slower progression of disease, with a median survival time of 6 yr representing the 2nd pattern of disease. Many patients in this group have a negative viral culture or PCR in the 1st wk of life and are therefore considered to be infected intrapartum. In a typical patient, the viral load rapidly increases, peaking by 2-3 mo of age (median: 100,000 copies/mL) and then slowly declines over a period of 24 mo. The slow decline in viral load is in sharp contrast to the rapid decline after primary infection seen in adults. This observation can be explained only partially by the immaturity of the immune system in newborns and infants.

The 3rd pattern of disease occurs in <5% of perinatally infected children, referred to as long-term survivors, who have minimal or no progression of disease with relatively normal CD4 counts and very low viral loads for longer than 8 yr. Mechanisms for the delay in disease progression include efficient humoral immunity and/or CTL responses, host genetic factors (e.g., human leukocyte antigen profile), and infection with attenuated (defective gene) virus. A subgroup of the long-term survivors called “elite survivors” has no detectable viruses in the blood and may reflect different or greater mechanisms of protection from disease progression.

HIV-infected children have changes in the immune system that are similar to those in HIV-infected adults. CD4 cell depletion may be less dramatic because infants normally have a relative lymphocytosis. A value of 1,500 CD4 cells/μL in children younger than 1 yr of age is indicative of severe CD4 depletion and is comparable to <200 CD4
cells/µL in adults. Lymphopenia is relatively rare in perinatally infected children and is usually only seen in older children or those with end-stage disease. Although cutaneous anergy is common during HIV infection, it is also frequent in healthy children younger than 1 yr of age, and thus its interpretation is difficult in infected infants. The depletion of CD4 cells also decreases the response to soluble antigens such as in vitro mitogens phytohemagglutinin and concanavalin A.

Polyclonal activation of B cells occurs in most children early in the infection, as evidenced by elevation of immunoglobulin (Ig) A, IgM, IgG, and particularly IgG (hypermaglobulinemia), with high levels of anti–HIV-1 antibody. This response may reflect both dysregulation of T-cell suppression of B-cell antibody synthesis and active CD4 enhancement of B-lymphocyte humoral response. As a result, antibody response to routine childhood vaccinations may be abnormal. The B-cell dysregulation precedes the CD4 depletion in many children, and may serve as a surrogate marker of HIV infection in symptomatic children in whom specific diagnostic tests (PCR, culture) are not available or are too expensive. Despite the increased levels of immunoglobulins, some children lack specific antibodies or protective antibodies. Hypermaglobulinemia is very rare (<1%).

Central nervous system (CNS) involvement is more common in pediatric patients than in adults. Macroglia and microglia play an important role in HIV neuropathogenesis, and data suggest that astrocytes may also be involved. Although the specific mechanisms for encephalopathy in children are not yet clear, the developing brain in young infants is affected by at least 2 mechanisms. The virus itself may directly infect various brain cells or cause indirect damage to the nervous system by the release of cytokines (IL-1α, IL-1β, TNF-α, IL-2) or reactive oxygen from HIV-infected lymphocytes or macrophages.

Appropriate therapy with antiretroviral agents may result in immune reconstitution inflammatory syndrome (IRIS), which is characterized by an increased inflammatory response from the recovered immune system to subclinical opportunistic infections (e.g., Mycobacterium, herpes simplex virus [HSV] infection, toxoplasmosis, cytomegalovirus [CMV] infection, Pneumocystis, cryptococcal infection). This condition is more commonly observed in patients with progressive disease and severe CD4 T-lymphocyte depletion. Patients with IRIS develop fever and worsening of the clinical manifestations of the opportunistic infection or new manifestations (e.g., enlargement of lymph nodes, pulmonary infiltrates), typically within the 1st few weeks after initiation of antiretroviral therapy. Determining whether the symptoms represent IRIS, worsening of a current infection, a new opportunistic infection, or drug toxicity is often very difficult. If the syndrome does represent IRIS, adding nonsteroidal antiinflammatory agents or corticosteroids may alleviate the inflammatory reaction, although the use of corticosteroids is controversial. The inflammation may take weeks or months to subside. In most cases, continuation of anti-HIV treatment while treating the opportunistic infection (with or without antinflammatory agents) is sufficient. If opportunistic infection is suspected prior to initiation of antiretroviral therapy, appropriate antimicrobial treatment should be given first.

### CLINICAL MANIFESTATIONS

The clinical manifestations of HIV infection vary widely among infants, children, and adolescents. In most infants, physical examination at birth is normal. Initial symptoms may be subtle, such as lymphadenopathy and hepatosplenomegaly, or nonspecific, such as failure to thrive, chronic or recurrent diarrhea, respiratory symptoms, or oral thrush and may be distinguishable only by their persistence. Whereas systemic and pulmonary findings are common in the United States and Europe, chronic diarrhea, pneumonia, wasting, and severe malnutrition predominate in Africa. Clinical manifestations found more commonly in children than adults with HIV infection include recurrent bacterial infections, chronic parotid swelling, lymphocytic interstitial pneumonitis (LIP), and early onset of progressive neurologic deterioration.

The CDC Surveillance Case Definition for HIV infection was revised in 2014 and has consolidated the staging system for children with adolescents and adults. It is based on age-specific CD4 T-lymphocyte count or CD4 T-lymphocyte percentage of total lymphocytes (Table 276-1), except when a stage 3-defining opportunistic illness (Table 276-2) supersedes the CD4 data. Age adjustment of the absolute CD4 count is necessary because counts that are relatively high in normal infants decline steadily until age 6 yr, when they reach adult norms. The CD4 count takes precedence over the CD4 T-lymphocyte percentage, and the percentage is considered only if the count is missing.

### Infections

Approximately 20% of AIDS-defining illnesses in children are recurrent bacterial infections caused primarily by encapsulated organisms such as Streptococcus pneumoniae and Salmonella as a result of disturbances in humoral immunity. Other pathogens, including Staphylococcus, Enterococcus, Pseudomonas aeruginosa, Haemophilus influenzae, and other Gram-positive and Gram-negative organisms, may also be seen. The most common serious infections in HIV-infected children are bacteremia, sepsis, and bacterial pneumonia, accounting for more than 50% of infections in these patients. Meningitis, urinary tract infections, deep-seated abscesses, and bone/joint infections occur less frequently. Milder recurrent infections, such as otitis media, sinusitis, and skin and soft tissue infections, are very common and may be chronic with atypical presentations.

Opportunistic infections are generally seen in children with severe depression of the CD4 count. In adults, these infections usually represent reactivation of a latent infection acquired early in life. In contrast, young children generally have primary infection and often have a more fulminant course of disease reflecting the lack of prior immunity. This principle is best illustrated by Pneumocystis carinii pneumonia, the most common opportunistic infection in the pediatric population (see Chapter 244). The peak incidence of Pneumocystis pneumonia occurs at age 3–6 mo in the setting of undiagnosed perinatally acquired disease, with the highest mortality rate in children younger than 1 yr of age. Aggressive approaches to treatment have improved the outcome substantially. While the overall

<table>
<thead>
<tr>
<th>Table 276-1</th>
<th>HIV Infection Stage* Based on Age-Specific CD4 T-Lymphocyte Count or CD4 T-Lymphocyte Percentage of Total Lymphocytes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stage</strong></td>
<td><strong>&lt;1 Yr</strong></td>
</tr>
<tr>
<td>1</td>
<td>≥1,500</td>
</tr>
<tr>
<td>2</td>
<td>750-1,499</td>
</tr>
<tr>
<td>3</td>
<td>&lt;750</td>
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</table>

*Stage is based primarily on the CD4 T-lymphocyte count. The CD4 T-lymphocyte count takes precedence over the CD4 T-lymphocyte percentage, and the percentage is considered only if the count is missing.

Table 276-2  Stage 3—Defining Opportunistic Illnesses in HIV Infection

| Bacterial infections, multiple or recurrent* | 
| Candidiasis of bronchi, trachea, or lungs | 
| Candidiasis of esophagus | 
| Cervical cancer, invasive | 
| Coccidioidomycosis, disseminated or extrapulmonary | 
| Cryptococcosis, extrapulmonary | 
| Cryptosporidiosis, chronic intestinal (>1 mo duration) | 
| Cytomegalovirus disease (other than liver, spleen, or nodes), onset at age >1 mo | 
| Cytomegalovirus retinitis (with loss of vision) | 
| Encephalopathy attributed to HIV | 
| Herpes simplex: chronic ulcers (>1 mo duration) or bronchitis, pneumonitis, or esophagitis (onset at age >1 mo) | 
| Histoplasmosis, disseminated or extrapulmonary | 
| Isosporiasis, chronic intestinal (>1 mo duration) | 
| Kaposi sarcoma | 
| Lymphoma, Burkitt (or equivalent term) | 
| Lymphoma, immunoblastic (or equivalent term) | 
| Lymphoma, primary, of brain | 
| Mycobacterium avium complex or Mycobacterium kansasii, disseminated or extrapulmonary | 
| Mycobacterium tuberculosis of any site, pulmonary, disseminated, or extrapulmonary | 
| Mycobacterium, other species or unidentified species, disseminated or extrapulmonary | 
| Pneumocystis jiroveci (previously known as Pneumocystis carinii) pneumonia | 
| Pneumonia, recurrent | 
| Progressive multifocal leukoencephalopathy | 
| Salmonella septicemia, recurrent | 
| Toxoplasmosis of brain, onset at age >1 mo | 
| Wasting syndrome attributed to HIV | 

*Only among children aged <6 yr.
†Only among adults, adolescents, and children aged ≥6 yr.
‡Suggested diagnostic criteria for these illnesses, which might be particularly important for HIV encephalopathy and HIV wasting syndrome, are described in the following references: Centers for Disease Control and Prevention: 1994 Revised classification system for human immunodeficiency virus infection in children less than 13 years of age. MMWR 43(No. RR-12), 1994. Centers for Disease Control and Prevention: 1993 Revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. MMWR 41(No. RR-17), 1992.

The incidence of opportunistic infections has markedly declined since the era of combination antiretroviral therapy, opportunistic infections still occur in patients with severe immunodeficiency as the result of unchecked viral replication, which often accompanies poor antiretroviral therapy adherence.

The classic clinical presentation of Pneumocystis pneumonia includes acute onset of fever, tachypnea, dyspnea, and marked hypoxemia; in some children, more indolent development of hypoxemia may precede other clinical or x-ray manifestations. Chest x-ray findings most commonly consist of interstitial infiltrates or diffuse alveolar disease, which rapidly progresses. Nodular lesions, streaky or lobar infiltrates, or pleural effusions may occasionally be seen. Diagnosis is established by demonstration of P. jiroveci with appropriate staining of induced sputum or bronchoalveolar fluid lavage; rarely, an open lung biopsy is necessary.

The 1st-line therapy for Pneumocystis pneumonia is intravenous trimethoprim-sulfamethoxazole (TMP-SMZ) (15-20 mg/kg/day of the TMP component every 6 hr IV) with adjunctive corticosteroids if the \( Pao2 \) is <70 mm Hg while breathing room air. When the patient has improved, therapy with oral TMP-SMZ should be continued for a total of 21 days while the corticosteroids are weaned. Alternative therapy for Pneumocystis pneumonia includes intravenous administration of pentamidine (4 mg/kg/day). Other regimens such as TMP plus dapsone, clindamycin plus primaquine, or atovaquone are used as alternatives in adults but have not been widely used in children to date.

Non tuberculous mycobacterial infection, with Mycobacterium avium intracellulare complex (MAC), may cause disseminated disease in HIV-infected children who are severely immunosuppressed. The incidence of MAC infection in antiretroviral therapy-naïve children with <100 CD4 cells/mm\(^3\) is estimated to be as high as 10%, but effective cART that results in viral suppression makes MAC infections rare. Disseminated MAC infection is characterized by fever, malaise, weight loss, and night sweats; diarrhea, abdominal pain, and frequently, intestinal perforation or jaundice (a result of biliary tract obstruction by lymphadenopathy) may also be present. Diagnosis is made by isolation of MAC from blood, bone marrow, or tissue; the isolated presence of MAC in the stool does not confirm a diagnosis of disseminated MAC. Treatment can reduce symptoms and prolong life but is at best only capable of suppressing the infection if severe CD4 depletion persists. Therapy should include at least 2 drugs: clarithromycin or azithromycin and ethambutol. A 3rd drug (rifabutin, rifampin, ciprofloxacin, levofloxacin, or amikacin) is generally added to decrease the emergence of drug-resistant isolates. Careful consideration of possible drug interactions with antiretroviral agents is necessary before initiation of disseminated MAC therapy. Drug susceptibilities should be ascertained, and the treatment regimen should be adjusted accordingly in the event of inadequate clinical response to therapy. Because of the great potential for toxicity with most of these medications, surveillance for adverse effects should be ongoing.

Oral candidiasis is the most common fungal infection seen in HIV-infected children. Oral nystatin suspension (2-5 mL qid) is often effective. Clotrimazole troches or fluconazole (3-6 mg/kg PO qd) are an effective alternative. Oral thrush progresses to involve the esophagus in as many as 20% of children with severe CD4 depletion, presenting with symptoms such as anorexia, dysphagia, vomiting, and fever. Treatment with oral fluconazole for 7-14 days generally results in rapid improvement in symptoms. Fungemia rarely occurs, usually in the setting of indwelling venous catheters, and up to 50% of cases may be caused by non–albicans species. Disseminated histoplasmosis, coccidioidomycosis, and cryptococcosis are rare in pediatric patients but may occur in endemic areas. Parasitic infections such as intestinal cryptosporidiosis and microsporidiosis and rarely isosporiasis or gobartis are other opportunistic infections that cause significant morbidity. Although these intestinal infections are usually self-limiting in healthy hosts, they cause severe chronic diarrhea in HIV-infected children with low CD4 counts, often leading to malnutrition. Nitazoxanide therapy is partially effective at improving cryptosporidia diarrhea, but immune reconstitution with cART is the most important factor for clearance of the infection. Albendazole has been reported to be effective against some microsporidia, and TMP-SMZ appears to be effective for isosporiasis.

Viral infections, especially with the herpesvirus group, pose significant problems for HIV-infected children. HSV causes recurrent gingivostomatitis, which may be complicated by local and distant cutaneous dissemination. Primary varicella-zoster virus infection (chickenpox) may be prolonged and complicated by bacterial infections or visceral dissemination, including pneumonitis. Recurrent, atypical, or chronic episodes of herpes zoster are often debilitating and require prolonged therapy with acyclovir; in rare instances, varicella-zoster virus has developed resistance to acyclovir, requiring the use of foscarinet. Disseminated CMV infection occurs in the setting of severe CD4 depletion (<50 CD4 cells/µL) and may involve single or multiple organs. Retinitis, pneumonitis, esophagitis, gastritis with pyloric obstruction, hepatitis, colitis, and encephalitis have been reported, but these complications are rarely seen if cART is given. Ganciclovir (6 mg/kg bid IV) and foscarinet (60 mg/kg tid IV) are the drugs of choice and are often given together in children with sight-threatening CMV retinitis. Intraocular injections of foscarinet or intraocular ganciclovir implants plus oral valganciclovir have also been efficacious in adults and older children with CMV retinitis. Measles may occur despite immunization and may present without the typical rash. It often disseminates to the lung or brain with a high mortality rate.
Respiratory viruses such as respiratory syncytial virus and adenovirus may present with prolonged symptoms and persistent viral shedding. In parallel with the increased prevalence of genital tract human papillomavirus infection, cervical intraepithelial neoplasia and anal intraepithelial neoplasia also occur with increased frequency among HIV-1-infected adult women compared with HIV-seronegative women. The relative risk for cervical intraepithelial neoplasia is 5-10 times higher for HIV-1 seropositive women. Multiple modalities are used to treat human papillomavirus infection (see Chapter 266), although none is uniformly effective and the recurrence rate is high among HIV-1-infected persons.

Central Nervous System
The incidence of CNS involvement in perinatally infected children is as high as 50-90% in resource-limited countries but significantly lower in developed countries, with a median onset at 19 mo of age. Manifestations may range from subtle developmental delay to progressive encephalopathy with loss or plateau of developmental milestones, cognitive deterioration, impaired brain growth resulting in acquired microcephaly, and symmetric motor dysfunction. Encephalopathy may be the initial manifestation of the disease or may present much later when severe immune suppression occurs. With progression, marked apathy, spasticity, hyperreflexia, and gait disturbance may occur, as well as loss of language and oral, fine, and/or gross motor skills. The encephalopathy may progress intermittently, with periods of deterioration followed by transiently stable plateaus. Older children may exhibit behavioral problems and learning disabilities. Associated abnormalities identified by neuroimaging techniques include cerebral atrophy in up to 85% of children with neurologic symptoms, increased ventricular size, basal ganglia calcifications, and, less frequently, leukomalacia.

Fortunately, since the advent of cART, the incident rate of encephalopathy has dramatically declined to as low as 0.08% in 2006. However, as HIV-infected children progress through adolescence and young adulthood, other subtle manifestations of CNS disease are evident, such as cognitive deficits, attention problems, and psychiatric disorders. Living with a chronic, often stigmatizing, disease, parental loss, and the requirement for lifelong pristine medication adherence compounds these issues, making it challenging for these youth as they inherit responsibility for managing their disease as adults.

Focal neurologic signs and seizures are unusual and may imply a comorbid pathologic process such as a CNS tumor, opportunistic infection, or stroke. CNS lymphoma may present with new onset focal neurologic findings, headache, seizures, and mental status changes. Characteristic findings on neuroimaging studies include a hyperdense or isodense mass with variable contrast enhancement or a diffusely infiltrating contrast-enhancing mass. CNS toxoplasmosis is exceedingly rare in young infants, but may occur in HIV-infected adolescents and is typically associated with serum antitoxoplasma IgG as a marker of infection. Other opportunistic infections of the CNS are rare and include infection with CMV, JC virus (progressive multifocal leukoencephalopathy), HSV, Cryptococcus neoformans, and Coccidioides immitis. Although the true incidence of cerebrovascular disorders (both hemorrhagic and nonhemorrhagic strokes) is unclear, 6-10% of children from large clinical series have been affected.

Respiratory Tract
Recurrent upper respiratory tract infections such as otitis media and sinusitis are very common. Although the typical pathogens (S. pneumoniae, H. influenzae, Moraxella catarrhalis) are most common, unusual pathogens such as P. aeruginosa, yeast, and anaerobes may be present in chronic infections and result in complications such as invasive sinusitis and mastoiditis.

LIP is the most common chronic lower respiratory tract abnormality reported to the Centers for Disease Control and Prevention (CDC); historically this occurred in approximately 25% of HIV-infected children, although the incidence has declined in the cART era. LIP is a chronic process with nodular lymphoid hyperplasia in the bronchial and bronchial epithelium, often leading to progressive alveolar capillary block over months to years. It has a characteristic chronic diffuse reticulonodular pattern on chest radiography rarely accompanied by hilar lymphadenopathy, allowing a presumptive diagnosis to be made radiographically before the onset of symptoms. There is an insidious onset of tachypnea, cough, and mild to moderate hypoxemia with normal auscultatory findings or minimal rales. Progressive disease presents with symptomatic hypoxemia, which usually resolves with oral corticosteroid therapy, accompanied by digital clubbing. Several studies suggest that LIP is a lymphoproliferative response to a primary Epstein-Barr virus infection in the setting of HIV infection. Most symptomatic HIV-infected children experience at least 1 episode of pneumonia during the course of their disease. S. pneumoniae is the most common bacterial pathogen, but P. aeruginosa and other Gram-negative bacterial pneumonias may occur in end-stage disease and are often associated with acute respiratory failure and death. Rarely, severe recurrent bacterial pneumonia results in bronchiectasis. Pneumocystis pneumonia is the most common opportunistic infection, but other pathogens, including CMV, Aspergillus, Histoplasma, and Cryptococcus, can cause pulmonary disease. Infection with common respiratory viruses, including respiratory syncytial virus, parainfluenza, influenza, and adenovirus, may occur simultaneously and have a protracted course and period of viral shedding from the respiratory tract. Pulmonary and extrapulmonary tuberculosis (TB) has been reported with increasing frequency in HIV-infected children in low-resource countries, although it is considerably more common in HIV-infected adults. Because of drug interactions between rifampin and ritonavir-based antiretroviral therapy and poor tolerability of the combination of multiple drugs required, treatment of TB/HIV coinfection is particularly challenging in children.

Cardiovascular System
Cardiac dysfunction, including left ventricular hypertrophy, left ventricular dilation, reduced left ventricular fractional shortening, and/or heart failure occurred in 18-39% of HIV-infected children in the pre-cART era; among those affected, lower nadir CD4 percent and a higher viral load were associated with lower cardiac function. However, a more recent evaluation of HIV-infected children taking long-term cART found that echocardiographic findings were closer to normal and none had symptomatic heart disease, suggesting that ART has a cardioprotective effect. What is still unclear is whether an increased rate of premature cardiovascular disease that has been seen in adults will be seen in children who have disease- or treatment-related hyperlipidemia, and prospective studies will be needed to assess this risk.

Gastrointestinal and Hepatobiliary Tract
Oral manifestations of HIV disease include erythematous or pseudo-membranous candidiasis, periodontal disease (e.g., ulcerative gingivitis or periodontitis), salivary gland disease (i.e., swelling, xerostomia), and rarely ulcerations or oral hairy leukoplakia. Gastrointestinal tract involvement is common in HIV-infected children. A variety of pathogens can cause gastrointestinal disease, including bacteria (Salmonella, Campylobacter, MAC), protozoa (Giardia, Cryptosporidium, Isospora, microsporidia), viruses (CMV, HSV, rotavirus), and fungi (Candida). MAC and the protozoal infections are most severe and protracted in patients with severe CD4 cell depletion. Infections may be localized or disseminated and affect any part of the gastrointestinal tract from the oropharynx to the rectum. Oral or esophageal ulcerations, either viral in origin or idiopathic, are painful and often interfere with eating. AIDS enteropathy, a syndrome of malabsorption with partial villous atrophy not associated with a specific pathogen, has been postulated to be a result of direct HIV infection of the gut. Disaccharide intolerance is common in HIV-infected children with chronic diarrhea.

The most common symptoms of gastrointestinal disease are chronic or recurrent diarrhea with malabsorption, abdominal pain, dysphagia, and failure to thrive. Prompt recognition of weight loss or poor growth velocity in the absence of diarrhea is critical. Linear growth impairment often correlates with the level of HIV viremia. Supplemental enteral feedings should be instituted, either by mouth or with nighttime nasogastric tube feedings in cases associated with more severe chronic
growth problems; placement of a gastrostomy tube for nutritional supple-
mentation may be necessary in severe cases. The wasting syndrome, de-
defined as a loss of >10% of body weight, is not as common as failure to
thrive in pediatric patients, but the resulting malnutrition is associated
with a grave prognosis. Chronic liver inflammation evidenced by fluc-
tuating serum levels of transaminases with or without cholestasis is
relatively common, often without identification of an etiologic agent.
Cryptosporidial cholecystitis is associated with abdominal pain, jaun-
dice, and elevated γ-glutamyltransferase. In some patients, chronic
hepatitis caused by CMV, hepatitis B, hepatitis C, or MAC may lead to
portal hypertension and liver failure. Several of the antiretroviral drugs
or other drugs such as didanosine, protease inhibitors, nevirapine, and
dapsone may also cause reversible elevation of transaminases.

Pancreatitis with increased pancreatic enzymes with or without
abdominal pain, vomiting, and fever may be the result of drug therapy
(e.g., with pentamidine, didanosine, or lamivudine) or, rarely, oppor-
tunistic infections such as MAC or CMV.

**Renal Disease**

Nephropathy is an unusual presenting symptom of HIV infection,
more commonly occurring in older symptomatic children. A direct
effect of HIV on renal epithelial cells has been suggested as the cause,
but immune complexes, hyperviscosity of the blood (secondary to
hyperglobulinemia), and nephrotoxic drugs are other possible factors.
A wide range of histologic abnormalities has been reported, including
focal glomerulosclerosis, mesangial hyperplasia, segmental necrotizing
glomerulonephritis, and minimal change disease. Focal glomeruloscle-
rosis generally progresses to renal failure within 6–12 mo, but other
histologic abnormalities in children may remain stable without signifi-
cant renal insufficiency for prolonged periods. Nephrotic syndrome is
the most common manifestation of pediatric renal disease, with edema,
hyaloalbuminuria, proteinuria, and azotemia with normal blood pres-
sure. Cases resistant to steroid therapy may benefit from cyclosporine
therapy. Polyuria, oliguria, and hematuria have also been observed in
some patients.

**Skin Manifestations**

Many cutaneous manifestations seen in HIV-infected children are
inflammatory or infectious disorders that are not unique to HIV infec-
tion. These disorders tend to be more disseminated and respond less
consistently to conventional therapy than in the uninfected child. Seb-
orrhoeic dermatitis or eczema that is severe and unresponsive to treat-
ment may be an early nonspecific sign of HIV infection. Recurrent or
chronic episodes of HSV, herpes zoster, molluscum contagiosum, flat
warts, anogenital warts, and candidal infections are common and may
be difficult to control. Allergic drug eruptions are also common, in particular related to
nonnucleoside reverse transcription inhibitors, and generally respond
to withdrawal of the drug but also may resolve spontaneously without
drug interruption: rarely, progression to Stevens-Johnson syndrome
has been reported. Epidermal hyperkeratosis with dry, scaling skin is
frequently observed, and sparse hair or hair loss may be seen in the
later stages of the disease.

**Hematologic and Malignant Diseases**

Anemia occurs in 20–70% of HIV-infected children, more commonly
in children with AIDS. The anemia may be a result of chronic infection,
poor nutrition, autoimmune factors, virus-associated conditions
(hemophagocytic syndrome, parvovirus B19 red cell aplasia), or the
adverse effect of drugs (zidovudine).

Leukopenia occurs in almost 30% of untreated HIV-infected chil-
dren, and neutropenia often occurs. Multiple drugs used for treatment
or prophylaxis for opportunistic infections, such as *Pneumocystis*
pneumonia, MAC, and CMV, or antiretroviral drugs (zidovudine) may
also cause leukopenia and/or neutropenia. In cases in which therapy
cannot be changed, treatment with subcutaneous granulocyte colony-
stimulating factor may be necessary.

Thrombocytopenia has been reported in 10–20% of patients. The
etiology may be immunologic (i.e., circulating immune complexes or
antiplatelet antibodies) or, less commonly, from drug toxicity, or the
cause may be unknown. Antiretroviral (ARV) therapy may also reverse
thrombocytopenia in ARV-naïve patients. In the event of sustained
severe thrombocytopenia (<10,000 platelets/µL), treatment with intra-
venous immunoglobulin or anti-D offers temporary improvement in
most patients already taking ARVs. If ineffective, a course of steroids
may be an alternative, but consultation with a hematologist should be
sought. Deficiency of clotting factors (factors II, VII, IX) is not rare in
children with advanced HIV disease and is often easy to correct with
vitamin K. A novel disease of the thymus has been observed in a few
HIV-infected children. These patients were found to have characteris-
tic anterior mediastinal multilocular thymic cysts without clinical
symptoms. Histologic examination shows focal cystic changes, follicu-
lar hyperplasia, and diffuse plasmacytosis and multinucleated giant
cells. Treatment with cART may result in resolution, or spontaneous
involution occurs in some cases.

In contrast to the more frequent occurrence in adults, malignant
diseases have been reported infrequently in HIV-infected children,
representing only 2% of AIDS-defining illnesses. Non-Hodgkin lym-
phoma, primary CNS lymphoma, and leiomyosarcoma are the most
commonly reported neoplasms among HIV-infected children. Epstein-
Barr virus is associated with most lymphomas and with all leiomyo-
sarcomas (see Chapter 254). Kaposi sarcoma, which is caused by
human herpesvirus 8, occurs frequently among HIV-infected adults
but is exceedingly uncommon among HIV-infected children in
resource-rich countries (see Chapter 257).

**DIAGNOSIS**

All infants born to HIV-infected mothers test antibody-positive at
birth because of passive transfer of maternal HIV antibody across the
placenta during gestation. Most uninfected infants without ongoing
exposure (i.e., who are not breastfed) lose maternal antibody between
6 and 12 mo of age and are known as seronegatives. Because a small
proportion of uninfected infants continue to test HIV antibody-
positive for up to 18 mo of age, positive IgG antibody tests, including
the rapid tests, cannot be used to make a definitive diagnosis of HIV
infection in infants younger than this age. The presence of IgA or IgM
anti-HIV in the infant's circulation can indicate HIV infection, because
these immunoglobulin classes do not cross the placenta; however, IgA
and IgM anti-HIV assays have been both insensitive and nonspecific
and therefore are not valuable for clinical use. In any child older than
18 mo of age, demonstration of IgG antibody to HIV by a repeatedly
reactive enzyme immunoassay and confirmatory Western blot test
establishes the diagnosis of HIV infection. Breastfed infants should
have antibody testing performed 12 wk following cessation of breast-
feeding to identify those who became infected at the end of lactation
by the HIV-infected mother. Certain diseases (e.g., syphilis, autoim-
mune diseases) may cause false-positive or indeterminate results. In
such cases specific viral diagnostic tests (see later) have to be done.

Several rapid HIV tests are currently available with sensitivity and
specificity better than those of the standard enzyme immunoassay.
Many of these tests require only a single step that allows test results to
be reported within less than 30 min. Incorporating rapid HIV testing
during delivery or immediately after birth is crucial for the care of
HIV-exposed newborns whose HIV status was unknown during preg-
nancy. A positive rapid test has to be confirmed by Western blot testing.
However, if 2 different rapid tests (testing different HIV-associated
antibodies) are positive, there is no need for further verification with
Western blot testing. In infants who are at risk of exposure to HIV-2
infection (e.g., born to an HIV-infected woman from West Africa), a
rapid test that can detect both HIV-1 and HIV-2 should be used.
However, if the HIV testing is negative or the Western blot test reveals
an unusual pattern, further diagnostic tests should be considered. In
addition, they should be tested with HIV-2 specific DNA PCR assay.

Viral diagnostic assays, such as HIV DNA or RNA PCR or HIV
culture, are considerably more useful in young infants, allowing a
definitive diagnosis in most infected infants by 1–6 mo of age
(Table 276-3). By 3–4 mo of age, the HIV culture and/or PCR identifies
all infected infants. HIV DNA PCR is the preferred virologic assay in
The infection can be excluded definitively if the same parameters are met: logic testing (by 18 years of age). Close clinical monitoring with seroconversion (i.e., outside of the United States), interpretation of a negative PCR test result performed on peripheral blood mononuclear cells. False negatives can occur in non-B subtype HIV-1 infections.

Diagnosis of HIV-1 infection in children younger than 18 months in the United States, Pediatrics 120:e1547–e1562, 2007.

Data from American Academy of Pediatrics, Committee of Pediatric AIDS: Diagnosis of HIV-1 infection in children younger than 18 months in the United States, Pediatrics 120:e1547–e1562, 2007.

Viral diagnostic testing should be performed within the 1st 12-24 hr of life. Almost 40% of HIV-infected children can be identified at this time. It seems that many of these children have a more rapid progression of their disease and deserve more aggressive therapy. Data suggest that if anti-HIV treatment will start at this point, the outcome will be much better. In exposed children with negative virologic testing at 1-2 wk of age, and at 4-6 mo of age; some also favor testing at age 14 days as almost 90% of the infected infants can be identified and ARV therapy can be initiated earlier. A positive virologic assay (i.e., detection of HIV by PCR, culture, or p24 antigen) suggests HIV infection and should be confirmed by a repeat test on a second specimen as soon as possible. A diagnosis of HIV infection can be made with 2 positive virologic test results obtained from different blood samples.

The perinatal use of ARV prophylaxis (either single drug or combination) to prevent vertical transmission has not affected the predictive value of viral diagnostic testing. In addition, the intensive antiviral combinations (protease inhibitors) in pregnant women do not affect the DNA PCR; however, these combinations may have an effect on the RNA PCR. HIV infection can be reasonably excluded if an infant has had at least 2 negative virologic test results with at least 1 test performed at ≥4 mo of age. In some parts of the world where non–subtype B strains are common (i.e., outside of the United States), interpretation of a negative PCR test result should be done with caution because the assay may not detect the particular subtype (e.g., group O). Close clinical monitoring with serologic testing (by 18 mo of age) or culture (if possible) is recommended. In older infants, 2 or more negative HIV antibody tests performed at least 1 mo apart past 6 mo of age in the absence of hypogammaglobulinemia or clinical evidence of HIV disease can reasonably exclude HIV infection. The infection can be excluded definitively if the same parameters are met when the infant is at least 18 mo of age.

Few surrogate markers (e.g., neopterin, β₂-microglobulin) were shown to improve the predictive information of CD4⁺ T-cell counts. These markers may be useful in places where CD4⁺ T-cell counts are not available. Neopterin is an early marker of HIV infection and its level rises further as the disease progresses.

TREATMENT

The currently available therapy does not eradicate the virus and cure the patient; instead it suppresses the virus for extended periods of time and changes the course of the disease to a chronic process. Decisions about ARV therapy for pediatric HIV-infected patients are based on the magnitude of viral replication (viral load), CD4 lymphocyte count or percentage, and clinical condition. Because ARV therapy changes as new drugs become available, decisions regarding therapy should be made in consultation with an expert in pediatric HIV infection. Plasma viral load monitoring and measurement of CD4 values have made it possible to implement rational treatment strategies for viral suppression as well as to assess the efficacy of a particular drug combination. The following principles form the basis for ARV treatment: (1) uninterrupted HIV replication causes destruction of the immune system and progression to AIDS; (2) the magnitude of the viral load predicts the rate of disease progression, and the CD4 cell count reflects the risk of opportunistic infections and HIV infection complications; (3) cART, which includes at least 3 drugs with at least 2 different mechanisms of action, should be the initial treatment. Potent combination therapy that suppresses HIV replication to an undetectable level restricts the selection of ARV-resistant mutants; drug-resistant strains are the major factor limiting successful viral suppression and delay of disease progression; (4) the goal of sustainable suppression of HIV replication is best achieved by the simultaneous initiation of combinations of ARV agents to which the patient has not been exposed previously and that are not crossresistant to drugs with which the patient has been treated previously; (5) drug-related interactions and toxicities should be minimal; and (6) adherence to the complex drug regimens is crucial for a successful outcome.

Combination Therapy

As of 2014, 21 ARV drugs were approved by the FDA for use in HIV-infected adults and adolescents and 19 of them (Table 276-4) for the pediatric population (most of them available as liquid, powder, or small tablet/capsules). ARV drugs are categorized by their mechanism of action, such as preventing viral entrance into CD4⁺ T cells, inhibiting the HIV reverse transcriptase or protease enzymes, or inhibiting integration of the virus into the human DNA. Within the reverse transcriptase inhibitors, a further subdivision can be made: nucleoside (or nucleotide) reverse transcriptase inhibitors (NRTIs) and nonnucleoside reverse transcriptase inhibitors (NNRTIs) (see Fig. 276-3). The NRTIs have a similar structure to the building blocks of DNA (e.g., thymidine, cytosine). When incorporated into DNA, they act like chain terminators and block further incorporation of nucleosides, preventing viral DNA synthesis. Among the NRTIs, thymidine analogs (e.g., stavudine, zidovudine [ZDV]) are found in higher concentrations in activated or dividing cells producing >99% of the HIV virions population) and nonthymidine analogs (e.g., didanosine, lamivudine) have more activity in resting cells, which account for <1% of the HIV virions but may serve as a reservoir for HIV. Suppression of replication in both populations is thought to be an important component of long-term viral control. NNRTIs (i.e., nevirapine, efavirenz, etravirine, rilpivirine) act differently than the NRTIs. They attack to the reverse transcriptase and restrict its motility, reducing the activity of the enzyme. The protease inhibitors are potent agents that act farther along the viral replicative cycle. They bind to the site where the viral long poly peptides are cut to individual, mature, and functional core proteins that produce the infectious virions before they leave the cell. The virus entry into the cell is a complex process that involves several cellular receptors and fusion. Several drugs have been developed to prevent this process. The fusion inhibitor, enfuvirtide, which binds to viral gp41, causes conformational changes that prevent fusion of the virus with the CD4⁺ cell and entry into the cell. Maraviroc is an example of a selective CCR5 coreceptor antagonist that blocks the attachment of the virus to this chemokine (an essential process in the viral binding and fusion to the cell).
### Table 276-4  Summary of Antiretroviral Therapies Available in 2014

<table>
<thead>
<tr>
<th>DRUG (TRADE NAMES, FORMULATIONS)</th>
<th>DOSING</th>
<th>SIDE EFFECTS</th>
<th>COMMENTS</th>
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<tr>
<td><strong>NUCLEOSIDE/NUCLEOTIDE REVERSE TRANSCRIPTASE INHIBITORS</strong></td>
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<tr>
<td>Abacavir (ABC)</td>
<td>Children: ≥3 mo to 13 yr: 8 mg/kg bid (maximum dose 300 mg bid) &gt;30 kg: 300 mg bid Children with viral load &lt;40 copies/mm³: 16 mg/kg once daily (max 600 mg) Adolescents &gt;16 yr and adults: 600 mg once daily Trizivir (&gt;40 kg): 1 tablet bid Epzicom (&gt;16 yr of age): 1 tablet bid</td>
<td>Can be given with food Genetic screening for HLAB*5701 is recommended prior to initiation of ABC-containing treatment. If test is positive avoid ABC. Do not restart ABC in patients who had hypersensitivity-like symptoms (e.g., flu-like symptoms)</td>
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<td>Didanosine</td>
<td>2 wk to &lt;3 mo: 50 mg/m² bid 3-8 mo: 100 mg/m² bid &gt;8 mo: 120 mg/m² (maximum 200 mg per dose) bid Adolescents (&gt;13 yr) and adults &lt;60 kg: 250 mg once daily &gt;60 kg: 400 mg once daily (to increase adherence) If combined with tenofovir &lt;60 kg–200 mg once daily &gt;60 kg–250 mg once daily</td>
<td>Common: diarrhea, abdominal pain, nausea, vomiting Less common: pancreatitis, peripheral neuropathy, electrolyte abnormalities, lactic acidosis with hepatic steatosis, lactic acidosis with hepatitis steatosis, hepatomegaly, retinal depigmentation</td>
<td>Food decreases bioavailability up to 50%. Take 30 min before or 2 hr after meal. Tablets dissolved in water are stable for 1 hr (4 hr in buffered solution). Drug interactions: antacids/gastric acid antagonists may increase bioavailability; possible decreased absorption of fluoroquinolones, ganciclovir, ketoconazole, itraconazole, dapsone, and some protease inhibitors. Combination with d4T enhances toxicity, also common if combined with tenofovir</td>
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<td>Videx EC</td>
<td>Children: not established 20-25 kg: 200 mg once daily 25-60 kg: 250 mg once daily ≥60 kg: 400 mg once daily</td>
<td>Same as for ddl Same as for ddl</td>
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<tr>
<td>Emtricitabine</td>
<td>Infants: 0-3 mo: 3 mg/kg once daily Children ≥3 mo to 17 yr: 6 mg/kg (maximum 240 mg) once daily &gt;33 kg, adolescent and adult: 200 mg capsule or 240 mg solution once daily Truvada or Atripla or Complera or Stribild adult dose: 1 tablet once daily</td>
<td>Common: headache, insomnia, diarrhea, nausea, skin discoloration Less common: lactic acidosis with hepatic steatosis, neuropenia Closely monitor patients with hepatitis B coinfection Can be given without regard to food. Oral solution should be refrigerated if temperature above 25°C (77°F)</td>
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<td>Lamivudine</td>
<td>Neonates (&lt;30 days): 2 mg/kg bid &gt;1 mo: 4 mg/kg bid (maximum 150 mg bid) ≥30 kg: 150 mg bid or 300 mg once daily Children with VL &lt;40 copies/mL: 8-10 mg/kg qd Complira, Trizivir (&gt;30 kg): 1 tablet bid Epzicom (&gt;16 yr): 1 tablet qd</td>
<td>Common: headache, nausea Less common: pancreatitis, peripheral neuropathy, lactic acidosis with hepatic steatosis, lipodystrophy No food restrictions Combination with ZDV may prevent ZDV resistance. Patient should be screened for hepatitis B virus (HBV) and if positive watched for HBV exacerbation when lamivudine is discontinued</td>
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<td>Stavudine</td>
<td>Neonates (0-13 days): 0.5 mg/kg bid 14 days to 30 kg: 1 mg/kg bid &gt;30 kg: 30 mg bid</td>
<td>Common: headache, nausea, hyperlipidemia, fat maldistribution Less common: peripheral neuropathy, pancreatitis, lactic acidosis, hepatic steatosis No food restrictions. Should not be administered with ZDV because of virologic antagonism. Higher incidence of lactic acidosis. Increased toxicity if combined with ddI</td>
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Continued
### Table 276-4: Summary of Antiretroviral Therapies Available in 2014—cont’d

<table>
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<tr>
<th>DRUG (TRADE NAMES, FORMULATIONS)</th>
<th>DOSING</th>
<th>SIDE EFFECTS</th>
<th>COMMENTS</th>
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<tr>
<td><strong>Tenofovir</strong>&lt;br&gt;Viread, TDF&lt;br&gt;Tablet: 150, 200, 250, 300 mg&lt;br&gt;Powder: 40 mg per 1 gr powder&lt;br&gt;Truvada: combination of FTC, TDF (200, 300 mg)&lt;br&gt;Atripla: Combination of FTC, TDF, EFV (200, 300, 600 mg)&lt;br&gt;Complera: combination of FTC, TDF, EFV, COBI (200, 300, 150, 150 mg)&lt;br&gt;Stribild: combination of FTC, TDF, EVG, COBI (200, 300, 150, 150 mg)</td>
<td>2 to &lt;12 yr: 8 mg/kg qd&lt;br&gt;&gt;12 yr and 35 kg, adolescent&lt;br&gt;&gt;12 yr and 35 kg and adult: 300 mg once daily&lt;br&gt;Truvada, Atripla, Complera, and Stribild (see FTC)</td>
<td>Common: nausea, vomiting, diarrhea&lt;br&gt;Less common: lactic acidosis with hepatic steatosis, hepatomegaly, reduced bone density, renal toxicity</td>
<td>High-fat meal increases absorption; coadministration with ddl may increase ddl toxicity, decrease atazanavir (ATV) levels (therefore boosting ATV with ritonavir is required). ATV and lopinavir (LPV) increase TDF levels and potential toxicity. Screen for HBV before TDF given, as exacerbation of hepatitis may occur when TDF is discontinued</td>
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<td><strong>Zidovudine</strong>&lt;br&gt;Retrovir, AZT, ZDV&lt;br&gt;Capsule: 100 mg&lt;br&gt;Tablet: 300 mg&lt;br&gt;Syrup: 10 mg/mL&lt;br&gt;Injection: 10 mg/mL&lt;br&gt;Combivir: combination of ZDV, lamivudine (300, 150 mg)&lt;br&gt;Trizivir: Combination of ZDV, lamivudine, ABC (300, 150, 300 mg)</td>
<td>Prophylaxis: 0-6 wk:&lt;br&gt;Premature infants:&lt;br&gt;1.5 mg/kg IV every 12 hr&lt;br&gt;or&lt;br&gt;2 mg/kg orally every 12 hr for 2 wk (for gestational age 30 to 35 wk) or 4 wk (for gestational age &lt;30 wk); then increase to 3 mg/kg every 6 hr to complete 6 wk (if needed)&lt;br&gt;For gestational age &gt;35 wk:&lt;br&gt;3 mg/kg/dose IV every 12 hr&lt;br&gt;or&lt;br&gt;4 mg/kg orally every 12 hr&lt;br&gt;Treatment:&lt;br&gt;6 wk to 18 yr: 240 mg/m² every 12 hr&lt;br&gt;or&lt;br&gt;4 kg to &lt;9 kg: 12 mg/kg bid&lt;br&gt;9 kg to &lt;30 kg: 9 mg/kg bid&lt;br&gt;30 kg, adolescent and adult:&lt;br&gt;200 mg tid or 300 mg bid&lt;br&gt;Combivir or Trizivir: 1 tablet bid</td>
<td>Common: bone marrow suppression (e.g., macrocytic anemia, leukopenia), headache, nausea, vomiting, anorexia&lt;br&gt;Less common: liver toxicity, lactic acidosis with hepatic steatosis, myopathy, fat redistribution</td>
<td>No food restrictions&lt;br&gt;Drug interactions: should not be given with d4T or doxorubicin&lt;br&gt;Rifampin may increase metabolism&lt;br&gt;Ganciclovir, IFN-α, ribavirin increase ZDV toxicity</td>
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<td><strong>Efavirenz</strong>&lt;br&gt;Sustiva, EFV&lt;br&gt;Capsule: 50, 200 mg&lt;br&gt;Tablet: 600 mg&lt;br&gt;Atripla combination of EFV, FTC, TDF (600, 200, 300 mg)</td>
<td>Children &lt;3 yr: consult with expert&lt;br&gt;Children ≥3 yr:&lt;br&gt;10 to &lt;15 kg: 200 mg qd&lt;br&gt;15 to &lt;20 kg: 250 mg qd&lt;br&gt;20 to &lt;25 kg: 300 mg qd&lt;br&gt;25 to &lt;32.5 kg: 350 mg qd&lt;br&gt;32.5 to &lt;40 kg: 400 mg qd&lt;br&gt;40 kg: 600 mg qd or&lt;br&gt;370 mg/m² body surface area&lt;br&gt;Atripla (see FTC)</td>
<td>Common: skin rashes, CNS abnormalities (e.g., abnormal dreams, impaired concentration, insomnia, depression, hallucination)&lt;br&gt;Less common: increased liver enzymes; potentially teratogenic</td>
<td>Capsules can be opened for mixing in food. Can be given without regard to food except fatty foods (because absorption is increased 50%)&lt;br&gt;Drug interactions: Efavirenz induces/inhibits CYP3A4 enzymes. Increase clearance of drugs metabolized by this pathway (e.g., anthistamines, sedatives and hypnotics, ciapride, ergot derivatives, warfarin, ethyl estradiol) and several other ARVs (i.e., protease inhibitors). Drugs that induce CYP3A4 (e.g., phenobarbital, rifampin, rifabutin) decrease efavirenz levels. Clarithromycin levels decrease with EFV and azithromycin should be considered</td>
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<tr>
<td><strong>Etravirine (ETR), Intenelle, ETR, tablet: 25, 100, 200 mg</strong>&lt;br&gt;Children &lt;6 yr: consult with expert&lt;br&gt;16 to &lt;20 kg: 100 mg bid&lt;br&gt;20 to &lt;25 kg: 125 mg bid&lt;br&gt;25 to &lt;30 kg: 150 mg bid&lt;br&gt;30 kg, adolescent and adult: 200 mg bid</td>
<td>Common: nausea, rash, diarrhea&lt;br&gt;Less common: hypersensitivity reactions</td>
<td>Given only with food. Tablets can be dispersed in water&lt;br&gt;Inducer of CYP3A4 enzymes and inhibitor of CYP2C9 and CYP2C19, causing multiple interactions that should be checked before initiating ETR. Should not be given in combination with TPV, Fos-APV, ATZ, or other nonnucleoside reverse transcriptase inhibitors</td>
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<td>DRUG (TRADE NAMES, FORMULATIONS)</td>
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<td>Nevirapine Viramune, NVP Tablet: 200 mg Extended-release (XR) tablet: 100, 400 mg Suspension: 10 mg/mL</td>
<td>Prophylaxis: For infant of woman with no antepartum ARV treatment: 2 mg/kg birth to 48 hr 2 mg/kg 48 hr after 1st dose 2 mg/kg 96 hr after 2nd dose Treatment: &lt;8 yr: 200 mg/m² once daily for 14 days; then same dose bid (maximum 200 mg per dose) or XR 400 mg qd &gt;8 yr: 120-150 mg/m² once daily for 14 days; then bid (maximum 200 mg per dose) Adolescent and adult: 200 mg once daily for 14 days; then 200 mg bid or XR 400 mg qd</td>
<td>Common: skin rash, headache, fever, nausea, abnormal liver function tests Less common: hepatotoxicity (rarely life-threatening), hypersensitivity reactions</td>
<td>No food restrictions Drug interactions: induces hepatic CYP450A enzymes (including CYP3A and CYP2B6) activity and decreases protease inhibitor concentrations (e.g., INI, SQV, LPV). Should not be given with ATV. Reduces ketoconazole concentrations (fluconazole should be used as an alternative). Rifampin decreases nevirapine serum levels. Anticonvulsants and psychotropic drugs using same metabolic pathways as NVP should be monitored. Oral contraceptives may also be affected</td>
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<td>Rilpivirine Edurant, RPV Tablet: 25 mg Complera combination of RPV, FTC, TDF (25, 200, 300 mg)</td>
<td>Pediatrics: consult with expert Adolescent (&gt;18 yr) and adult: 25 mg</td>
<td>Headache, insomnia, rash, depression, mood changes</td>
<td>Given with food only Should not be used if viral load &gt;100,000 copies/mL or drugs that induce CYP3A or with proton pump inhibitors</td>
</tr>
<tr>
<td>Atazanavir Reyataz, ATV Capsules: 100, 150, 200, 300 mg</td>
<td>&lt;6 yr: consult with expert 6-18 yr: 15 to &lt;20 kg: 150 mg + 100 RTV qd 20 to 40 kg: 200 mg + 100 RTV qd &gt;40 kg, adolescent and adult: 300 mg + 100 RTV qd or 400 mg if unboosted with food If given with EFV (600 mg) or TDF (300 mg): 400 mg + 100 RTV qd</td>
<td>Common: elevation of indirect bilirubin; headache, arthralgia, depression, insomnia, nausea, vomiting, diarrhea, paresthesias Less common: prolongation of PR interval on electrocardiogram (ECG); rash, rarely Stevens-Johnson syndrome, diabetes mellitus, nephrolithiasis</td>
<td>Administer with food to increase absorption. Review drug interactions before initiating because ATV inhibits CYP3A4, CYP1A2, CYP2C9, and UGT1A1 enzymes. Use with caution with cardiac conduction disease or liver impairment. Combination with EFV should not be used in treatment-experienced patients because it decreases ATV levels. TDF, antacids, H₂-receptor antagonists, and proton-pump inhibitors decreases ATV concentrations. Patients taking buffered ddl should take it at least 2 hr before ATV</td>
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<tr>
<td>Darunavir Prezista, DRV Tablets: 75, 150, 400, 600, 800 mg Suspension: 100 mg/mL</td>
<td>&lt;3 yr: consult with expert 3 to &lt;18 yr: 10 to &lt;15 kg: 20 mg/kg DRV + 3 mg/kg RTV 15 to &lt;30 kg: 375 mg DRV + 50 mg RTV bid 30 to &lt;40 kg: 450 DRV mg + 100 mg RTV bid &gt;40 kg, adolescent and adult: 600 mg DRV + 100 mg RTV bid or Adolescent (&gt;12 yr and 40 kg) and adult: 800 mg DRV + 100 mg RTV qd with food If any DRV resistance is found: 600 mg DRV = 100 mg RTV bid</td>
<td>Common: diarrhea, nausea, vomiting, abdominal pain, fatigue, headache Less common: skin rashes (including Stevens-Johnson syndrome), lipid and liver enzyme elevations, hyperglycemia, fat maldistribution</td>
<td>DRV should not be given without food. Contraindicated for concurrent therapy with cisapride, ergot alkaloids, benzodiazepines, pimozide, or any major CYP3A4 substrates. Use with caution in patients taking strong CYP3A4 inhibitors, or moderate/strong CYP3A4 inducers. Adjust dose with concurrent rifamycin therapy. Contains sulfite moiety: potential for cross-sensitivity with sulfonamide class</td>
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<tr>
<th>DRUG (TRADE NAMES, FORMULATIONS)</th>
<th>DOSING</th>
<th>SIDE EFFECTS</th>
<th>COMMENTS</th>
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<tr>
<td><strong>Fosamprenavir</strong>&lt;br&gt;Lexiva, FPV&lt;br&gt;Tablets: 700 mg&lt;br&gt;Suspension: 50 mg/mL</td>
<td>6 mo to 18 yr:&lt;br&gt; &lt;11 kg: 45 mg/kg FPV + 7 mg/kg RTV bid&lt;br&gt;11 to &lt;15 kg: 30 mg/kg + 3 mg/kg RTV bid&lt;br&gt;15 to &lt;20 kg: 23 mg/kg + 3 mg/kg RTV bid&lt;br&gt;&gt;20 kg: 18 mg/kg (max 700 mg) + 3 mg/kg (max: 100 mg) RTV bid&lt;br&gt;Adolescent &gt;18 yr and adult:&lt;br&gt;FPV 700 mg + RTV 100 mg bid&lt;br&gt;or&lt;br&gt;FPV 1,400 mg + RTV 200 mg qd</td>
<td>Common: nausea, vomiting, perioral paresthesias, headache, rash, lipid abnormalities&lt;br&gt;Less common: Stevens-Johnson syndrome, fat redistribution, neutropenia, elevated creatine kinase, hyperglycemia, diabetes mellitus, elevated liver enzymes, angioedema, nephrolithiasis</td>
<td>Should be given with food. FPV is an inhibitor of the CYP450 system and an inducer, inhibitor, and substrate of CYP3A4, which can cause multiple drug interactions. Use with caution in sulfa-allergic individuals</td>
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<tr>
<td><strong>Indinavir</strong>&lt;br&gt;Crixivan, IDV&lt;br&gt; Capsule: 100, 200, 400 mg</td>
<td>Infants: not approved&lt;br&gt;Children: 500 mg/m² every 8 hr (max dose: 800 mg per dose) or 400 mg/m² + RTV 100 mg/m² bid&lt;br&gt;Adolescent and adult: 800 mg IDV + 100 or 200 mg RTV bid</td>
<td>Common: nausea, abdominal pain, hyperbilirubinemia, headache, dizziness, lipid abnormalities, nephrolithiasis, metallic taste&lt;br&gt;Less common: fat redistribution, hyperglycemia, diabetes mellitus, hepatitis, acute hemolytic anemia</td>
<td>Administer on empty stomach if given without RTV. Reduce dose (600 mg IDV every 8 hr) with mild to moderate liver dysfunction. Adequate hydration (at least 48 oz fluid/day in adults) necessary to minimize risk of nephrolithiasis. IDV is cytochrome P450 3A4 inhibitor and substrate, which can cause multiple drug interactions: rifampin reduces levels; ketoconazole, ritonavir, and other protease inhibitors increase IDV levels. Do not coadminister with EFV, astemizole cisapride, terfenadine</td>
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<tr>
<td><strong>Lopinavir/Ritonavir</strong>&lt;br&gt;Kaletra, LPV/r&lt;br&gt;Tablets: 100/25 mg, 200/50 mg&lt;br&gt;Solution: 80/20 mg per/mL (contains 42% alcohol)</td>
<td>14 days to 18 yr: 300 mg/m² LPV +75 mg/m² RTV bid&lt;br&gt;Adolescent (&gt;18 yr) and adult: 400 mg LPV +100 mg RTV bid or 800 mg LPV +200 mg RTV qd&lt;br&gt;If taken with NVP, EFV, FPV, or NFV: LPV 600 mg + RTV 150 mg bid</td>
<td>Common: diarrhea, headache, nausea and vomiting, lipid elevation&lt;br&gt;Less common: fat redistribution, hyperglycemia, diabetes mellitus, pancreatitis, hepatitis, PR interval prolongation</td>
<td>No food restrictions. High-fat meal and flavoring of solution to increase palatability are recommended if oral solution is used. Interacts with drugs using CYP3A4, which can cause multiple drug interactions</td>
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<tr>
<td><strong>Nelfinavir</strong>&lt;br&gt;Viracept, NFV&lt;br&gt;Tablet: 250, 625 mg</td>
<td>&lt;2 yr: not recommended&lt;br&gt;Children 2-13 yr: 45-55 mg/kg bid&lt;br&gt;Adolescents and adults: 1,250 mg bid</td>
<td>Common: diarrhea asthenia, abdominal pain, skin rashes, lipid abnormalities&lt;br&gt;Less common: exacerbation of liver disease, fat redistribution, hyperglycemia, diabetes mellitus, elevation of liver enzymes</td>
<td>Administer with a meal to optimize absorption; avoid acidic food or drink (e.g., orange juice). Tablet can be crushed or dissolved in water to administer as a solution&lt;br&gt;Drug interactions: Nelfinavir inhibits CYP3A4 activity, which may cause multiple drug interactions. Rifampin, phenobarbital, and carbamazepine reduce levels. Ketoconazole, ritonavir, indinavir, and other protease inhibitors increase levels. Do not coadminister astemizole, cisapride, terfenadine. RTV boosting has no effect. Because of very high variation in plasma levels, TDM should be used for dose adjustment</td>
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### Table 276-4 Summary of Antiretroviral Therapies Available in 2014—cont’d

<table>
<thead>
<tr>
<th>DRUG (TRADE NAMES, FORMULATIONS)</th>
<th>DOSING</th>
<th>SIDE EFFECTS</th>
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<tr>
<td><strong>Ritonavir</strong>&lt;br&gt;Norvir, RTV&lt;br&gt;Tablet: 100 mg&lt;br&gt;Solution: 80 mg/mL (contains 43% alcohol)</td>
<td>Only use is to enhance other PIs; dose varies (see information for specific PI)</td>
<td>Common: nausea, headache, vomiting, abdominal pain, diarrhea, taste aversion, lipid abnormalities, perioral paresthesias&lt;br&gt;Less common: fat redistribution, hyperglycemia, diabetes mellitus, pancreatitis, hepatitis, PR interval prolongation, allergic reactions</td>
<td>Administration with food enhances bioavailability and reduces gastrointestinal symptoms. RTV solution should not be refrigerated&lt;br&gt;RTV is potent inhibitor of CYP3A4 and CYP2D6 and inducer of CYP3A4 and CYP1A2 that leads to many drug interactions (e.g., protease inhibitors, antiarrhythmics, antidepressants, cisapride). Use cautiously with inhaled steroids</td>
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<tr>
<td><strong>Saquinavir</strong>&lt;br&gt;Invirase, SQV&lt;br&gt;Hard gel: 200 mg&lt;br&gt;Film-coated tablets: 500 mg</td>
<td>Infants and children &lt;2 yr: not established&lt;br&gt;SQV must be boosted with RTV&lt;br&gt;  &gt;2 yr: 5 to &lt;15 kg: 50 mg/kg + 3 mg/kg RTV bid&lt;br&gt;  15-40 kg: 50 mg/kg + 2.5 mg/kg RTV bid&lt;br&gt;  &gt;40: 50 mg/kg + 100 RTV bid&lt;br&gt;Adolescent and adult: SQV 1,000 mg + 100 mg RTV bid</td>
<td>Common: diarrhea, abdominal pain, headache, nausea, skin rashes, lipid abnormalities&lt;br&gt;Less common: exacerbation of chronic liver disease, diabetes mellitus, pancreatitis, elevated liver transaminases, fat maldistribution, increase in both QT and PR in ECG</td>
<td>Administration with a high-fat meal to enhance bioavailability. Use only in combination with ritonavir boosting dose. SQV is metabolized by CYP3A4, which may cause many drug interactions: rifampin, phenobarbital, and carbamazepine decrease serum levels. Saquinavir may decrease metabolism of calcium channel antagonists, azoles (e.g., ketoconazole), macrolides</td>
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<tr>
<td><strong>Tipranavir</strong>&lt;br&gt;Aptivus, TPV&lt;br&gt;Capsule: 250 mg&lt;br&gt;Solution 100 mg/mL (contains 116 IU vitamin E/mL)</td>
<td>  &lt;2 yr: not established.&lt;br&gt;2-18 yr: 375 mg/m² TPV + 150 mg/m² RTV (maximum 500 mg TPV + 200 mg RTV) bid&lt;br&gt;or&lt;br&gt;14 mg TPV + 6 mg RTV per kg (maximum-same) bid&lt;br&gt;Adolescent (&gt;18 yr) and adult: 500 mg TPV + 200 mg RTV bid</td>
<td>Common: diarrhea, nausea, vomiting, fatigue, headache, skin rashes, elevated liver enzymes, lipid abnormalities&lt;br&gt;Less common: fat redistribution, hepatitis, hyperglycemia, diabetes mellitus, intracranial hemorrhage</td>
<td>No food restrictions. Better tolerated with meal. TPV must be boosted with RTV. Can inhibit human platelet aggregation: use with caution in patients at risk for increased bleeding (trauma, surgery, etc.) or in patients receiving concurrent medications that may increase the risk of bleeding. TPV is metabolized by CYP3A4, which may cause many drug interactions. Contraindicated in patients with hepatic insufficiency or receiving concurrent therapy with amiodarone, cisapride, ergot alkaloids, benzodiazepines, pimozide. TPV contains sulfonamide moiety and caution should be taken in patients with sulfonamide allergy</td>
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<tr>
<td><strong>FUSION INHIBITORS</strong>&lt;br&gt;Enfuvirtide&lt;br&gt;Fuzeon, ENF&lt;br&gt;Injection: lyophilized powder of 108 mg reconstituted in 1.1 mL of sterile water delivers 90 mg/mL</td>
<td>  &lt;6 yr: not established&lt;br&gt;  Children ≥6 yr to 16 yr: 2 mg/kg SQ (maximum 90 mg) bid&lt;br&gt;  Adolescent and adult: 90 mg SQ bid</td>
<td>Common: Local injection site reactions in 98% (e.g., erythema, induration nodules, cysts, ecchymoses)&lt;br&gt;Less common: increased incidence of bacterial pneumonia, hypersensitivity, fever, nausea, vomiting, chills, elevated liver enzymes, hypotension, immune-mediated reactions (e.g., glomerulonephritis, Guillain-Barré syndrome, respiratory distress)</td>
<td>Must be given subcutaneously. Severity of reactions increased if given intramuscularly. Apply ice after injection and massage the area to reduce local reactions. Injection sites should be rotated</td>
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Continued
Antiretroviral drugs often have significant drug–drug interactions, with each other and with other classes of medicines, which should be reviewed before initiating any treatment. Drug interactions can limit the potential efficacy of antiretroviral therapy at all sites, such as the CNS, thereby limiting their potential efficacy at this site.

Table 276-4  Summary of Antiretroviral Therapies Available in 2014—cont’d

<table>
<thead>
<tr>
<th>DRUG (TRADE NAMES, FORMULATIONS)</th>
<th>DOSING</th>
<th>SIDE EFFECTS</th>
<th>COMMENTS</th>
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<tr>
<td><strong>ENTRY INHIBITORS</strong></td>
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<tr>
<td>Maraviroc</td>
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<td>Selzentry, MVC</td>
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<tr>
<td>Tablets: 150, 300 mg</td>
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<tr>
<td>Not approved for children or adolescents &lt;1 yr</td>
<td>Common: fever, upper respiratory infection–like symptoms, rash, abdominal pain, musculoskeletal symptoms, dizziness</td>
<td>No food restrictions. MVC is a CYP3A4 and P-glycoprotein (Pgp) substrate, which may cause many drug interactions. Tropism assay to exclude the presence of CXCR4 HIV is required before using MVC. Caution should be used when given to patients with hepatic impairment or cardiac disease or receiving CYP3A4 or Pgp modulating drugs.</td>
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<td>Adolescents &gt;16 yr and adults: 150 mg bid if given with potent CYP3A inhibitor (e.g., protease inhibitor except TPV) 300 mg bid if given with not potent CYP3A4 inhibitors (e.g., NRTI, TPV, NVP, ENF, RAL) 600 mg bid if given with potent CYP3A4 inhibitor (e.g., EFV, ETR, rifampin, phenobarbital)</td>
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<td></td>
<td><strong>INTEGRASE INHIBITORS</strong></td>
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<tr>
<td>Daltegravir</td>
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<td>Tivicay, DTG</td>
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<td>Tablet: 50 mg</td>
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<tr>
<td>Children &lt;12 yr: consult with expert 12 yr and 40 kg, adolescents, and adults: 50 mg qd If taken with EFV, FPV, TPV, or rifampin: 50 mg bid</td>
<td>Insomnia</td>
<td>No food restrictions UGT1A1 and CYP450 (CYP) 3A substrate Should be taken 2 hr before or 6 hr after taking laxatives, sucralfate, iron or calcium supplements, or buffered medications</td>
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<tr>
<td>Elvitegravir</td>
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<td>EVG</td>
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<tr>
<td>Only as Stribild combination of EVG, FTC, TDF, cobicistat (COBI) (150, 200, 300, 150 mg)</td>
<td>Children and adolescents &lt;18 yr: not established Adolescent (&gt;18 yr) and adult: 1 tablet qd</td>
<td>Common: nausea, diarrhea Less common: increased serum creatinine, urea, and phosphate, decreased bone density, lactic acidosis, hepatomegaly with stenosis</td>
<td>Administer with food EVG is metabolized by CYP3A4 and modestly induces CYP2D6 that can cause multiple drug interactions. Cautiously use with nephrotoxic drugs. Stribild should not be used with ritonavir</td>
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<tr>
<td>Raltegravir</td>
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<td>Isentress, RAL</td>
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<tr>
<td>Film-coated tablet: 400 mg</td>
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<tr>
<td>Chewable tablet: 25, 100 mg</td>
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<tr>
<td>Solution: 20 mg/ml</td>
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<td>Oral solution: 3 to &lt;4 kg: 20 mg bid 4 to &lt;6 kg: 30 mg bid 6 to &lt;8 kg: 40 mg bid 8 to &lt;11 kg: 60 mg bid 11 to &lt;14 kg: 80 mg bid 14 to &lt;20 kg: 100 mg bid Chewable tablet: 10 to &lt;14 kg: 75 mg bid 14 to &lt;20 kg: 100 mg bid 20 to &lt;28 kg: 150 mg bid 28 to &lt;40 kg: 200 mg bid Adolescent (&gt;12 yr) and adult: 400 mg bid</td>
<td>Less common: increased serum creatinine, urea, and phosphate, decreased bone density, lactic acidosis, hepatomegaly with stenosis</td>
<td>No food restrictions Film-coated tablet and chewable tablet are not interchangeable RAL is metabolized by UGT1A1 glucuronidation, and inducers of this system (e.g., rifampin, TPV) will reduce NGV levels, whereas inhibitors (e.g., ATV) will increase it</td>
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Antiretroviral drugs often have significant drug–drug interactions, with each other and with other classes of medicines, which should be reviewed before initiating any new medication.

The information in this table is not all-inclusive. Updated and additional information on dosing, drug–drug interactions, and toxicities is available on the AIDSinfo website at http://www.aidsinfo.nih.gov


CD4+ cells). **Integrase inhibitors** like raltegravir block the enzyme that catalyzes the incorporation of the viral genome into the host’s DNA. While the principal site of viral replication is lymphoid tissue, sanctuary sites such as the CNS may harbor residual virions with the potential to be a source of local or persistent disease. Impaired penetration of drugs to these compartments could result in development of resistance. Although data on CNS penetration of antiviral agents are presently limited, ZDV, stavudine, and lamivudine appear to achieve inhibitory concentrations in the CNS. Nevirapine and efavirenz also penetrate the cerebrospinal fluid, but protease inhibitors are actively transported out of the CNS, thereby limiting their potential efficacy at this site.

By targeting different points in the viral life cycle and stages of cell activation and by delivering drug to all tissue sites, maximal viral suppression may be feasible. Combinations of 3 drugs, a thymidine analog NRTI (abacavir or ZDV) and a nonthymidine analog NRTI (lamivudine) to suppress replication in both active and resting cells and a protease inhibitor (atazanavir or lopinavir/ritonavir) or an NNRTI (efavirenz) produce prolonged viral suppression. Less-potent combinations, such as triple NRTIs (abacavir, zidovudine, lamivudine), may be considered in special situations (e.g., children <3 yr with concomitant tuberculosis when nevirapine-based cART is unacceptable or in rare cases when there are concerns about significant drug interactions or adherence to a complex drug regimen). The use of 3 drugs from 3 different classes should be avoided as it has the potential to cause resistance to 3 drug classes. Combination treatment increases the rate of toxicities (see Table 276-4), and complex drug–drug interactions exist among many of the antiretroviral drugs. Many protease inhibitor drugs are inducers or inhibitors of the cytochrome P450 system and are therefore likely to have serious interactions with multiple drug classes, including nonsedating antihistamines and psychotropics, vasoconstrictor, antimycobacterial, cardiovascular, analgesic, and gastrointestinal drugs (cisapride). Whenever new medications are added...
to an antiretroviral treatment regimen, especially a protease inhibitor–
containing regimen, a pharmacist and/or HIV specialist should be
consulted to address possible drug interactions. The inhibitory effect
of ritonavir (a protease inhibitor) on the cytochrome P450 system has
been exploited, and small doses of the drug are added to several other
protease inhibitors (e.g., lopinavir, tipranavir, atazanavir, darunavir) to
slow their metabolism by the P450 system and to improve their phar-
macokinetic profile. This strategy provides more effective drug levels
with less toxicity and less-frequent dosing. Recently, the development
of cobicistat provides an alternative to ritonavir. Although cobicistat is
a potent inhibitor of cytochrome P450 3A, it is a weak inhibitor of
CYP2D6 and other CYP isoforms (e.g., CYP1A2), making pharmacoki-
tetic interactions with many drugs more predictable than for ritonavir,
which is also active against these isoforms. Preliminary studies with
cobicistat suggest that it has a good tolerability profile and less effect
on adipocytes (resulting in milder accumulation of lipid and response
to insulin). The better solubility of cobicistat compared to ritonavir
may foster the availability of more single-tablet combination regimens
with cobicistat.

Adherence

Adherence to the medication schedules and dosages is fundamental to
ARV therapy success. Therefore, assessment of the likelihood of adher-
ence to treatment is an important factor in deciding whether and when
to initiate therapy. Numerous studies show that compliance of <90%
results in less-successful suppression of the viral load. In addition,
several studies document that almost half of the pediatric patients
surveyed were nonadherent to their regimen. Poor adherence to pre-
scribed medication regimens results in subtherapeutic drug concentra-
tions and encounters development of resistance. Several barriers to
adherence are unique to children with HIV infection. Combination
antiretroviral regimens are often unpalatable and require extreme dedi-
cation on the part of the caregiver and child; a reluctance to disclose
the child’s disease to others reduces social support; there may be a
tendency to skip doses if the caregiver is not around or when the child
is in school. Adolescents have other issues that reduce adherence.
Denial and/or fear of their infection, unstructured lifestyle, conduct
or emotional disorder, wishing to be the same as their peers, depression,
fatigue from taking a lifelong regimen, anxiety, and alcohol and sub-
stance abuse are just a few of the barriers for a long-term adherence in
this growing population. These and other barriers make participation
of the family in the decision to initiate therapy essential. Intensive
education on the relationship of drug adherence to viral suppression,
training on drug administration, frequent follow-up visits, peer
support, pager messaging, and commitment of the caregiver and the
patient (despite the inconvenience of adverse effects, dosing schedule)
are critical for successful antiviral treatment. Multiple methods such
as viral load response, self-reporting of missed doses during the last
3-7 days, and pharmacy/pill counting or monitoring drugs’ concentra-
tions in the blood should be used to assess adherence.

Initiation of Therapy

The decision on when to initiate cART is controversial and keeps
evolving. Even the recent adult guidelines that recommend initiation
of cART in individuals with CD4 cell counts <500 cells/µL acknowledge
that treatment of individuals with higher CD4 cell counts may be
beneficial. Therefore, the following recommendations for pediatric
patients are only accurate for the time they were written (August 2014),
and physicians providing care to few HIV-exposed or infected children
should periodically consult physicians with expertise in pediatric HIV
infection as well as the U.S. pediatric guidelines for treatment of HIV-

Children younger than 1 yr of age are at high risk for disease pro-
gression, and immunologic and virologic tests to identify those likely
to develop rapidly progressive disease are less predictive than in older
children. Therefore, HIV-infected infants younger than 1 yr of age
should be treated with ARV agents as soon as the diagnosis of HIV
infection has been confirmed, regardless of clinical or immunologic
status or viral load. Data suggest that HIV-infected infants who are
treated before the age of 3 mo control their HIV infection better than
infants whose ARV therapy started later than 3 mo of age. Some of
these infants even become HIV seronegative and lose their HIV spe-
cific immune response.

There is still a debate on when to start therapy in children older than
1 yr of age. The 2014 U.S. Pediatric Guidelines Panel recommends,
with varying strength of the recommendations, treating all children ≥1
year of age with Stage 3 CD4 counts, significant clinical symptoms, or
HIV RNA >1,000,000 copies/mL. Children 1–6 yr of age should be
entered with CD4 counts between 500-999 cells/mm³, and treatment
should be considered if the child has minimal/no symptoms and a CD4
count ≥2,000 cells/mm³. Children ≥6 yr of age should be treated with
CD4 counts between 200-499 cells/mm³, and treatment should be con-
sidered if the child has minimal/no symptoms and a CD4 count ≥500
cells/mm³. These guidelines are reviewed yearly, and care providers
should check for revisions at http://aidsinfo.nih.gov. Some clinicians
advocate treating all HIV-infected children regardless of their clinical
stage, viral load, or CD4+ T-cell status to prevent the inevitable immu-
nologic deterioration that will otherwise occur.

Dosing

Children are usually treated with higher doses (per kg weight) than
adults because of reduced absorption or increased elimination. Data
on ARV drug dosages for neonates, especially premature infants, are
often limited. Because of the immaturity of the neonatal liver, there
must often be an increase in the dosing interval of drugs primarily
cleared through hepatic glucuronidation. In addition, drug absorption
from the gastrointestinal tract may be problematic. Therefore, moni-
toring of drugs plasma levels should be considered, if available.
Adolescents should have ARV dosages prescribed on the basis of
Tanner staging of puberty rather than on the basis of age. Pediatric
dosing ranges should be used during early puberty (Tanner stages I, II,
and III), whereas adult dosing schedules should be followed in adoles-
cents in late puberty (Tanner stages IV and V). Efavirenz should be
avoided in females who may become pregnant and do not use effective
contraception because of its potential teratogenicity. Because some
protease inhibitors may change the metabolism of oral contraceptives
and decrease their effectiveness, monthly injections of medroxypro-
gestosterone (DMPA) or use of an intrauterine device should be consid-
ered, or the protease inhibitor can be changed, if needed, to an
integrase inhibitor, which has no interaction with estrogen-based
contraceptives.

Changing Antiretroviral Therapy

Therapy should be changed when the current regimen is judged ine-
effective as evidenced by increase in viral load, deterioration of the CD4
cell count, or clinical progression. Development of toxicity or intoler-
ance to drugs is another reason to consider a change in therapy. When
a change is considered, the patient and family should be reassessed for
adherence problems. Because adherence is a major issue in this popula-
tion, resistance testing (while on ARV medications) is important in
identifying adherence issues (e.g., detectable virus sensitive to current
drugs will suggest lack of adherence) or development of resistance (e.g.,
evidence of resistance mutations to given drugs). In both situations,
other contributing factors such as poor absorption, incorrect dose, or
drug–drug interactions should be carefully reviewed. While consider-
ing possible new drug choices, potential cross-resistance should be
addressed. In addition, few patients who have virologic failure may
still demonstrate improved CD4 cell counts (discordant response).
Impaired replication ability of the resistant virus (also called reduced
viral fitness) and enhanced CTL effects are some of the reasons for this
discordant response. In these patients, delay in changing therapy
should be considered as long as the immunologic benefit is evident.
Ideally, when a decision is made to change the ARV therapy, all drugs
should be changed. However, in many situations (previous ARV expe-
rience, intolerance, toxicity) this is not possible, thus at least 2 drugs
should be changed based on the resistance mutation genotype or phe-
notype (if available) or evaluation of the drugs used in the previous
regimen.
Monitoring Antiretroviral Therapy
To ensure proper monitoring, the CD4 cells count, viral load, complete blood count, chemistries, urinalysis, and serum lipids should be done before initiation or change in cART to have a baseline for comparisons while on treatment. Children need to be seen within 1-2 wk after initiation of new ARV therapy to ensure compliance and to screen for potential side effects. Virologic and immunologic surveillance (using HIV RNA copy number and CD4 lymphocyte count or percentage) as well as clinical assessment should be performed regularly during ARV therapy. Initial virologic response (i.e., at least a 50% [0.7 log10 reduction in viral load]) should be achieved within 4-8 wk of initiating antiretroviral therapy. The maximum response to therapy usually occurs within 12-16 wk, but may be later (24 wk) in very young infants. Thus, HIV RNA levels should be measured at 4 wk and 3-4 mo after therapy initiation. Once an optimal response has occurred, viral load should then be measured at least every 3-6 mo. If the response is unsatisfactory, another viral load should be performed as soon as possible to verify the results before a change in therapy is considered. The CD4 cells respond more slowly to successful treatment and, therefore, can be monitored less frequently. Potential toxicity should be monitored closely for the 1st 8-12 wk (including complete blood count, serum chemistries, urinalysis, and lipids), and if no clinical or laboratory toxicity is documented, a follow-up visit every 3-4 mo is adequate. Monitoring for potential toxicity should be tailored to the drugs taken. These toxicities include but are not limited to hemato logic complications (e.g., ZDV); hypersensitivity rash (e.g., efavirenz); lipodystrophy (e.g., redistribution of body fat seen with NRTIs, protease inhibitors); hyperlipidemia (elevation of cholesterol and triglyceride concentrations); hyperglycemia, and insulin resistance (e.g., protease inhibitors); mitochondrial toxicity leading to severe lactic acidosis (e.g., stavudine, didanosine); electrocardiogram abnormalities (e.g., atazanavir, lopinavir); abnormal bone mineral metabolism (e.g., tenofovir); and hepatic toxicity, including severe hepatomegaly with steatosis.

Resistance to Antiretroviral Therapy
Young children usually are at greater risk than adults for developing resistance because they have higher viral loads than adults and are more limited by which ARV options are available. The high mutation rate of HIV (mainly as a result of the absence of error-correcting mechanisms) severely impairs the success of ARV therapy. Failure to reduce the viral load to <40 copies/mL increases the risk for developing resistance. Even effectively treated patients do not completely suppress viral replication, and persistence of HIV transcription and evolution of envelope sequences continues in the latent cellular reservoirs. The accumulation of resistance mutations progressively diminishes the potency of the ARV therapy and challenges the physician to find new regimens. For some drugs (e.g., nevirapine, lamivudine) a single mutation is associated with resistance, whereas for other drugs (e.g., ZDV, lopinavir) several mutations are needed before resistance develops. Testing for drug resistance, especially when devising a new regimen, is becoming the standard of care. Two types of tests are available: (1) The phenotypic assay measures the virus susceptibility in various concentrations of the drug that allows calculation of the drug concentration that inhibits viral replication by 50% (IC50). The ratio of the IC50 and a reference virus IC50 is reported as fold resistance change. (2) The genotypic assay predicts the virus susceptibility from mutations identified in the HIV genome isolated from the patient. Several online sites (e.g., http://hivdb.stanford.edu) can assist in interpreting the test's results. Several studies show that treatment success is higher in patients whose ARV therapy was guided by genotype or phenotype testing. Neither method may detect drug resistance if the amount of the resistant virus is <10% of the circulating population or if it is present only in the latent reservoir.

It is recommended to test for drug resistance before initiating therapy and before changing treatment because of failure. When changing therapy, the resistance test results should be considered in the context of previous resistance tests results, if done, and drugs used in previous regimens.

Supportive Care
Even before ARV drugs were available, a significant impact on the quality of life and survival of HIV-infected children was achieved when supportive care was given. A multidisciplinary team approach is desirable for successful management. Following initiation or change of cART, more frequent visits or contacts with the patient/caregivers for support and education will help in their acceptance and adjustment to the new regimen and will contribute to a better adherence. Close attention should be paid to nutritional status, which is often delicately balanced and may require aggressive supplementation. Painful oropharyngeal lesions and dental caries may interfere with eating, and thus routine dental evaluations and careful attention to oral hygiene should be encouraged. Paradoxically, an increasing number of adolescents with perinatally acquired or behavioral risk-acquired disease are obese. Some teens experience ARV-related central lipo-accumulation, but others have poor dietary habits and inactivity as the cause of their obesity, in parallel to epidemic obesity in the United States. Development should be evaluated regularly with provision of necessary physical, occupational, and/or speech therapy. Recognition of pain in the young child may be difficult, and effective nonpharmacologic and pharmacologic protocols for pain management should be instituted.

All infants born to HIV-infected mothers should receive ZDV prophylaxis for 4-6 wk. Additional ARV therapy should be considered if the risk of acquiring HIV by the newborn is high. For example, if the mother has not received cART during pregnancy, 3 doses of nevirapine (at birth, 48 hr, and 144 hr of life) should be added. If the mother's HIV status is unknown, rapid HIV-testing of either the mother or the newborn should be done immediately after delivery and if positive, ARV prophylaxis should be started as soon as possible without waiting for the confirmatory test results. Guidelines for prophylaxis in newborns are updated at least yearly and can be accessed at http://www.aidsinfo.nih.gov. A complete blood count, differential leukocyte count, and platelet count should be performed at 4 wk of age to monitor ZDV toxicity. These tests should be continued every 1-3 mo to assess the hematologic effect of ZDV and prophylactic trimethoprim-sulfamethoxazole (TMP-SMZ), if given. If the child is found to be HIV infected, baseline laboratory assessment (e.g., CD4 count, HIV RNA, complete blood count, chemistries) should be done and cART should be started as soon as possible. Viral load and CD4 lymphocyte counts should be performed at 1 and 3 mo of age and should be repeated every 3 mo. All HIV-exposed and infected children should receive standard pediatric immunizations. In general, live oral polio vaccine should not be given (Fig. 276-4). The risk and benefits of rotavirus vaccination should be considered in infants born to HIV-infected mothers. Because <1% of these infants in resource-rich countries will develop HIV infection, the vaccine should be given. In other situations, the considerable attenuation of the vaccine's strains should be taken into account and unless the infant has clinical symptoms of AIDS or CD4 <15%, vaccination seems to be appropriate. Other live bacterial vaccines (e.g., bacillus Calmette-Guérin) should be avoided because of the high incidence of bacillus Calmette-Guérin–related disease in HIV-infected infants. Varicella and measles-mumps-rubella vaccines are recommended for children who are not severely immunosuppressed (i.e., CD4 cell percentage ≥15%), but these vaccines should not be given to severely immunocompromised children (i.e., CD4 cell <15%). Of note, prior immunizations do not always provide protection, as evidenced by outbreaks of measles and pertussis in immunized HIV-infected children. Durability of vaccine-induced titers is often short, especially if vaccines are administered when the child's CD4 cell is <15%, and re-immunization when the CD4 count has increased (i.e., >15%) may be indicated.

Prophylactic regimens are integral for the care of HIV-infected children. All infants between 4-6 wk and 1 yr of age who are prone to be HIV-infected should receive prophylaxis to prevent P carinii (also called P. jiroveci) infection regardless of the CD4 lymphocyte count or percentage (Tables 276-5 and 276-6). Infants exposed to HIV-infected mothers should receive the same prophylaxis until they are proven to be noninfected; however, prophylaxis does not have to be initiated if there is strong presumptive evidence of noninfection (i.e., non-breastfed
<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Birth</th>
<th>1 mo</th>
<th>2 mo</th>
<th>4 mo</th>
<th>6 mo</th>
<th>12 mo</th>
<th>15 mo</th>
<th>18 mo</th>
<th>24 mo</th>
<th>4-6 yr</th>
<th>11-12 yr</th>
<th>14-16 yr</th>
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<tbody>
<tr>
<td>Hepatitis B</td>
<td>Hep B</td>
<td>Hep B</td>
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<tr>
<td>Measles, Mumps, Rubella*</td>
<td>PCV</td>
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<td>Influenza</td>
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<td>Pneumococcal Conjugate</td>
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<td>and Hemophilus b</td>
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<td>Diphtheria, Tetanus, Pertussis</td>
<td>DTap</td>
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<td>Polio (inactivated)</td>
<td>Polio</td>
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<td>Varicella</td>
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<tr>
<td>Hepatitis A</td>
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<tr>
<td>Rotavirus*</td>
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</tbody>
</table>

* See text.
† Contraindicated in children with AIDS or CD4 \(^+\) <15%. Give 2 doses 1-3 mo apart.
‡ Revaccination is recommended every year. Attenuated vaccine can be used >2 yr of age only if CD4 \(^+\) >15%.
§ Revaccination with pneumococcal polysaccharide vaccine (PPV) every 5 yr.
¶ Two doses at least 6 mo apart.
* First dose 6 through 14 wk of age and final dose no later than 8 mo 0 days of age. If using Rotarix, only 2 doses (2 and 4 mo) are needed.

**Figure 276-4** Routine childhood immunization schedule for HIV-infected children.

### Table 276-5: Recommendations for PCP Prophylaxis and CD4 Monitoring for HIV-Exposed Infants and HIV-Infected Children, by Age and HIV Infection Status

<table>
<thead>
<tr>
<th>AGE/HIV INFECTION STATUS</th>
<th>PCP PROPHYLAXIS</th>
<th>CD4 MONITORING</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth to 4-6 wk, HIV exposed</td>
<td>No prophylaxis</td>
<td>None</td>
</tr>
<tr>
<td>HIV infection reasonably excluded*</td>
<td>No prophylaxis</td>
<td>None</td>
</tr>
<tr>
<td>&lt;1 yr, HIV-infected or indeterminate</td>
<td>Prophylaxis regardless of CD4 count or percentage</td>
<td>According to local practice for initiation or follow-up of cART</td>
</tr>
<tr>
<td>1-5 yr, HIV infected</td>
<td>Prophylaxis if: CD4 &lt;500 cells/µL or &lt;15%†</td>
<td>According to local practice for initiation or follow-up of cART</td>
</tr>
<tr>
<td>&gt;6 yr, HIV infected</td>
<td>Prophylaxis if: CD4 &lt;200 cells/µL or &lt;15%‡</td>
<td>According to local practice for initiation or follow-up of cART</td>
</tr>
</tbody>
</table>

*More frequent monitoring (e.g., monthly) is recommended for children whose CD4 counts or percentages are approaching the threshold at which prophylaxis is recommended.
†Prophylaxis should be considered on a case-by-case basis for children who might otherwise be at risk for PCP, such as children with rapidly declining CD4 counts or percentages or children with category C conditions. Children who have had PCP should receive PCP prophylaxis until their CD4 count is >20% (for >6 yr of age) or >25% (for 2-5 yr of age) on continuous cART.
‡Prophylaxis should be considered on a case-by-case basis for children who might otherwise be at risk for PCP, such as children with rapidly declining CD4 counts or percentages or children with category C conditions. Children who have had PCP should receive PCP prophylaxis until their CD4 count is >20% (for >6 yr of age) or >25% (for 2-5 yr of age) on continuous cART.

The National Perinatal HIV Hotline (1-888-448-8765) provides consultation on all aspects of perinatal HIV care.

Based on adult data, primary prophylaxis against opportunistic infections may be discontinued if patients have experienced sustained (>6 mo duration) immune reconstitution with cART, even if they had previous opportunistic infections such as *Pneumocystis* pneumonia or disseminated MAC. HIV-infected children are at higher risk for TB and thus should have tuberculin skin testing (5 tuberculin units purified protein derivation) for TB at least once per year; an induration of 5 mm or more should be considered positive. If the child is living in close contact with a person with TB, the child should be tested more frequently. Of note, the sensitivity of purified protein derivation is reduced in severely immunocompromised patients and other laboratory tests should be used. For example, assays that determine IFN-γ release from lymphocytes following stimulation by specific *Mycobacterium tuberculosis* antigens were found to be more specific than the skin testing in adults. Limited data suggest that they are less sensitive in diagnosing TB in children, and therefore caution should be used in interpreting negative results of such tests in children. The “Guidelines for Prevention and Treatment of...
Table 276-6  Prophylaxis to Prevent First Episode of Opportunistic Infections Among HIV-Exposed and HIV-Infected Infants and Children, United States

<table>
<thead>
<tr>
<th>PATHOGEN</th>
<th>INDICATION</th>
<th>Preventive Regimen</th>
<th>ALTERNATIVE</th>
</tr>
</thead>
<tbody>
<tr>
<td>STRONGLY RECOMMENDED AS STANDARD OF CARE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Pneumocystis pneumonia</em></td>
<td>HIV-infected or HIV-indeterminate infants aged 1-12 mo; HIV-infected children aged 1-5 yr with CD4 count of &lt;500 cells/µL or CD4 percentage of &lt;15%; HIV-infected children aged 6-12 yr with CD4 count of &lt;200 cells/µL or CD4 percentage of &lt;15%</td>
<td>TMP-SMX, 150/750 mg/m² body surface area per day (max: 320/1600 mg) orally qd or bid 3 times weekly on consecutive days or qd or bid orally 3 times weekly on alternate days</td>
<td>Dapsone: age ≥1 mo: 2 mg/kg (max: 100 mg) orally qd; or 4 mg/kg (max: 200 mg) orally once a week</td>
</tr>
<tr>
<td>Malaria</td>
<td>Living or traveling to area in which malaria is endemic</td>
<td>Same as HIV-infected and HIV-uninfected children. Refer to <a href="http://www.cdc.gov/malaria/">http://www.cdc.gov/malaria/</a> for the most recent recommendations. Mefloquine, 5 mg/kg orally 1 time weekly (max: 250 mg)</td>
<td>Atovaquone/proguanil (Malarone) qd 11-20 kg: 62.5 mg/25 mg (1 pediatric tablet) 21-30 kg: 2 pediatric tablets 31-40 kg: 3 pediatric tablets &gt;40 kg: 1 adult tablet (250 mg/100 mg)</td>
</tr>
<tr>
<td>Mycobacterium tuberculosis</td>
<td>TST reaction ≥5 mm or Prior positive TST result without treatment or Close contact with any person who has contagious TB; TB disease must be excluded before start of treatment</td>
<td>Isoniazid, 10-15 mg/kg body weight (max: 300 mg) qd for 9 mo or 20-30 mg/kg body weight (max: 900 mg) orally 2 times weekly for 9 mo</td>
<td>Rifampin, 10-20 mg/kg body weight (max: 600 mg) orally daily for 4-6 mo</td>
</tr>
<tr>
<td>Isoniazid-resistant</td>
<td>Same as previous pathogen; increased probability of exposure to isoniazid-resistant TB</td>
<td>Rifampin, 10-20 mg/kg body weight (max: 600 mg) orally daily for 4-6 mo</td>
<td>Uncertain</td>
</tr>
<tr>
<td>Multidrug-resistant</td>
<td>Same as previous pathogen; increased probability of exposure to multidrug-resistant TB</td>
<td>Choice of drugs requires consultation with public health authorities and depends on susceptibility of isolate from source patient</td>
<td></td>
</tr>
<tr>
<td><em>Mycobacterium avium complex</em></td>
<td>For children age ≥6 yr with CD4 count of &lt;50 cells/µL; age 2-5 yr with CD4 count of &lt;75 cells/µL; age 1-2 yr with CD4 count of &lt;500 cells/µL; age &lt;1 yr with CD4 count of &lt;750 cells/µL</td>
<td>Clarithromycin, 7.5 mg/kg (max: 500 mg) orally bid or Azithromycin, 20 mg/kg (max: 1,200 mg) orally once a week</td>
<td>Azithromycin, 5 mg/kg body weight (max: 250 mg) orally qd or Children age ≥6 yr or Rifabutin, 300 mg orally qd or Acyclovir 20 mg/kg (max: 800 mg) 4 times a day for 5-7 days or IVIG, 400 mg/kg, administered once</td>
</tr>
<tr>
<td>Varicella-zoster virus†</td>
<td>Exposure to varicella or shingles with no history of varicella or Zoster or seronegative status for VZV or Lack of evidence for age-appropriate vaccination</td>
<td>Varicella-zoster immunoglobulin (VariZIG), 125 IU per 10 kg (max: 625 IU) IM, administered within 96 hr after exposure†</td>
<td></td>
</tr>
<tr>
<td>Vaccine-preventable pathogens</td>
<td>Standard recommendations for HIV-exposed and HIV-infected children</td>
<td>Routine vaccinations (see Fig. 276-3)</td>
<td></td>
</tr>
</tbody>
</table>
Opportunistic Infections Among HIV-Exposed and HIV-Infected Children (http://aidsinfo.nih.gov) should be consulted for these and other opportunistic infections that may occur in these populations. To reduce the incidence of opportunistic infections, parents should be counseled about (1) the importance of good hand washing, (2) avoiding raw or undercooked food (Salmonella), (3) avoiding drinking or swimming in lake or river water or being in contact with young farm animals (Cryptosporidium), and (4) the risk of playing with pets (Toxoplasma and Bartonella from cats, Salmonella from reptiles).

**PROGNOSIS**

The improved understanding of the pathogenesis of HIV infection in children and the availability of more effective antiretroviral drugs has changed the prognosis considerably. The earlier cART is started, the better the prognosis; a clinical trial aims to start treatment as close to delivery as possible will test the possibility of curing perinatally infected newborns. In settings with ready access to early diagnosis and antiretroviral therapy, progression of the disease to AIDS has significantly diminished. Since the advent of cART in the mid-1990s, mortality in perinatally infected children has declined more than 90% and many of the children survive to adolescence and adulthood. Even with only partial reduction of viral load, children may have both significant immunologic and clinical benefits. In general, the best prognostic indicators are the sustained suppression of plasma viral load and restoration of a normal CD4+ lymphocyte count. If determinations of viral load and CD4 lymphocytes are available, the results can be used to evaluate prognosis. It is unusual to see rapid progression in an infant with a viral load <100,000 copies/mL. In contrast, a high viral load (>100,000 copies/mL) over time is associated with greater risk for disease progression and death. CD4 lymphocyte percentage is another prognostic indicator, and the mortality rate is higher in patients with a CD4 lymphocyte percentage <15%. To define prognosis more accurately, the use of changes in both markers (CD4 lymphocyte percentage and plasma viral load) is recommended. Even in resource-limited countries where ARV therapy and molecular diagnostic tests are less available, the use of cART had a substantial benefit on the survival of HIV-infected children and reduced the hazard of mortality by 75%. Children with opportunistic infections (e.g., Pneumocystis pneumonia, MAC), encephalopathy and regressing developmental milestones, or wasting syndrome have the worst prognosis, with 75% dying before 3 yr of age. A higher risk of mortality was documented in children who did not receive TMP-SMZ preventive therapy. Persistent fever and/or oral thrush, serious bacterial infections (meningitis, pneumonia, sepsis), hepatitis, persistent anemia (<8 g/dL), and/or thrombocytopenia (<100,000/mL) also suggest a poor outcome, with >30% of such children dying before 3 yr of age. In contrast, lymphadenopathy, spleenomegaly, hepatomegaly, lymphoid interstitial pneumonitis, and parotitis are indicators of a better prognosis.

**PREVENTION**

Use of antiretroviral therapy for interruption of perinatal transmission from mother-to-child has been one of the greatest achievements of HIV research. Maternal cART is documented to decrease the rate of

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### Table 276-6

**Prophylaxis to Prevent First Episode of Opportunistic Infections Among HIV-Exposed and HIV-Infected Infants and Children, United States—cont’d**

<table>
<thead>
<tr>
<th>PATHOGEN</th>
<th>INDICATION</th>
<th>FIRST CHOICE</th>
<th>ALTERNATIVE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>USUALLY RECOMMENDED</strong></td>
<td></td>
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</tr>
<tr>
<td><em>Toxoplasma gondii</em>†</td>
<td>Seropositive IgG to <em>Toxoplasma</em> and severe immunosuppression: age &lt;6 yr with CD4 &lt;15%; age ≥6 yr with CD4 &lt;100 cells/µL</td>
<td><em>TMP-SMZ, 150/750 mg/m² orally bid</em> or Same dosage qd 3 times weekly on consecutive days or bid 3 times weekly on alternate days</td>
<td><em>Dapsone, age ≥1 mo: 2 mg/kg or 15 mg/m² (max: 25 mg) orally qd plus</em></td>
</tr>
<tr>
<td>Invasive bacterial infections</td>
<td>Hypogammaglobulinemia (i.e., IgG &lt;400 mg/dL)</td>
<td><em>IVIG 400 mg/kg body weight every 2-4 wk</em></td>
<td><em>Pyrimethamine, 1 mg/kg (max: 25 mg) orally qd plus</em></td>
</tr>
<tr>
<td>Cytomegalovirus</td>
<td>CMV antibody positivity and severe immunosuppression (CD4 &lt;50 cells/µL)</td>
<td><em>Valganciclovir, 900 mg orally qd</em></td>
<td><em>Leucovorin, 5 mg orally twice a week or Atovaquone, age 1-3 mo and &gt;24 mo, 30 mg/kg orally qd</em></td>
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</tbody>
</table>

*Children routinely being administered intravenous immunoglobulin (IVIG) should receive VarizIG if the last dose of IVIG was administered more than 21 days before exposure.
†As of 2007, VarizIG can be obtained only under a treatment Investigational New Drug protocol (1-800-843-7477, FFF Enterprises, Temecula, CA).
§Protection against toxoplasmosis is provided by the preferred anti-Pneumocystis regimen and possibly by atovaquone.

perinatal HIV-1 transmission to <2%, and <1% if the mother's viral RNA level is <1,000 copies/mL at delivery. Therefore, it is recommended that all pregnant women be tested for HIV and if positive, treated with a cART regimen, irrespective of viral load or CD4 count during pregnancy. This should be in conjunction with 4-6 wk of ZDV prophylaxis for the infant and with collaboration between the HIV-specialist and the obstetrician. Cesarean section (C-section) as a prevention strategy was examined in a multinational meta-analysis, which showed that the combination of elective C-section and maternal ZDV treatment reduced transmission by 87%. However, these data were obtained prior to the advent of cART, and the additional benefit of elective C-section to the cART-treated mother whose viral load is <1,000 copies/mL is negligible. Thus, elective C-section at 38 wk of gestation should be considered only for women whose viral load is >1,000 copies/mL in late gestation, to further reduce the risk of vertical transmission.

A multinational randomized, controlled trial in non-breastfed neonates whose mothers received no ARVs during pregnancy showed that prophylaxis with a two- or three-drug ARV regimen is superior to ZDV alone for the prevention of intrapartum HIV transmission. Based on these data, the U.S. Guidelines Panel recommends that infants born to HIV-infected women who have received no antepartum or only intrapartum ARVs, or who have HIV RNA >1000 copies/mL near delivery, should receive prophylaxis with ZDV for 6 wk combined with three doses of NVP in the 1st wk of life (i.e., at birth, 48 hr later, and 96 hr after the second dose), begun as soon after birth as possible (see Table 276-4).

The WHO recommends that all pregnant women receive a cART regimen appropriate for their own health, which should be continued at least throughout breastfeeding (in resource-limited areas) and for the remainder of their lives. This approach has the potential to reduce transmission during breastfeeding and future pregnancies, lowers the transmission risk to sexual partners, improves maternal survival, and promotes simplified universal treatment regimens. Breastfed infants should receive NVP for 6 wk if the mother is receiving cART, or NVP for the duration of breastfeeding if the mother is not on therapy. Formula-fed infants in resource-limited countries should receive ZDV bid or NVP qd for 6 wk.

Although the most effective way to prevent postpartum transmission of HIV is to eliminate breastfeeding altogether and substitute replacement feeding, there is evidence that early weaning may not be safe in resource-limited settings because of the high risk of malnutrition and diarrhea in formula-fed infants without a consistent source of clean water. Furthermore, exclusive breastfeeding (no additional solids or fluids other than water) results in less transmission than mixed feeding. Guidelines have evolved to recommend that HIV-infected mothers living in resource-limited settings should breastfeed their infants until at least 12 mo of age, with exclusive breastfeeding for the 1st 6 mo, and ARVs should continue to be provided, either to the mother or to the infant, at least until 1 wk after all breastfeeding has ceased. In settings where there are safe alternatives to breastfeeding, formula feeding is recommended. U.S. guidelines for prevention of mother-to-child transmission are regularly updated at http://aidsinfo.nih.gov/ and the international guidelines are regularly updated at the WHO website (http://www.who.int/hiv/topics/mtct/en/).

Now that it is clear that perinatal transmission can be reduced dramatically by treating pregnant mothers, a compelling argument can be made for prenatal identification of HIV-1 infection in the mother. The benefit of therapy both for the mother's health and to prevent transmission to the infant cannot be overemphasized. The recommended universal prenatal HIV-1 counseling and HIV-1 testing for all pregnant women has reduced the number of new infections dramatically in many areas of the United States and Europe. For women not tested during pregnancy, the use of rapid HIV antibody testing during labor or on the 1st day of the infant's life is a way to provide perinatal prophylaxis to an additional group of at-risk infants.

Prevention of sexual transmission involves avoiding the exchange of bodily fluids. In sexually active adolescents, condoms should be an integral part of programs to reduce sexually transmitted diseases, including HIV-1. Unprotected sex with older partners or with multiple partners and use of recreational drugs is common among HIV-1–infected adolescents, increasing their risk. Educational efforts about avoidance of risk factors are essential for older school-age children and adolescents and should begin before the onset of sexual activity. In addition, promising research for sexually active adults may translate to increased prevention for adolescents. Three African trials demonstrated that male circumcision was associated with a 50-60% reduction in risk of HIV acquisition in young men. For women, use of a 1% vaginal gel formulation of tenofovir during intercourse was found to reduce HIV acquisition by nearly 40%. Other topical microbicides are being investigated. A double-blind study of preexposure prophylaxis in MSM using once daily dosing of coformulated tenofovir and emtricitabine resulted in a 44% reduction in the incidence of HIV (95% confidence interval, 15-63; P = 0.005). Of interest, the incidence of HIV transmission was reduced by 73% when participants took the drug on 90% or more days. In addition, a large randomized multinational clinical trial of HIV serodiscordant adults demonstrated that effective ARV therapy in the HIV-infected partner reduced secondary transmission to an uninfected sexual partner by 96%. However, none of the studies that have shown promise for prevention in at-risk populations has included adequate representation in youth, making it difficult to interpret the effect on this population.

Despite prolonged suppression of viremia, it is obvious that cART may not fully restore health and may be associated with long-term toxicity. In addition, adherence is a major challenge and constrained resources will limit the ability to expand cART to all patients who need it. However, recent discoveries of new antiretroviral drugs, new vaccines, and advances in our understanding of HIV latency are encouraging developments on the long road to a cure.

Bibliography is available at Expert Consult.
ETIOLOGY
Human T-lymphotropic viruses 1 (HTLV-1) and 2 (HTLV-2) are members of the Deltaretrovirus genus of the Retroviridae family, which are single-stranded RNA viruses that encode reverse transcriptase, an RNA-dependent DNA polymerase that transcribes the single-stranded viral RNA into a double-stranded DNA copy. HTLV-1 was the first human retrovirus to be associated with cancer, as the cause of adult T-cell leukemia/lymphoma (ATL).

HTLV-1 and -2 share a genome homology of approximately 65% and infect T cells, B cells, and synovial cells via the ubiquitous glucose transporter type 1, which serves as the virus receptor. The genome contains gag, pol, and env genes and the pX region, which encodes nonstructural proteins. The nonstructural proteins include the Tax and Rex regulatory proteins, the novel proteins essential for virus spread (p30, p12, and p13), and the antisense-encoded HTLV-1 basic leucine zipper factor. Circular viral DNA is transported into the nucleus where it is integrated into chromosomal DNA (provirus), evading the typical mechanisms of immune surveillance and facilitating lifelong infection. The host response is mediated by cytotoxic T lymphocytes, resulting in lysis of infected cells. An exuberant inflammatory response with overproduction of cytokines contributes to developing nonmalignant disease.

EPIDEMIOLOGY
HTLV-1 infects 15-20 million persons globally. It is endemic in south-western Japan (where >10% of adults are seropositive), areas of the
Caribbean, including Jamaica and Trinidad (up to 6%), and in parts of sub-Saharan Africa (up to 5%). Lower seroprevalence rates are found in South America (up to 2%) and Taiwan (0.1-1%). There is microclustering with marked variability within geographic regions.

The seroprevalence of HTLV-1 and HTLV-2 in the United States in the general population is 0.01-0.03% for each virus, with higher rates with increasing age. The prevalence of HTLV-1 infection is highest in babies born in endemic areas or in persons who have had sexual contact with persons from endemic areas. The prevalence of HTLV-2 infection correlates with intravenous illicit drug use. A prevalence of approximately 18% was found in a study of illicit drug users in the United States, often with concomitant HIV infection.

HTLV-1 and -2 are transmitted as cell-associated viruses by vertical transmission from mother to child and horizontal transmission through genital secretions, contaminated blood products, and intravenous illicit drug use. Higher maternal HTLV-1 proviral load may be associated with greater risk of vertical transmission, which occurs primarily via breastfeeding from infected mothers with a 3-fold increased risk of transmission with breastfeeding for longer than 6 mo. Intrauterine and intrapartum transmissions account for <5% of vertical transmissions. In Japan, approximately 20-25% of children born to infected mothers become infected, and more than 90% of HTLV-1–infected children have HTLV-1–infected mothers. HTLV-2 may also be transmitted via breastfeeding, but it has a slightly lower reported transmission rate via breast milk of approximately 14%.

**DIAGNOSIS**

HTLV-1 and HTLV-2 infections are diagnosed by screening using 2nd-generation enzyme immunoassay with confirmation by immunoblot, indirect immunofluorescence, or line immunoassays. Polymerase chain reaction can also be used to distinguish HTLV-1 from HTLV-2 infection.

**CLINICAL MANIFESTATIONS**

The lifetime risk of disease associated with HTLV-1 infection is estimated at 5-10% and is highest following vertical transmission. HTLV-1 is associated with ATL and several nonmalignant conditions, including the neurodegenerative disorder HTLV-1–associated myelopathy (HAM), also known as tropical spastic paraparesis and sometimes termed HAM/tropical spastic paraparesis. The geographic epidemiologic characteristics of ATL and HAM are similar. HTLV-1–associated arthropathy mimics rheumatoid arthritis, including a positive rheumatoid factor. Treatment is with antinflammatory agents. HTLV-1–associated uveitis may be unilateral or bilateral, is more common among women, and resolves spontaneously, although it often recurs within 1-3 yr. Topical corticosteroids hasten recovery. HTLV-1–associated infective dermatitis is a chronic and recurrent eczematous disease occurring during childhood and adolescence. HTLV-1 infection predisposes to disseminated and recurrent Strongyloides stercoralis infection, increased risk of developing tuberculosis disease following latent infection, and severe scabies.

**Human T-Cell Lymphotrophic Virus-1–Associated Myelopathy**

HAM is more common in women than in men and has a relatively short incubation period after HTLV-1 infection, of 1-4 yr compared with 40-60 yr for ATL. HAM occurs in up to 4% of persons with HTLV-1 infection, usually developing during middle age. It is characterized by infiltration of mononuclear cells into the gray and white matter of the thoracic spinal cord, leading to severe white matter degeneration and fibrosis. HTLV-1 is found near but not directly within the lesions, suggesting that reactive inflammation is a major mechanism of disease. The cerebrospinal fluid typically shows a mildly elevated protein and a modest monocytic pleocytosis, along with anti-HTLV-1 antibodies. Neuroimaging studies are normal or show periventricular lesions in the white matter. Clinical manifestations include gradual onset of slowly progressive, symmetric neurologic degeneration of the corticospinal tracts and, to a lesser extent, the sensory system that leads to lower-extremity spasticity or weakness, lower back pain, and hyperreflexia of the lower extremities with an extensor plantar response. The bladder and intestines may become dysfunctional, and men may become impotent. Some patients develop dysesthesias of the lower extremities with diminished sensation to vibration and pain. Upper-extremity function and sensation, cranial nerves, and cognitive function are usually preserved. Treatment regimens have included corticosteroids, danazol, interferon, plasmapheresis, high-dose vitamin C, and antivirals, all with minimal effects.

**Adult T-Cell Leukemia/Lymphoma**

The age distribution of ATL peaks at approximately 50 yr, underscoring the long latent period of HTLV-1 infection. HTLV-1–infected persons remain at risk for ATL even if they move to an area of low HTLV-1 prevalence, with a lifetime risk for ATL of 2-4%. Most cases of ATL are associated with monoclonal integration of HTLV-1 provirus into the cellular genome of CD4 lymphocytes, resulting in unchecked proliferation of CD4 T cells. There is a spectrum of disease that is categorized into different forms: acute, lymphomatous, chronic, primary cutaneous smoldering, and primary cutaneous tumoral. The acute form of ATL comprises 35-75% of all cases. Smoldering, subclinical lymphoproliferation may spontaneously resolve, in approximately half of cases, or progress to chronic leukemia or lymphomatous or even acute ATL. **Chronic, low-grade, HTLV-1–associated lymphoproliferation (pre-ATL)** may persist for years with abnormal lymphocytes with or without peripheral lymphadenopathy before progressing to the acute form. Acute ATL is characterized by hypercalcemia, lytic bone lesions, lymphadenopathy that spares the mediastinum, hepatomegaly, splenomegaly, cutaneous lymphomas, and opportunistic infections. Leukemia may develop with circulating polylobulated malignant lymphocytes, called **flower cells**, possessing mature T-cell markers. Cyclophosphamide, doxorubicin, vincristine, and prednisolone (CHOP) is often the initial therapy for ATL, although chemotherapy is not curative and relapses are common. The median survival after diagnosis is 6-13 mo.

**Bibliography is available at Expert Consult.**
Bibliography

Transmissible Spongiform Encephalopathies

David M. Asher

The transmissible spongiform encephalopathies (TSEs) are slow infections of the human nervous system, consisting of at least 4 diseases of humans (Table 278-1): kuru; Creutzfeldt-Jakob disease (CJD) with its variants—sporadic CJD (sCJD), familial CJD (fCJD), iatrogenic CJD (iCJD), and new-variant or variant CJD (vCJD); Gerstmann-Sträussler-Scheinker syndrome (GSS); and fatal familial insomnia (FFI), or the even more rare sporadic fatal insomnia syndrome. TSEs also affect
animals; the most common and best-known TSEs of animals are scrapie in sheep, bovine spongiform encephalopathy (BSE or mad cow disease) in cattle, and a chronic wasting disease (CWD) of deer, elk, and moose found in parts of the United States and Canada. All TSEs have similar clinical manifestations and histopathology, and all are “slow” infections with very long asymptomatic incubation periods (often years), durations of several months or more, and overt disease affecting only the nervous system. TSEs are relentlessly progressive after illness begins and invariably fatal. The most striking neuropathologic change that occurs in each TSE, to a greater or lesser extent, is spongiform degeneration of the cerebral cortical gray matter.

**ETIOLOGY**

The TSEs are transmissible to susceptible animals by inoculation of tissues from affected subjects. Although the infectious agents replicate in some cell cultures, they do not achieve the high titers of infectivity found in brain tissues or cause recognizable cytopathic effects in cultures. Most studies of TSE agents have used in vivo assays, relying on the transmission of typical neurologic disease to animals as evidence that the agent was present and intact. Inoculation of susceptible recipient animals with small amounts of infectious TSE agent results, months later, in the accumulation in tissues of large amounts of agent with the same physical and biologic properties as the original agent. The TSE is propagated involves a self-replicating change in the folding host-specific mechanism by which the pathogen-specific information of TSE agents is encoded the amino acid methionine at both codons 129 of the prion-protein-encoding (PRNP) gene on chromosome 20, PRNP 129 MM, homozygous encoding the amino acid methionine at both codons 129 of the prion-protein-encoding (PRNP) gene on chromosome 20, BSE, bovine spongiform encephalopathy; CSF, cerebrospinal fluid; CJD, Creutzfeldt-Jakob disease; DWI, diffusion-weighted image; EEG, electroencephalography; FFI, fatal familial insomnia; FLAIR, fluid attenuation inversion recovery MRI; GSS, Gerstmann-Sträussler-Scheinker syndrome; iCJD, iatrogenic Creutzfeldt-Jakob disease; PRNP, prion protein encoding gene; PrP<sup>SME</sup>, abnormal prion protein; PSWCs, periodic sharp wave complexes; RBC, red blood cell; sCJD, sporadic Creutzfeldt-Jakob disease; vCJD, variant Creutzfeldt-Jakob disease.

**Table 278-1**

<table>
<thead>
<tr>
<th>DISEASE</th>
<th>CLINICAL FEATURES</th>
<th>SOURCE OF INFECTION</th>
<th>GEOGRAPHIC DISTRIBUTION AND PREVALENCE</th>
<th>USEFUL ANCILLARY TESTS</th>
<th>DURATION OF ILLNESS</th>
</tr>
</thead>
<tbody>
<tr>
<td>sCJD</td>
<td>Dementia, myoclonus, ataxia</td>
<td>Unknown</td>
<td>Worldwide; ≈1/1 million/yr; 85-95% of all CJD cases in U.S.</td>
<td>EEG—PSWCs; CSF 14-3-3</td>
<td>1-24 mo (mean: 4-6 mo)</td>
</tr>
<tr>
<td>fCJD</td>
<td>Dementia, myoclonus, ataxia</td>
<td>Genetic association (PRNP mutations) ?? Possible exogenous source of infection</td>
<td>Worldwide—geographic clusters; &gt;100 known families; 5-15% of CJD cases</td>
<td>Gene testing; EEG—PSWC rare; MRI/DWI (?)</td>
<td>Mean ≈15 mo</td>
</tr>
<tr>
<td>iCJD</td>
<td>Incoordination, dementia (late)</td>
<td>Cadaver dural grafts, human pituitary hormones, corneal transplantation, neurosurgical instruments, EEG depth electrodes</td>
<td>≈1% of CJD cases in toto (cadaver dural grafts), &gt;100 cases (human pituitary hormones), &gt;100 cases; corneal transplantation 3 cases; neurosurgical instruments, 6 cases, including 2 from cortical depth electrodes; RBC transfusions, 4 cases of vCJD infection, 3 clinical, 1 preclinical (U.K.); human plasma–derived factor VIII, 1 preclinical case of vCJD (U.K.)</td>
<td>Tonsil biopsy may show PrP&lt;sup&gt;SME&lt;/sup&gt;; MRI/FLAIR</td>
<td>1 mo-10 yr</td>
</tr>
<tr>
<td>vCJD</td>
<td>Mood and behavioral abnormalities, paresthesias, dementia</td>
<td>Linked to BSE in cattle, transfusion plasma products</td>
<td>&gt;220 clinical cases (see iatrogenic vCJD above)</td>
<td>EEG—no PSWCs; CSF 14-3-3 often negative; MRI (?)</td>
<td>8-36 mo (mean 14 mo)</td>
</tr>
<tr>
<td>Kuru</td>
<td>Incoordination, ataxia, tremors, dementia (late)</td>
<td>Linked to cannibalism</td>
<td>Fore people of Papua New Guinea (=2,600 known cases)</td>
<td>EEG—no PSWCs; CSF 14-3-3 often negative; MRI (?)</td>
<td>3-24 mo</td>
</tr>
<tr>
<td>GSS</td>
<td>Incoordination, chronic progressive ataxia, corticospinal tract signs, dementia (late), myoclonus (rare)</td>
<td>90% genetic (PRNP mutations)</td>
<td>Worldwide; &gt;50 families; ≈1-10/100 million/yr</td>
<td>PRNP gene sequencing</td>
<td>2-12 yr (mean = 57 mo)</td>
</tr>
<tr>
<td>FFI</td>
<td>Disrupted sleep, intractable insomnia; autonomic hyperactivity; myoclonus, ataxia, corticospinal tract signs; dementia</td>
<td>PRNP gene mutation (D 178L); very rare sporadic cases</td>
<td>≈27 families in Europe, U.K., U.S., Finland, Australia, China, Japan</td>
<td>EEG—PSWCs only rarely positive; MRI—no DWI abnormalities; CSF 14-3-3 positive in ≈50%</td>
<td>8 mo-6 yr (mean: PRNP 129 MM 12 ± 4 mo, 129 MV 21 ± 15 mo)</td>
</tr>
</tbody>
</table>

BSE, bovine spongiform encephalopathy; CSF, cerebrospinal fluid; CJD, Creutzfeldt-Jakob disease; DWI, diffusion-weighted image; EEG, electroencephalography; fCJD, familial Creutzfeldt-Jakob disease; FFI, fatal familial insomnia; FLAIR, fluid attenuation inversion recovery MRI; GSS, Gerstmann-Sträussler-Scheinker syndrome; iCJD, iatrogenic Creutzfeldt-Jakob disease; PRNP, prion protein encoding gene; PrP<sup>SME</sup>, abnormal prion protein; PSWCs, periodic sharp wave complexes; RBC, red blood cell; sCJD, sporadic Creutzfeldt-Jakob disease; vCJD, variant Creutzfeldt-Jakob disease.

PrP) to a β-sheet–rich structure in the protease-resistant conformation associated with infectivity. The existence of a second host-encoded protein—termed “protein X”—that participates in the transformation was also postulated to explain certain otherwise puzzling findings but never identified.

The prion hypothesis is still not universally accepted; it relies on the postulated existence of a genome-like coding mechanism based on differences in protein folding that have not been satisfactorily explained at a molecular level. In addition, it has yet to account convincingly for the many biologic strains of TSE agent that have been observed, although strain-specific differences in the abnormal forms of the PrP have been found and proposed as providing a plausible molecular basis for the coding. It fails to explain why pure PrP uncontaminated with nucleic acid from an infected host has not transmitted a convincingly typical spongiform encephalopathy associated with a serially self-propagating agent. Also troubling, in several experimental models and human illnesses, abnormal PrP and infectivity were not consistently associated. Particularly problematic is the finding that some illnesses associated with mutations in the PRNP gene and accompanied by abnormal PrP failed to transmit infection to animals. If the TSE agents ultimately prove to consist of protein and only protein, without any obligatory nucleic acid component, then the term prion will indeed be appropriate and the early proponents of the prion hypothesis will prove to have been prescient. If the agents are ultimately found to contain small nucleic acid genomes, then they might better be considered atypical viruses, for which the term virino has been suggested. Until the actual molecular structure of the infectious TSE pathogens and the presence or absence of a nucleic acid genome are rigorously established, it seems less contentious to continue calling them TSE agents, although many authorities now use the term prion (sometimes referring to the agent of a TSE and sometimes to the abnormal protein, even when nontransmissible).

The earliest evidence that abnormal proteins are associated with the TSE was morphologic: scrapie-associated fibrils were found in extracts of tissues from patients and animals with spongiform encephalopathies but not in normal tissues. Scrapie-associated fibrils resemble but are distinguishable from the amyloid fibrils that accumulate in the brains of patients with Alzheimer disease. A group of antigenically related protease-resistant proteins (PrPs) proved to be components of scrapie-associated fibril and to be present in the amyloid plaques found in the brains of patients and animals with TSEs. The abnormal forms of PrP are variously designated PrPSEN (scrapie-type PrP), PrP-res (protease-resistant PrP), PrPSENβ (TSE-associated PrP), or PrPSN (disease-associated PrP) by different authorities.

It remains unclear whether abnormal PrP constitutes the complete infectious particle of spongiform encephalopathies, is a component of those particles, or is a pathologic host protein not usually separated from the actual infectious entity by currently used techniques. The demonstration that PrP is encoded by a normal host gene seemed to favor the last possibility. Several studies suggest that agent-specific pathogenic information can be transmitted and replicated by different conformations of a protein with the same primary amino acid sequence in the absence of agent-specific nucleic acids. Properties of 2 fungal proteins were found to be heritable without encoding in nucleic acid, although those properties have not been transmitted to recipient fungi as infectious elements. Whatever its relationship to the actual infectious TSE particles, PrP clearly plays a central role in susceptibility to infection, because the normal PrP must be expressed in mice and cattle if they are to acquire a TSE or to sustain replication of the infectious agents. Furthermore, inherited normal variations in PrP phenotype are associated with increased susceptibility to vCJD and (to a lesser extent) to sCJD and with occurrence of iCJD.

PrPs are glycoproteins; protease-resistant PrPs, when aggregated, have the physical properties of amyloid proteins. The PrPs of different species of animals are very similar in their amino acid sequences and antigenicity but are not identical in structure. The primary structure of PrP is encoded by the host and is not altered by the source of the infectious agent provoking its formation. The function of the ubiquitous protease-sensitive PrP precursor (designated PrPSENβ, for “cellular” PrP or PrP-sen, for protease-sensitive PrP) in normal cells is unknown; it binds copper and may play some role in normal synaptic transmission, but it is not required for life or for relatively normal cerebral function in mice and cattle. As noted, expression of PrP is required both for development of scrapie disease and for replication of the transmissible scrapie agent in animals. The degree of homology between amino acid sequences of PrPs in different animal species may correlate with the “species barrier” that affects susceptibility of animals of 1 species to infection with a TSE agent adapted to grow in another species.

Attempts to find particles resembling those of viruses or virus-like agents in brain tissues of humans or animals with spongiform encephalopathies have been unsuccessful. Peculiar tubulovesicular structures reminiscent of some viruses have been seen in thin sections of TSE-infected brain tissues and cultured cells but not in normal cells. It has never been convincingly established that those structures are associated with infectivity.

### Epidemiology

Kuru once affected many children of both sexes ≥ 4 yr of age, adolescents, and young adults (mainly women) living in 1 limited area of Papua New Guinea. The complete disappearance of kuru among people born after 1957 suggests that the practice of ritual cannibalism (thought to have ended that year) was probably the only mechanism by which the infection was spread in Papua New Guinea.

CJD, the most common human spongiform encephalopathy, was formerly thought to occur only in older adults; however, iCJD and, much more rarely, sCJD (to date, 7 reports in adolescents—1 a 14 yr old girl) have affected young people. A single case of sporadic fatal insomnia was recognized in a U.S. adolescent. GSS has not been diagnosed in children or adolescents. vCJD, however, has a peculiar predilection for younger people. Of 174 cases of vCJD reported through 2010 in the United Kingdom, all except 23 were in people younger than 40 yr of age and 22 were younger than 20 yr of age; the youngest age at onset was 12 yr. sCJD has been recognized worldwide, at yearly rates of 0.25–2 cases/million population (not age-adjusted), with CJD foci of considerably higher incidence among Libyan Jews in Israel, in isolated villages of Slovakia, and in other limited areas. Sporadic CJD has not been convincingly linked to any common exposure, and the source of infection remains unknown. Proponents of the prion hypothesis are convinced that PrP can spontaneously misfold, becoming self-replicating and causing sCJD; skeptics favor infection with some ubiquitous TSE agent which, fortunately, has a very low attack rate except in persons with certain mutations in the PRNP gene. Neither of those possible etiologies has been proven. Person-to-person spread has been confirmed only for iatrogenic cases. Spouses and household contacts of patients are at very low risk of acquiring CJD, although 2 instances of conjugal CJD have been reported. However, medical personnel who have been exposed to brains of patients with CJD may be at some increased risk; at least 20 healthcare workers have been recognized with the disease.

The striking resemblance of CJD to scrapie prompted a concern that infected sheep tissues might be a source of spongiform encephalopathy in humans. No reliable epidemiologic evidence suggests that exposure to potentially scrapie-contaminated animals, meat, meat products, or experimental preparations of the scrapie agent have transmitted a TSE to humans. The potential of the CWD agent to infect human beings has also not been demonstrated but remains under investigation; deer, elk, and moose in 15 U.S. states and 2 Canadian provinces have been naturally infected; monkeys have been experimentally infected by injections with deer tissues containing the CWD agent. Exposure to contaminated meat, including venison from animals infected with the CWD agent, has not been implicated as a risk factor for sCJD.

The outbreak of BSE among cattle (possibly infected by eating scrapie-agent–contaminated meat-and-bone meal added to feed) was first recognized in the United Kingdom in 1986 and later reported in native cattle of 24 other countries, including Canada and the United States. The finding of a new TSE in ungulate and feline animals in British zoos and later in domestic cats raised a fear that some TSE agent (probably a strain of the scrapie agent), having crossed the species barrier from sheep to cattle, had acquired a broadened range
of susceptible hosts, posing a potential danger for humans. That remains a plausible explanation for the occurrence of vCJD, first described in adolescents in Britain in 1996 and as of November 2013 affecting at least 177 people in the United Kingdom (not counting a disturbing number of people with evidence of possible asymptomatic or “preclinical” vCJD infection) and more than 50 in other countries: 27 in France, 5 in Spain, 4 in Ireland, 3 in the Netherlands, 2 each in Italy and Portugal, and single cases in Japan and Saudi Arabia. Variant CJD has also occurred in former U.K. residents living in Ireland (2 cases), France (1 case), Canada (1 case), Taiwan (1 case), and the United States (2 cases); 2 additional cases of vCJD—1 in the United States and 1 in Canada—have been reported in former long-time residents of Saudi Arabia, a country that has not recognized BSE but might have imported contaminated meat products from the United Kingdom. A third case of vCJD was previously confirmed in a Saudi citizen residing in Saudi Arabia. Examination of resected appendixes in the United Kingdom for evidence of subclinical infection with prions suggested that many more people than expected had subclinical infection than those recognized with actual vCJD.

Iatrogenic transmissions of CJD have been recognized for more than 30 yr (Table 278-2). Such accidental transmissions of CJD have been attributed to use of contaminated neurosurgical instruments (no case reported since 1980) or operating facilities, use of cortical electrodes contaminated during epilepsy surgery, injections of human cadaveric pituitary growth hormone and gonadotropin (no longer marketed in the United States), and transplantation of contaminated corneas and allografts of human dura mater used as a surgical patching material. Pharmaceuticals and tissue grafts derived from or contaminated with human neural tissues, particularly when obtained from unselected donors and large pools of donors, pose special risks.

Studies of animals experimentally infected with TSE agents first suggested that blood and blood components from humans with preclinical CJD infections might pose a risk of transmitting disease to recipients, and since the 1980s such blood components have been withdrawn as a precaution in the United States when a donor was later found to have CJD and blood products were still in-date. While no epidemiologic study identified any subject exposed to such products obtained from donors later diagnosed with sporadic or vCJD, a surveillance program in the United Kingdom has already reported vCJD in 3 recipients of nonleukoreduced red blood cells from donors later diagnosed with vCJD; there was autopsy evidence of a preclinical vCJD infection in a fourth red cell recipient who died of another disease. Evidence of a preclinical vCJD infection was also found at autopsy in a patient with hemophilia A who was treated with human plasma-derived coagulation factor VIII to which at least 1 vCJD-infected donor contributed; the coagulation factor involved was never licensed in the United States.

### Table 278-2

<table>
<thead>
<tr>
<th>PRODUCT</th>
<th>NO. OF PATIENTS</th>
<th>INCUBATION TIME</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>Range</td>
</tr>
<tr>
<td>Pituitary extract</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Growth hormone</td>
<td>&gt;100</td>
<td>12 yr</td>
</tr>
<tr>
<td>Gonadotropin</td>
<td></td>
<td>5-38.5 yr</td>
</tr>
<tr>
<td>Red blood cells</td>
<td></td>
<td>13 yr</td>
</tr>
<tr>
<td></td>
<td></td>
<td>12-16 yr</td>
</tr>
<tr>
<td>Plasma-derived coagulation factor VIII</td>
<td>1</td>
<td>&gt; 11 yr</td>
</tr>
</tbody>
</table>

*There have been 28 cases reported among approximately 8,000 recipients of human cadaveric growth hormone in the United States; the remaining cases have been reported in other countries.

†The second transfusion-transmitted case of vCJD (Peden AH, Head MW, Ritchie DL, et al. Preclinical vCJD after blood transfusion in a PRNP codon 129 heterozygous patient, Lancet 364:S27–S29, 2004) died of unrelated causes about 5 yr after transfusion but was found to have accumulations of abnormal PrP in spleen and cervical lymph node—a finding unique to vCJD and interpreted as probable preclinical infection.

The diagnosis of vCJD infection attributed to treatment with human plasma-derived coagulation factor VIII (UK Health Protection Agency vCJD abnormal prion protein found in a patient with haemophilia at post-mortem, Press release 17 February 2009: http://webarchive.nationalarchives.gov.uk/20140714084352/http://www.hpa.org.uk/webv/HPAweb/HPAwebStandard/HPAweb_C/1234859690542?r=1231252394302) was also supported by immunohistochemical testing for abnormal PrP in the spleen of a person who died of other causes. Both patients with “preclinical” infections are thought to have died during the asymptomatic incubation period of vCJD.

### PATHOGENESIS AND PATHOLOGY

The probable portal of entry for the TSE agent in kuru is thought to have been either through the gastrointestinal tract or lesions in the mouth or integument incidentally exposed to the agent during cannibalism. Patients with vCJD (and animals with BSE and BSE-related TSEs) are thought to have been similarly infected with the BSE agent through exposure to a contaminated beef product, possibly through the intestinal tract. Except after direct introduction into the nervous system, the first site of replication of TSE agents appears to be in tissues of the reticuloendothelial system. TSE agents have been detected in low titers in blood of experimentally infected animals (mice, monkeys, hamsters, and sheep) and in the blood of persons with vCJD and perhaps sCJD; infectivity was mainly associated with nucleated cells, although plasma contained a substantial portion of total infectivity in blood. Circulating lymphoid cells seem to be required to infect mice by peripheral routes. Limited evidence suggests that TSE agents also spread to the central nervous system by ascending peripheral nerves. Several researchers claim to have developed tests that detected the CJD agent in human blood, although most attempts have failed. To date no blood-based test has been validated for antemortem testing of either humans or animals.

In human kuru, it seems probable that the only portal of exit of the agent from the body, at least in quantities sufficient to infect others, was through infected tissues exposed during cannibalism. In iatrogenically transmitted CJD, the brains and eyes of patients with CJD have been the probable sources of contamination. Experimental transmission of the agent to animals from kidney, liver, lung, lymph node, and spleen showed that those tissues as well as cerebrospinal fluid (CSF) sometimes contain the CJD agent; none of those sources has been implicated in accidental transmission of CJD to humans. At no time during the course of any TSE have antibodies or cell-mediated immunity to the infectious agents been convincingly demonstrated in either patients or animals. However, mice must be immunologically competent to be infected with the scrapie agent by peripheral routes of inoculation.

Typical changes in TSE include vacuolation and loss of neurons with hypertrophy and proliferation of glial cells, most pronounced in the cerebral cortex in patients with CJD and in the cerebellum in those with kuru. The central nervous system lesions are usually most severe in or even confined to gray matter, at least early in the disease. Loss of myelin appears to be secondary to degeneration of neurons. There generally is no inflammation, but a marked increase in the number and size of astrocytes is usual. Spongiform changes are not a striking autopsy finding in patients with FFI, and neuronal degeneration and gliosis are largely restricted to thalamic nuclei.

Amyloid plaques are found in the brains of all patients with GSS and in at least 70% of those with kuru. These plaques are less common in patients with CJD. Amyloid plaques are most common in the cerebellum but occur elsewhere in the brain as well. In brains of patients with vCJD, plaques surrounded by halos of vacuoles (described as flower-like or florid plaques) have been a consistent finding. TSE amyloid plaques react with antiserum prepared against PrP. Even in the absence of plaques, extracellular PrP can be detected in the brain parenchyma by immunostaining.
CLINICAL MANIFESTATIONS
Kuru, no longer seen, is a progressive degenerative disease of the cerebellum and brainstem with less obvious involvement of the cerebral cortex. The first sign of kuru was usually cerebellar ataxia followed by progressive incoordination. Coarse, shivering tremors were characteristic. Variable abnormalities in cranial nerve function appeared, frequently with impairment in conjugate gaze and swallowing. Patients died of inanition and pneumonia or of burns from cooking fires, usually within 1 yr after onset. Although changes in mentation were common, there was no frank dementia or progression to coma, as in CJD. There were no signs of acute encephalitis such as fever, headaches, and convulsions.

CJD occurs throughout the world. Patients initially have either sensory disturbances (most often visual) or confusion and inappropriate behavior, progressing over weeks or months to frank dementia, akinetic mutism, and ultimately coma. Some patients have cerebellar ataxia early in disease, and most patients experience myoclonic jerking movements. Mean survival of patients with vCJD has been <1 yr from the earliest signs of illness, although approximately 10% live for 2 yr. Variant CJD (Table 278-3) differs from the more common sCJD: patients with vCJD are much younger at onset (as young as 12 yr) and more often present with complaints of dysesthesia and subtle behavioral changes, often mistaken for psychiatric illness. Severe mental deterioration occurs later in the course of vCJD. Patients with vCJD have survived substantially longer than those with sCJD. (Attempts have been made to subclassify cases of CJD based on electrophoretic differences in PrP^* and variation in its sensitivity to digestion with the proteolytic enzyme proteinase (PK); the different variants are said to have somewhat different clinical features, including duration of illness, though all are ultimately fatal.)

GSS is a familial disease resembling CJD but with more prominent cerebellar ataxia and amyloid plaques. Dementia may appear only late in the course, and the average duration of illness is longer than typical sCJD. Progressively severe insomnia and dysautonomia as well as ataxia, myoclonus, and other signs resembling those of CJD and GSS characterize FFI and sporadic fatal insomnia. A case of sporadic fatal insomnia has been described in a young adolescent. GSS has not been diagnosed in children or adolescents.

A novel "prion disease" has been reported that is expressed in several generations with an autosomal dominant pattern associated with a unique mutation in the PRNP gene. The affected persons were middle-aged with a history of chronic diarrhea for years plus autonomic neuropathy and modest mental impairment but without full-blown dementia; PK-resistant PrP deposits with amyloid properties occurred in the brain, lymphoid tissues, kidney, spleen, and intestinal tract. The disease was not successfully transmitted to 3 lines of mice susceptible to several TSEs. It is not clear that such a syndrome—not a spongiform encephalopathy and apparently not associated with an infectious agent—should be lumped together with TSEs. It might well result from the abnormal PRNP gene product itself; if so, it would not pose the same potential threat to public health as do the TSEs.

DIAGNOSIS
Diagnosis of spongiform encephalopathies is most often determined on clinical grounds after excluding other diseases. The presence of 14-3-3 protein (see "Laboratory Findings") in CSF may aid in distinguishing between CJD and Alzheimer disease, although this is not a consideration in children. Elevations of 14-3-3 protein levels in CSF are not specific to TSEs and are common in viral encephalitis and other conditions causing rapid necrosis of brain tissue. Brain biopsy may be diagnostic of CJD, but it can be recommended only if a potentially treatable disease remains to be excluded or if there is some other compelling reason to make an antemortem diagnosis. Definitive diagnosis usually requires microscopic examination of brain tissue obtained at autopsy. The demonstration of protease-resistant PrP proteins in brain extracts can be useful to augment histopathologic diagnosis. Accumulation of the abnormal PrP in lymphoid tissues, even before the onset of neurologic signs, is typical of vCJD. Tonsil biopsy may avoid the need for brain biopsy when antemortem diagnosis of vCJD is indicated. Transmission of disease to susceptible animals by inoculation of brain suspension must be reserved for cases of special research interest.

LABORATORY FINDINGS

Virtually all patients with typical sporadic, iatrogenic, and familial forms of CJD have abnormal electroencephalograms (EEGs) as the disease progresses; the background becomes slow and irregular with diminished amplitude. A variety of paroxysmal discharges such as slow waves, sharp waves, and spike-and-wave complexes may also appear, and these may be unilateral or focal or bilaterally synchronous. Paroxysmal discharges may be precipitated by loud noise. Many patients have typical periodic suppression-burst complexes of high-voltage slow activity on EEG at some time during the illness. Patients with vCJD have had only generalized slowing, without periodic bursts of high-voltage discharges on EEG. CT or MRI may show cortical atrophy and large ventricles late in the course of CJD. Many patients with vCJD have an increase in density of the pulvinar on MRI. Reliable interpretation of the images might best be left to experienced radiologists.

<table>
<thead>
<tr>
<th>Table 278-3</th>
<th>Clinical and Histopathologic Features of Patients with Variant and Typical Sporadic Creutzfeldt-Jakob Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEATURE</td>
<td>VARIANT CJD (FIRST 10 PATIENTS)</td>
</tr>
<tr>
<td>Years of age at death* (range)</td>
<td>29 (19-74)</td>
</tr>
<tr>
<td>Duration of illness, mo (range)</td>
<td>12 (8-23)</td>
</tr>
<tr>
<td>Presenting signs</td>
<td>Abnormal behavior, dysesthesia</td>
</tr>
<tr>
<td>Later signs</td>
<td>Dementia, ataxia, myoclonus</td>
</tr>
<tr>
<td>Periodic complexes on EEG</td>
<td>Rare</td>
</tr>
<tr>
<td>PRNP 129 Met/Met</td>
<td>All tested (except 1 transfusion-transmitted case, 1 plasma-derivative transmitted case; 1 possible clinical case in United Kingdom where no tissue was available to confirm)</td>
</tr>
<tr>
<td>Histopathologic changes</td>
<td>Vacuolation, neuronal loss, astrocytosis, plaques (100%)</td>
</tr>
<tr>
<td>Florid PrP plaques1</td>
<td>100%</td>
</tr>
<tr>
<td>PrP^*E glycosylation pattern</td>
<td>BSE-like1</td>
</tr>
</tbody>
</table>

*Median age and duration for variant CJD; averages for typical sporadic CJD.
1Dense plaques with a pale periphery of surrounding vacuolated cells.
BSE, bovine spongiform encephalopathy; CJD, Creutzfeldt-Jakob disease; EEG, electroencephalogram; Met, codon 129 of one PRNP gene encoding for methionine; PRNP, prion protein—encoding gene; PrP, prion protein.
There may be modest elevation of CSF protein content in patients with TSE. Unusual protein spots were observed in CSF specimens after 2-dimensional separation in gels and silver staining; the spots were identified as 14-3-3 proteins, normal proteins (not related to PrP) abundant in neurons but not ordinarily detected in CSF. However, the finding of 14-3-3 protein in CSF has also been detected in CSF specimens from some patients with acute viral encephalitides and recent cerebral infarctions, and thus is not specific to CJD. Finding the 14-3-3 protein in CSF is neither sensitive nor specific but has been of some help in confirming the diagnosis of vCJD, especially when accompanied by increases in other cellular proteins. Diagnosis usually rests on recognizing the typical constellation of clinical findings, clinical course, and testing (CSF examination, CT or MRI, EEG), confirmed by histopathology and detection of PrP\textsubscript{Sc} in brain tissues at autopsy (or, less often, by tonsil or brain biopsy).

**TREATMENT**

No treatment has proven effective. Studies of cell cultures and rodents experimentally infected with TSE agents suggested that treatment with chlorpromazine, quinacrine, and tetracyclines might be of benefit, especially during the incubation period. Early reports of clinical trials based on those studies have been discouraging, and it seems unlikely that the severe brain damage found in late disease can be reversed by such treatment. Infusions with pentosan polysulphate directly into the cerebral ventricles appear to have delayed the progression of vCJD in a least 1 patient but did not reverse earlier brain damage. Appropriate supportive care should be provided to all CJD patients as for other progressive fatal neurologic diseases. On the basis of experimental studies in animals, several prophylactic postexposure treatment regimens have been suggested, but none has been widely accepted.

**GENETIC COUNSELING**

TSE sometimes occurs in families in a pattern consistent with an autosomal dominant mode of inheritance. In patients with a family history of CJD, the clinical and histopathologic findings are similar to those seen in sporadic cases. In the United States, only approximately 10% of cases of CJD are familial. GSS and FFI are always familial. In some affected families, approximately 50% of siblings and children of a patient with a familial TSE eventually acquire the disease; in other families, the “penetrance” of illness may be less.

The gene coding for PrP is closely linked if not identical to that controlling the incubation periods of scrapie in sheep and both scrapie and CJD in mice. The gene encoding PrP in humans is designated the PRNP gene and is located on the short arm of chromosome 20. It has an open reading frame of about 759 nucleotides (253 codons), in which more than 20 different point mutations and a variety of inserted sequences encoding extra tandem-repeated octapeptides are linked to the occurrence of spongiform encephalopathy in families with a pattern consistent with autosomal dominance of variable penetrance.

The same nucleotide substitution at codon 178 of the PRNP gene associated with CJD in some families has been found in all patients with FFI. Homozygosity for valine and especially for methionine at codon 129 seems to increase susceptibility to iCJD and sCJD. Almost all patients with vCJD to be genotyped have been homozygous for methionine at codon 129 of the PRNP gene. A few probable preclinical vCJD infections and 1 clinically typical case of vCJD have been reported in persons with other genotypes. It is of interest that when the PRNP genes from appendices containing accumulations of what appears to be PrP\textsubscript{Sc} in the United Kingdom were sequenced, a surprising number were homozygous for valine—the genotype of only approximately 10% of U.K. subjects and never found in a case of vCJD. The significance of this finding is not clear. U.K. authorities have adopted the precautionary assumption that some persons with PrP\textsubscript{Sc} in lymphoid tissues may have latent infections. Whether the blood and tissues of such persons are infectious is unknown.

Although the interpretation of these findings in regard to the prion hypothesis is in dispute, persons from families with CJD or GSS who have the associated mutations in the PRNP gene have a high probability of eventually acquiring spongiform encephalopathy. The significance of mutations in the PRNP genes of individuals from families with no history of spongiform encephalopathy is not known. It seems wise to avoid alarming those from unaffected families who have miscellaneous mutations in the PRNP gene, because the implications are not yet clear; in the United States, such persons are deferred from donating blood if a blood relative has been diagnosed with a TSE.

**PROGNOSIS**

The prognosis of all spongiform encephalopathies is uniformly poor. Approximately 10% of patients may survive for longer than 1 yr, but the quality of life is poor.

**FAMILY SUPPORT**

The CJD Foundation (http://www.cjdvision.org), organized and maintained by family members and friends of patients with CJD and related disorders, working closely with the Centers for Disease Control and Prevention (http://www.cdc.gov/ncidod/dvrd/prions) and with the National Prion Disease Pathology Surveillance Center, Case Western Reserve University, Cleveland, Ohio (http://www.cjd surveilliance.com), is a support and educational group and a useful source of information regarding available resources for those dealing with the diseases.

**PREVENTION**

Exposure to the BSE agent in meat products clearly poses a special danger. Authorities in Canada, the United States, and other countries have responded by implementing progressively more stringent agricultural and public health measures during the past 20 yr, with elimination of most bovine-derived materials from animal feeds probably the most effective measure. Three cases of BSE in native cattle have been recognized in the United States since 2004—the last in 2012; a case was also recognized in a Canadian cow imported into the United States in 2003. Canada found 19 native cattle with BSE between 2003 and 2010 (and imported a case from the United Kingdom in 1993). In spite of encouraging epidemiologic studies that failed to implicate exposure to scrapie or CWD agents in human TSEs, it seems prudent to avoid exposing children to meat and other products likely to be contaminated with any TSE agent.

The safety of human blood, blood components, and plasma derivatives in the United States and Canada is protected by deferring those donors with histories suggesting an increased risk of TSEs: persons treated with cadaveric pituitary hormones (no longer used) or dura mater allografts, patients with a family history of CJD (unless sequencing shows that the TSE-affected blood relative or the donor has revealed no TSE-related mutation in either PRNP gene), and persons who spent substantial periods of time in specified countries during years when BSE was prevalent. Persons transfused with blood in the United Kingdom and France after 1980 should be deferred from donating blood (similar deferral policies are in place for donors of human cells and tissues). U.K. authorities have warned persons treated with U.K.-sourced pooled coagulation factor concentrates or antithrombin between 1989 and 2001 that they may be “at risk of vCJD for public health purposes” and that “special infection control precautions” apply to them.

In principle, it would be better to identify the few blood and tissue donors actually infected with a TSE rather than deferring all those at increased risk of exposure, because most of them are unlikely to have been infected. Accordingly, antemortem donor screening tests that might identify persons with preclinical TSE infections are currently under development but have not been clinically validated. Another attractive approach would be to remove TSE agents from blood. Along these lines, a committee of expert advisors to the U.K. government recommended considering the use of an investigational device to filter red cells intended to transfuse children, because some unknown but possibly substantial number of U.K. blood donors might be incubating vCJD; authorities in the United Kingdom (and Ireland) evaluated, but have not adopted, this advice.

Standard precautions should be used to handle all human tissues, blood, and body fluids. Materials and surfaces contaminated with tissues or fluids from patients suspected of having CJD must be treated with great care. Whenever possible, discard contaminated instruments
by careful packaging and incineration. Contaminated tissues and biologic products probably cannot be completely freed of infectivity without destroying their structural integrity and biologic activity; therefore, the medical and family histories of individual tissue donors should be carefully reviewed to exclude a diagnosis of TSE. Histopathologic examination of brain tissues of cadaveric donors and testing for abnormal PrP might be performed where feasible to provide an additional assurance of safety. Although no method of sterilization can be relied on to remove all infectivity from contaminated surfaces, exposures to moist heat, sodium hydroxide, chlorine bleach, concentrated formic acid, acidified detergent, and guanidine salts markedly reduced infectivity in experimental studies.

*Bibliography is available at Expert Consult.*


Chapter 279  ♦  Principles of Antiparasitic Therapy  1673

Parasites are divided into 2 main groups taxonomically: protozoans, which are unicellular, and helminths, which are multicellular. Chemo- therapeutic agents appropriate for 1 group may not be appropriate for the other, and not all drugs are readily available (Table 279-1). Some drugs are available only from the manufacturer, some are not available in the United States, and some are available through the Centers for Disease Control and Prevention (CDC). Availability of drugs can be ascertained by contacting the Parasitic Diseases Public Inquiries Branch (1-404-718-4745; e-mail INTER REF chagas@cdc.gov). For after-hours emergencies, practitioners can contact the CDC Emergency Operations Center (770-488-7100) and ask for the on-call parasitic diseases physician. For assistance in the management of malaria, healthcare should call the CDC Malaria Hotline: 770-488-7788 or 855-856-4713 toll-free (M-F, 9 AM-5 PM, Eastern time). For emergency consultation after hours, clinicians can phone 770-488-7100 and request to speak with a CDC Malaria Branch clinician.

**SELECTED ANTIPARASITIC DRUGS FOR PROTOZOANS**

**Nitazoxanide (Alinia)**

Nitazoxanide is a nitrothiazole benzamide, initially developed as a veterinary anthelmintic. Nitazoxanide inhibits pyruvate-ferrodoxin oxidoreductase, which is an enzyme necessary for anaerobic energy metabolism. In humans, nitazoxanide is effective against many protozoans and helminths. Nitazoxanide is approved for the treatment of diarrhea caused by Cryptosporidium species in children 1-11 yr of age and by *Giardia intestinalis* in children 1 yr of age and older.

Nitazoxanide is available as an oral suspension, which has a pink color and strawberry flavor. The bioavailability is doubled with food. The drug is well absorbed from the gastrointestinal tract. One third is excreted in urine, and two thirds is excreted in feces as the active metabolite, tizoxanide. Although in vitro metabolism studies have not demonstrated cytochrome P450 enzyme effects, no pharmacokinetic studies have been performed yet in patients with compromised renal or hepatic function. In addition, no studies have been performed in pregnant or lactating women. Common adverse effects include abdominal pain, diarrhea, and nausea. Rare side effects include anorexia, flatulence, increased appetite, fever, pruritus, and dizziness. Intriguingly, nitazoxanide has activity against both hepatitis C and rotavirus, although the use of the agent against these viruses is investigational.

**Tinidazole (Tindamax)**

Tinidazole is a synthetic nitroimidazole with a chemical structure similar to metronidazole. It is FDA approved for treatment of trichomoniasis and for giardiasis and amebiasis in children 3 yr of age and older. In the treatment of giardiasis, it has the advantages of very few side effects and only requiring a single dose. Its mechanism of action against *Trichomonas* may be secondary to the generation of free nitro radicals by the protozoan. The mechanism of action against *Giardia lamblia* and *Entamoeba histolytica* is unknown. After oral administration, tinidazole is rapidly and completely absorbed and distributes into almost all tissues and body fluids, including crossing the blood–brain barrier and placental barrier. It is excreted via urine and feces. Hemodialysis increases clearance of drug. No studies have been performed for patients undergoing peritoneal dialysis or for patients with compromised hepatic function. Tinidazole carries a pregnancy category C classification and can be detected in breast milk. Breastfeeding should be interrupted during treatment and for 3 days after treatment.

**Atovaquone/Proguanil (Malarone)**

Atovaquone is a hydroxynaphthoquinone and has been used in the past predominantly against *Pneumocystis* pneumonia in AIDS patients. Its mechanism of action is via disruption of mitochondria membrane potential through interaction with cytochrome B. Atovaquone can also effectively inhibit liver stages of all *Plasmodium* species.

Proguanil is approved for use in the United States. Its mechanism of action is inhibition of the parasite dihydrofolate reductase enzyme by the active form, cycloguanil. When used alone, it has poor efficacy for prophylaxis.

Proguanil acts in synergy with atovaquone on the cytochrome B enzyme in *Plasmodia* mitochondria. The exact mechanism of synergy is unknown. In 2000, the FDA approved atovaquone/proguanil for the prevention and treatment of acute, uncomplicated *Plasmodium falciparum* malaria. Atovaquone alone in combination with proguanil is the only drug to completely inhibit the liver stage, which provides the advantage of only needing to use the drug for 7 days after departing a malaria-endemic area (compared to several weeks).

Two double-blind, randomized clinical trials assessing malaria prophylaxis demonstrated that atovaquone/proguanil was at least comparable to (and perhaps better than) chloroquine plus proguanil, and that atovaquone/proguanil was comparable to mefloquine. Atovaquone/proguanil was better tolerated than chloroquine plus proguanil and mefloquine. Atovaquone/proguanil treatment of acute uncomplicated *P. falciparum* infection has demonstrated higher or comparable cure rates when compared with other *P. falciparum* treatment drugs. Compared with other antimalaria treatment therapies, atovaquone/proguanil treatment has the highest cost.

**Artemisinin Derivatives and Artemether/ Lumefantrine (Coartem, Artemether, Artesunate)**

Artemisinin is a sesquiterpene lactone isolated from the weed *Artemisia annua*. It was developed in China where it is known as qinghaosu. Artemisinins act very rapidly against *Plasmodium vivax* as well as chloroquine-sensitive and chloroquine-resistant *P. falciparum*. Artemisinins are also rapidly eliminated. Emerging resistance to artemisinins has been seen in Cambodia, but not all of Southeast Asia. Coartem is the first artemisinin-containing drug approved for use by the FDA. It is a fixed-dose combination of 2 novel antimalarials, artemether (20 mg) and lumefantrine (120 mg). It is a highly effective 3 day malaria treatment with cure rates of >96%, even in areas of multidrug resistance.

Text continued on p. 1687
Parasitic infections are found throughout the world. With increasing travel, immigration, use of immunosuppressive drugs, and the spread of AIDS, physicians anywhere may see infections caused by previously unfamiliar parasites. The table below lists first-choice and alternative drugs for most parasitic infections.

**Table 279-1  Drugs for Parasitic Infections**

Parasitic infections are found throughout the world. With increasing travel, immigration, use of immunosuppressive drugs, and the spread of AIDS, physicians anywhere may see infections caused by previously unfamiliar parasites. The table below lists first-choice and alternative drugs for most parasitic infections.

<table>
<thead>
<tr>
<th>INFECTION</th>
<th>DRUG</th>
<th>ADULT DOSAGE</th>
<th>PEDIATRIC DOSAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acanthamoeba keratitis</td>
<td>Drug of choice: See footnote 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amebiasis (Entamoeba histolytica)</td>
<td>Drug of choice: Iodoquinol</td>
<td>650 mg PO tid x 20 days 30-40 mg/kg/day (max 2 g)</td>
<td>30-40 mg/kg/day in 3 doses PO x 20 days</td>
</tr>
<tr>
<td>or</td>
<td>Paromomycin</td>
<td>25-35 mg/kg/day PO in 3 doses x 7 days</td>
<td>25-35 mg/kg/day PO in 3 doses x 7 days</td>
</tr>
<tr>
<td>Alternative: Diloxanide furoate²</td>
<td>500 mg tid PO x 10 days</td>
<td>20 mg/kg/day PO in 3 doses x 10 days</td>
<td></td>
</tr>
<tr>
<td>Mild to moderate intestinal disease³</td>
<td>Drug of choice: Metronidazole</td>
<td>500-750 mg tid PO x 7-10 days 35-50 mg/kg/day</td>
<td>30-40 mg/kg/day PO in 3 doses x 7-10 days</td>
</tr>
<tr>
<td>or</td>
<td>Tinidazole³</td>
<td>2 g PO once daily x 3 days 50 mg/kg/day</td>
<td>30-40 mg/kg/day PO in 3 doses x 20 days</td>
</tr>
<tr>
<td>Either followed by: Iodoquinol</td>
<td>650 mg PO tid x 20 days</td>
<td>30-40 mg/kg/day PO in 3 doses x 20 days</td>
<td></td>
</tr>
<tr>
<td>or</td>
<td>Paromomycin</td>
<td>25-35 mg/kg/day PO in 3 doses x 7 days</td>
<td>25-35 mg/kg/day PO in 3 doses x 7 days</td>
</tr>
<tr>
<td>Severe intestinal and extraintestinal disease³</td>
<td>Drug of choice: Metronidazole</td>
<td>750 mg PO tid x 7-10 days 35-50 mg/kg/day</td>
<td>30-40 mg/kg/day PO in 3 doses x 7-10 days</td>
</tr>
<tr>
<td>or</td>
<td>Tinidazole³</td>
<td>2 g PO once daily x 5 days 50 mg/kg/day</td>
<td>30-40 mg/kg/day PO in 3 doses x 20 days</td>
</tr>
<tr>
<td>Either followed by: Iodoquinol</td>
<td>650 mg PO tid x 20 days</td>
<td>30-40 mg/kg/day PO in 3 doses x 20 days</td>
<td></td>
</tr>
<tr>
<td>or</td>
<td>Paromomycin</td>
<td>25-35 mg/kg/day PO in 3 doses x 7 days</td>
<td>25-35 mg/kg/day PO in 3 doses x 7 days</td>
</tr>
<tr>
<td>Amebic meningocoecephalitis, primary and granulomatous Naegleria</td>
<td>Drug of choice: Amphotericin B⁴⁷</td>
<td>1.5 mg/kg/day IV in 2 doses x 3 days, then 1.5 mg/kg/day IV x 6 days</td>
<td>1.5 mg/kg/day IV in 2 doses x 3 days, then 1 mg/kg/day IV x 6 days</td>
</tr>
<tr>
<td>or</td>
<td>Rifampin</td>
<td>1 mg/kg IV once/day plus 0.5 mg/day intraventricularly (max of 1.5 mg/kg by both routes)</td>
<td>1 mg/kg IV once/daily plus 0.5 mg/d intraventricularly (max of 1.5 mg/kg by both routes)</td>
</tr>
<tr>
<td>or</td>
<td>Fluconazole</td>
<td>10 mg/kg IV once/daily (max 600 mg/d)</td>
<td>10 mg/kg IV once/daily (max 600 mg/d)</td>
</tr>
<tr>
<td>or</td>
<td>Azithromycin</td>
<td>12 mg/kg IV once/daily</td>
<td>12 mg/kg IV once/daily</td>
</tr>
<tr>
<td>Acanthamoeba</td>
<td>Drug of choice: See footnote 8</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

²For treatment of keratitis caused by Acanthamoeba, concurrent topical use of 0.1% propamidine isethionate (Broene) plus neomycin-polymyxin B-granicidin ophthalmic solution has been successful (Hargrave SL, et al: Ophthalmology 106:952, 1999). In some European countries, propamidine is not available and hexamidine (Desmodine) has been used (Seal AV. Eye 17:893, 2003). In addition, 0.02% topical polyhexamethylene biguanide (PHMB) and/or chlorhexidine has been used successfully in a large number of patients (Tabin G, et al: Cornea 20:757, 2001; Wysenbeek SY, et al: Cornea 19:464, 2000). PHMB is available from Leiter’s Park Avenue Pharmacy, San Jose, CA (800-292-6773, www.leiterrx.com). The combination of chlorhexidine, natamycin (pimaricin), and debridement also has been successful (Kitagawa K, et al: Jpn J Ophthalmol 47:616, 2003).

³The drug is not available commercially, but as a service can be compounded by Panorama Compounding Pharmacy, 6744 Balboa Blvd, Van Nuys, CA 91406 (800-247-9767) or Medical Center Pharmacy, New Haven, CT (203-688-6816).

⁴Treatment should be followed by a course of iodoquinol or paromomycin in the dosage used to treat asymptomatic amebiasis.

⁵Nitazoxanide is FDA approved as a pediatric oral suspension for treatment of Cryptosporidium in immunocompetent children younger than 12 yr old and for Giardia (Med Lett 2003;45:29). It may also be effective for mild to moderate amebiasis (Diaz E, et al: Am J Trop Med Hyg 68:384, 2003). Nitazoxanide is available in 500 mg tablets and an oral suspension; it should be taken with food.

⁶A nitrimidazole similar to metronidazole, tinidazole was recently approved by the FDA and appears to be as effective and better tolerated than metronidazole. It should be taken with food to minimize GI adverse effects. For children and patients unable to take tablets, a pharmacist may crush the tablets and mix them with cherry syrup (Humco, and others). The syrup suspension is good for 7 days at room temperature and must be shaken before use. Omidazole, a similar drug, is also used outside the United States.


⁸An approved drug, but considered investigational for this condition by the FDA.

**Table 279-1**  Drugs for Parasitic Infections—cont’d

<table>
<thead>
<tr>
<th>INFECTION</th>
<th>DRUG</th>
<th>ADULT DOSAGE</th>
<th>PEDIATRIC DOSAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Balamuthia mandrillaris</em></td>
<td>Drug of choice:</td>
<td>See footnote 9</td>
<td></td>
</tr>
<tr>
<td><em>Sappinia diploidea</em></td>
<td>Drug of choice:</td>
<td>See footnote 10</td>
<td></td>
</tr>
<tr>
<td><em>Ancylostoma caninum</em></td>
<td>Drug of choice:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Albendazole</td>
<td>400 mg PO once</td>
<td>400 mg PO once</td>
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<td></td>
<td>or</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mebendazole</td>
<td>100 mg PO bid x 3 days</td>
<td>100 mg PO bid x 3 days</td>
</tr>
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<td></td>
<td>or</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pyrantel pamoate</td>
<td>11 mg/kg PO (max 1 g) x 3 days</td>
<td>11 mg/kg PO (max 1 g) x 3 days</td>
</tr>
<tr>
<td></td>
<td>or</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Endoscopic removal</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Ancylostoma duodenale</em>, see Hookworm</td>
<td></td>
<td></td>
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</tr>
<tr>
<td><em>Angiostrongylus</em> (Angiostrongylus cantonensis, Angiostrongylus costaricensis)</td>
<td>Drug of choice:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>See footnote 11</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Anisakiasis</em> (Anisakis spp.)</td>
<td>Treatment of choice</td>
<td>Surgical or endoscopic removal</td>
<td></td>
</tr>
<tr>
<td><em>Ascaris lumbricoides, roundworm</em></td>
<td>Drug of choice:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Albendazole</td>
<td>400 mg PO once</td>
<td>400 mg PO once</td>
</tr>
<tr>
<td></td>
<td>or</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mebendazole</td>
<td>100 mg PO bid x 3 days or 500 mg PO once</td>
<td>100 mg PO bid x 3 days or 500 mg PO once</td>
</tr>
<tr>
<td></td>
<td>or</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ivermectin</td>
<td>150-200 µg/kg PO once</td>
<td>150-200 µg/kg PO once</td>
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<tr>
<td><em>Babesiosis</em> (Babesia microti)</td>
<td>Drugs of choice:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Atovaquone</td>
<td>750 mg PO bid x 7-10 days</td>
<td>20 mg/kg PO bid x 7-10 days</td>
</tr>
<tr>
<td></td>
<td>plus azithromycin</td>
<td>600 mg PO daily x 7-10 days</td>
<td>10 mg/kg PO on day 1 (max 500 mg/dose), then 5 mg/kg/d (max 250 mg/dose) PO days 2-10</td>
</tr>
<tr>
<td></td>
<td>or</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Clindamycin</td>
<td>300-600 mg IV qid or 600 mg tid PO x 7-10 days</td>
<td>20-40 mg/kg/day IV or PO in 3 or 4 doses x 7-10 days (max 600 mg/dose)</td>
</tr>
<tr>
<td></td>
<td>plus quinine</td>
<td>650 mg tid PO x 7-10 days</td>
<td>24 mg/kg/day PO in 3 doses x 7-10 days</td>
</tr>
<tr>
<td><em>Balantidiasis</em> (Balantidium coli)</td>
<td>Drug of choice:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tetracycline</td>
<td>500 mg PO qid x 10 days</td>
<td>40 mg/kg/day PO (max 2 g) in 4 doses x 10 days</td>
</tr>
<tr>
<td></td>
<td>or</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Metronidazole</td>
<td>750 mg PO tid x 5 days</td>
<td>35-50 mg/kg/day PO in 3 doses x 5 days</td>
</tr>
<tr>
<td></td>
<td>Iodoquinol</td>
<td>650 mg PO tid x 20 days</td>
<td>40 mg/kg/day PO in 3 doses x 20 days</td>
</tr>
</tbody>
</table>

*A free-living leptomixid ameba that causes subacute to fatal granulomatous CNS disease. Several cases of Balamuthia encephalitis have been successfully treated with flucytosine, pentamidine, fluconazole, and sulfadiazine plus either azithromycin or clarithromycin (phenothiazines were also used) combined with surgical resection of the CNS lesion (Deets TR, et al. Clin Infect Dis 37:1304, 2003; Jung S, et al. Arch Pathol Lab Med 128:466, 2004). Miltefosine is another option currently being evaluated but it is not approved for any indication in the United States at this time. Case reports and in vitro data suggest it may have some antiamebic activity (AC Aichelburg et al., Emerg Infect Dis 2008; 14:1743; DY Martinez et al., Clin Infect Dis 2010; 51:e7; FL Schuster et al., J Eukaryot Microbiol 2006; 53:121). Miltefosine (Impavidos) is manufactured in 10 or 50 mg capsules by Paladin (Canada) and is available in the United States from the CDC for treatment of infections with free-living amebas.

*A free-living ameba not previously known to be pathogenic to humans. It has been successfully treated with azithromycin, IV pentamidine, itraconazole, and flucytosine combined with surgical resection of the CNS lesion (Gelman BB, et al. J Neuropathol Exp Neurol 62:990, 2003).

*Most patients have a self-limited course and recover completely. Analgesics, corticosteroids, and careful removal of CSF at frequent intervals can relieve symptoms from increased intracranial pressure (Lo Re V III, Gluckman SJ, Am J Med 114:217, 2003). No anthelmintic drug is proven to be effective, and some patients who were not severely ill, combination therapy with atovaquone and azithromycin was as effective as clindamycin and quinine and may have been better tolerated (Krause PJ, et al. N Engl J Med 343:1454, 2000). Highly immunosuppressed patients should be treated for a minimum of 6 wk and at least 2 wk past the last positive smear (PJ Krause et al., Clin Infect Dis 2008; 46:570). High doses of azithromycin (600-1,000 mg) have been used in combination with atovaquone for the treatment of immunocompromised patients (LM Weiss et al., N Engl J Med 2001; 344:773). Resistance to atovaquone plus azithromycin has been reported in immunocompromised patients treated with a single subcutaneous course of this regimen (GP Wormser et al., Clin Infect Dis 2010; 50:381).

Use of tetracyclines is contraindicated in pregnancy and in children younger than 8 yr old.

Continued
<table>
<thead>
<tr>
<th>INFECTION</th>
<th>DRUG</th>
<th>ADULT DOSAGE</th>
<th>PEDIATRIC DOSAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baylisascariasis</td>
<td>Drug of choice: See footnote 15</td>
<td></td>
<td></td>
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<tr>
<td>Blastocystis hominis</td>
<td>Drug of choice: See footnote 16</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Capillariasis (Capillaria philippinensis)</td>
<td>Drug of choice: Mebendazole7 200 mg PO bid × 20 days 400 mg PO daily × 10 days</td>
<td>200 mg PO bid × 20 days 400 mg PO daily × 10 days</td>
<td></td>
</tr>
<tr>
<td>Alternatives: Albendazole7 400 mg PO daily × 10 days</td>
<td></td>
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<tr>
<td>Chagas disease, see Trypanosomiasis</td>
<td></td>
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<tr>
<td>Clonorchis sinensis, see Fluke infection</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Cryptosporidiosis (Cryptosporidium)</td>
<td>Drug of choice: Nitazoxanide4 500 mg PO bid × 3 days7</td>
<td>1-3 yr: 100 mg PO bid × 3 days 4-11 yr: 200 mg PO bid × 3 days</td>
<td></td>
</tr>
<tr>
<td>Immunocompetent HIV infected</td>
<td>Drug of choice: See footnote 17</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cutaneous larva migrans (creeping eruption, dog and cat hookworm)</td>
<td>Drug of choice18: Albendazole7 400 mg PO daily × 3 days 200 μg/kg PO daily × 1-2 days</td>
<td>400 mg PO daily × 3 days 200 μg/kg PO daily × 1-2 days</td>
<td></td>
</tr>
<tr>
<td>or Ivermectin1 200 μg/kg PO daily × 1-2 days</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Alternative: Thiabendazole Topically</td>
<td>Topically</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyclosporiasis (Cyclospora cayetanensis)</td>
<td>Drug of choice19: Trimethoprim-sulfamethoxazole (TMP-SMX)7 TMP 160 mg/SMX 800 mg (1 DS tab) PO bid × 7-10 days</td>
<td>TMP 5 mg/kg, SMX 25 mg/kg bid PO × 7-10 days</td>
<td></td>
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<tr>
<td>Alternative: Ciprofloxacin 500 mg PO bid × 7 days</td>
<td>-</td>
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<tr>
<td>Cysticercosis, see Tapeworm infection</td>
<td>Drug of choice:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cystoisosporiasis (Cystoisospora belli, formerly known as Isospora)</td>
<td>Drug of choice: Trimethoprim-sulfamethoxazole (TMP-SMX)7 TMP 160 mg/SMX 800 mg (1 DS tab) PO bid × 10 days</td>
<td>TMP 5 mg/kg, SMX 25 mg/kg PO bid × 10 days</td>
<td></td>
</tr>
<tr>
<td>Dientamoeba fragilis infection20</td>
<td>Paromomycin7 25-35 mg/kg/day PO in 3 doses × 7 days</td>
<td>25-35 mg/kg/day PO in 3 doses × 7 days</td>
<td></td>
</tr>
<tr>
<td>or Iodoquinol 650 mg PO tid × 20 days</td>
<td>30-40 mg/kg/day PO (max 2 g) in 3 doses × 20 days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>or Metronidazole 500-750 mg tid × 10 days</td>
<td>20-40 mg/kg/day in 3 doses × 10 days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diphyllobothrium latum, see Tapeworm infection</td>
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</tbody>
</table>

11No drugs have been consistently demonstrated to be effective. The combination of albendazole 37 mg/kg/d PO and high-dose steroids has been used successfully (JM Peters et al., Pediatrics 2012; 129:e806; S Haider, Emerg Infect Dis 2012; 18:347). Albendazole 25 mg/kg/d PO × 20 d started as soon as possible (up to 3 d after possible infection) might prevent clinical disease and is recommended for children with known exposure, such as in the setting of ingestion of raccoon stool or contaminated soil (WJ Murray and KR Kazacos, Clin Infect Dis 2004, 39:1484). Mebendazole, levamisole, or ivermectin can be tried if albendazole is not available. Ocular baylisascariasis has been treated successfully using laser photocoagulation therapy to destroy the intraretinal larvae. Clinical significance of these organisms is controversial; metronidazole 750 mg tid × 10 days, iodoquinol 650 mg tid × 20 days or trimethoprim-sulfamethoxazole 1 DS tab bid × 7 days have been reported to be effective (Stenzel DJ, Borenam PFL: Clin Microbiol Rev 9:563, 1996; Ok UZ, et al: Am J Gastroenterol 94:3245, 1999). Metronidazole resistance may be common (Haresh K, et al: Trop Med Int Health 4:274, 1999). Nitazoxanide has been effective in children (Diaz E, et al: Am J Trop Med Hyg 68:384, 2003).
12Nitazoxanide has not consistently been shown to be superior to placebo in HIV-infected patients (Amadi B, et al: Lancet 360;1375, 2002). For HIV-infected patients, potent antiretroviral therapy (ART) is the mainstay of treatment. Nitazoxanide (treatment duration of 5-21 days), paromomycin, or a combination of paromomycin and azithromycin may be tried to decrease diarrhea and recalcitrant malabsorption of antimicrobial drugs, which can occur with chronic cryptosporidiosis (B Pansenburg et al., Expert Rev Anti Infect Ther 2009; 7:385).
### Table 279-1 Drugs for Parasitic Infections—cont’d

<table>
<thead>
<tr>
<th>INFECTION</th>
<th>DRUG</th>
<th>ADULT DOSAGE</th>
<th>PEDIATRIC DOSAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Dracunculus medinensis</em> (guinea worm) infection</td>
<td>Drug of choice: See footnote 21</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Echinococcus</em>, see Tapeworm Infection</td>
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<tr>
<td><em>Entamoeba histolytica</em>, see Amebiasis</td>
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</tr>
<tr>
<td><em>Enterobius vermicularis</em> (pinworm) infection</td>
<td>Drug of choice: Albendazole (^7) 400 mg PO once; repeat in 2 wk</td>
<td></td>
<td></td>
</tr>
<tr>
<td>or</td>
<td>Mebendazole 100 mg PO once; repeat in 2 wk</td>
<td></td>
<td></td>
</tr>
<tr>
<td>or</td>
<td>Pyrantel pamoate 11 mg/kg base PO once (max 1 g); repeat in 2 wk</td>
<td></td>
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</tr>
<tr>
<td><em>Fasciola hepatica</em>, see Fluke infection</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Filariasis</em> (^23)</td>
<td></td>
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</tr>
<tr>
<td><em>Wuchereria bancrofti</em>, <em>Brugia malayi</em>, <em>Brugia timori</em></td>
<td>Drug of choice: Diethylcarbamazine 6 mg/kg PO in 3 doses (\times) 14 days (^25)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>or</td>
<td>Ivermectin (^7) 150 µg/kg PO once</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Loa loa</em></td>
<td>Drug of choice: Diethylcarbamazine 9 mg/kg PO in 3 doses (\times) 14 days (^25)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Mansonella ozzardi</em></td>
<td>Drug of choice: See footnote 27</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Mansonella perstans</em></td>
<td>Drug of choice: Doxycycline (^7), (^14) 100 mg bid PO (\times) 7 days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>or</td>
<td>Mebendazole 150 mg PO once; repeat in 2 wk</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Mansonella streptocerca</em> (^26)</td>
<td>Drug of choice: Diethylcarbamazine 6 mg/kg PO in 3 doses (\times) 14 days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>or</td>
<td>Ivermectin (^7) 150 µg/kg PO once</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Tropical pulmonary eosinophilia</em> (TPE) (^29)</td>
<td></td>
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</tr>
<tr>
<td><em>Onchocerca volvulus</em> (river blindness)</td>
<td>Drug of choice: Ivermectin (^7) 150 µg/kg PO once, repeated every 6-12 mo until asymptomatic</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

## Fluke, hemerphroditic infection

<table>
<thead>
<tr>
<th>INFECTION</th>
<th>DRUG</th>
<th>ADULT DOSAGE</th>
<th>PEDIATRIC DOSAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Annual treatment with ivermectin, 150 µg/kg, can prevent blindness from ocular onchocerciasis (Mabey D, et al. Ophthalmology 103:1001, 1996). Diethylcarbamazine should not be used for treatment of this disease.</td>
<td></td>
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</tr>
</tbody>
</table>

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21Treatment of choice is slow extraction of worm combined with wound care (*MMWR Morb Morbid Mortal Wkly Rep* 2011; 60:1450). 10 days’ treatment with metronidazole 250 mg tid in adults and 25 mg/kg/day in 3 doses in children is not curative, but decreases inflammation and facilitates removal of the worm. Mebendazole 400-800 mg/day \(\times\) 6 days has been reported to kill the worm directly.

22Since all family members are usually infected, treatment of the entire household is recommended.

23Antihistamines or corticosteroids may be required to decrease allergic reactions due to disintegration of microfilariae from treatment of filarial infections, especially those caused by *Loa loa*. Endosymbiotic *Wolbachia* bacteria may have a role in filarial development and host response, and may represent a new target for therapy. Treatment with doxycycline 100 or 200 mg/day \(\times\) 4-6 wk in lymphatic filariasis and onchocerciasis has resulted in substantial loss of *Wolbachia* with subsequent block of microfilariae production and absence of microfilaria when followed for 24 mo after treatment (*Hoerauf A, et al. Med Microbiol Immunol 192:211, 2003; Hoerauf A, et al. BMJ 326:207, 2003*).

24Most symptoms caused by adult worm. Single-dose combination of albendazole (400 mg) with either ivermectin (200 µg/kg) or diethylcarbamazine (6 mg/kg) is effective for reduction or suppression of *Wuchereria bancrofti* microfilariasis but does not kill the adult forms (*Addiss D, et al. Cochrane Database Syst Rev 2004;CD003753*).

25Relapse occurs and can be treated with diethylcarbamazine.

26Doxycycline 7 days (days 1-7) 100 mg PO one daily or ivermectin 150 µg/kg PO once usually is effective.

27Diethylcarbamazine is potentially curative because of activity against both adult worms and microfilariae. Ivermectin is only active against microfilariae. (The *Medical Letter: Drugs for parasitic infections*, ed 2, 2010.)

28Diethylcarbamazine should not be used for treatment of this disease.
### Table 279-1 Drugs for Parasitic Infections—cont’d

<table>
<thead>
<tr>
<th>INFECTION</th>
<th>DRUG</th>
<th>ADULT DOSAGE</th>
<th>PEDIATRIC DOSAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clonorchis sinensis</strong> (Chinese liver fluke)</td>
<td>Praziquantel</td>
<td>75 mg/kg/day PO in 3 doses × 1 day</td>
<td>75 mg/kg/day PO in 3 doses × 1 day</td>
</tr>
<tr>
<td>or</td>
<td>Albendazole</td>
<td>10 mg/kg PO × 7 days</td>
<td>10 mg/kg PO × 7 days</td>
</tr>
<tr>
<td><strong>Fasciola hepatica</strong> (sheep liver fluke)</td>
<td>Triclabendazole</td>
<td>10 mg/kg PO once or twice</td>
<td>10 mg/kg PO once or twice</td>
</tr>
<tr>
<td>Alternative:</td>
<td>Bithionol</td>
<td>30-50 mg/kg PO on alternate days × 10-15 doses</td>
<td>30-50 mg/kg PO on alternate days × 10-15 doses</td>
</tr>
<tr>
<td>or</td>
<td>Nitazoxanide</td>
<td>500 mg PO bid × 7 days</td>
<td>1-3 yr: 100 mg PO bid</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>4-11 yr: 200 mg PO bid</td>
</tr>
<tr>
<td><strong>Fasciolopsis buski</strong>, <strong>Heterophyes heterophyes</strong>, <strong>Metagonimus yokogawai</strong> (intestinal flukes)</td>
<td>Praziquantel</td>
<td>75 mg/kg/day PO in 3 doses × 1 day</td>
<td>75 mg/kg/day PO in 3 doses × 1 day</td>
</tr>
<tr>
<td><strong>Metorchis conjunctus</strong> (North American liver fluke)</td>
<td>Praziquantel</td>
<td>75 mg/kg/day PO in 3 doses × 2 days</td>
<td>75 mg/kg/day PO in 3 doses × 2 days</td>
</tr>
<tr>
<td>or</td>
<td>Albendazole</td>
<td>10 mg/kg/day PO × 7 days</td>
<td>10 mg/kg/day PO × 7 days</td>
</tr>
<tr>
<td><strong>Paragonimus westermani</strong> (lung fluke)</td>
<td>Praziquantel</td>
<td>75 mg/kg/day PO in 3 doses × 2 days</td>
<td>75 mg/kg/day PO in 3 doses × 2 days</td>
</tr>
<tr>
<td>or</td>
<td>Bithionol</td>
<td>30-50 mg/kg PO on alternate days × 10-15 doses</td>
<td>30-50 mg/kg PO on alternate days × 10-15 doses</td>
</tr>
<tr>
<td>or</td>
<td>Triclabendazole</td>
<td>10 mg/kg PO once or twice</td>
<td>10 mg/kg PO once or twice</td>
</tr>
<tr>
<td><strong>Giardiasis</strong> (Giardia duodenalis)</td>
<td>Metronidazole</td>
<td>250 mg PO tid × 5 days</td>
<td>15 mg/kg/day PO in 3 doses × 5 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>500 mg PO bid × 3 days</td>
<td>1-3 yr: 100 mg PO every 12 hr × 3 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>4-11 yr: 200 mg PO every 12 hr × 3 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>50 mg/kg PO once (max 2 g)</td>
</tr>
<tr>
<td>Alternatives</td>
<td>Paromomycin</td>
<td>25-35 mg/kg/day PO in 3 doses × 7 days</td>
<td>25-35 mg/kg/day PO in 3 doses × 7 days</td>
</tr>
<tr>
<td></td>
<td>Furazolidone</td>
<td>100 mg PO qid × 7-10 days</td>
<td>6 mg/kg/day PO in 4 doses × 7-10 days</td>
</tr>
<tr>
<td></td>
<td>Quinacrine</td>
<td>100 mg PO tid × 5 days</td>
<td>2 mg/kg tid PO × 5 days (max 300 mg/day)</td>
</tr>
<tr>
<td><strong>Gnathostomiasis</strong> (Gnathostoma spinigerum)</td>
<td>Albendazole</td>
<td>400 mg PO bid × 21 days</td>
<td>400 mg PO bid × 21 days</td>
</tr>
<tr>
<td>or</td>
<td>Ivermectin</td>
<td>200 µg/kg/day PO × 2 days</td>
<td>200 µg/kg/day PO × 2 days</td>
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<tr>
<td>±</td>
<td>Surgical removal</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Gongylonemiasis</strong> (Gongylonema sp.)</td>
<td>Albendazole</td>
<td>10 mg/kg/day PO × 3 days</td>
<td>10 mg/kg/day PO × 3 days</td>
</tr>
</tbody>
</table>

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31Unlike infections with other flukes, Fasciola hepatica infections may not respond to praziquantel. Triclabendazole (Egaten, Novartis) may be safe and effective but data are limited (Graham CS, et al: Clin Infect Dis 33:1, 2001). It is available from Victoria Pharmacy, Zurich, Switzerland (www.pharmaworld.com; 41-1-211-24-32) and should be given with food for better absorption. A single study has found that nitazoxanide has limited efficacy for treating fascioliasis in adults and children (Favennec L, et al: Aliment Pharmacol Ther 17:265, 2003).


34Triclabendazole may be effective in a dosage of 5 mg/kg once/day × 3 days or 10 mg/kg bid + 1 day (Calvopiña M, et al: Trans R Soc Trop Med Hyg 92:566, 1998). See footnote 31 for availability.


36Not absorbed; may be useful for treatment of giardiasis in pregnancy.

37Bithionol

Table 279-1  Drugs for Parasitic Infections—cont’d

<table>
<thead>
<tr>
<th>INFECTION</th>
<th>DRUG</th>
<th>ADULT DOSAGE</th>
<th>PEDIATRIC DOSAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hookworm infection (Ankylostoma duodenale, Necator americanus)</td>
<td>Drug of choice: Albendazole&lt;sup&gt;7&lt;/sup&gt;</td>
<td>400 mg PO once</td>
<td>400 mg PO once</td>
</tr>
<tr>
<td>or</td>
<td>Mebendazole</td>
<td>100 mg PO bid × 3 days or 500 mg once</td>
<td>100 mg PO bid × 3 days or 500 mg once</td>
</tr>
<tr>
<td>or</td>
<td>Pyrantel pamoate&lt;sup&gt;7&lt;/sup&gt;</td>
<td>11 mg/kg (max 1 g) PO × 3 days</td>
<td>11 mg/kg (max 1 g) PO × 3 days</td>
</tr>
<tr>
<td>Hydatid cyst, see Taeniasis infection</td>
<td>Hymenolepis nana, see Taeniasis infection</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leishmania infection</td>
<td>Visceral&lt;sup&gt;39, 40&lt;/sup&gt;</td>
<td>Drugs of choice: Sodium stibogluconate</td>
<td>20 mg Sb/kg/day IV or IM × 28 days&lt;sup&gt;41&lt;/sup&gt;</td>
</tr>
<tr>
<td>or</td>
<td>Meglumine antimonate</td>
<td>20 mg pentavalent antimony/kg/day IV or IM × 28 days&lt;sup&gt;41&lt;/sup&gt;</td>
<td>20 mg pentavalent antimony/kg/day IV or IM × 28 days&lt;sup&gt;41&lt;/sup&gt;</td>
</tr>
<tr>
<td>or</td>
<td>Amphotericin B&lt;sup&gt;7&lt;/sup&gt;</td>
<td>0.5-1 mg/kg IV daily or every 2 days for up to 8 wk</td>
<td>0.5-1 mg/kg IV daily or every 2 days for up to 8 wk</td>
</tr>
<tr>
<td>or</td>
<td>Liposomal amphotericin&lt;sup&gt;42&lt;/sup&gt;</td>
<td>3 mg/kg/day IV (days 1-5) followed by 3 mg/kg/day on days 14 and 21&lt;sup&gt;13&lt;/sup&gt;</td>
<td>3 mg/kg/day IV (days 1-5) followed by 3 mg/kg/day on days 14 and 21&lt;sup&gt;13&lt;/sup&gt;</td>
</tr>
<tr>
<td>or</td>
<td>Miltefosine</td>
<td>2.5 mg/kg/day PO (max 150 mg/day) × 28 days</td>
<td>2.5 mg/kg/day PO (max 150 mg/day) × 28 days</td>
</tr>
<tr>
<td>Alternative&lt;sup&gt;44&lt;/sup&gt;:</td>
<td>Pentamidine&lt;sup&gt;7&lt;/sup&gt;</td>
<td>4 mg/kg IV or IM daily or every 2 days for 15-30 doses</td>
<td>4 mg/kg IV or IM daily or every 2 days for 15-30 doses</td>
</tr>
<tr>
<td>Cutaneous&lt;sup&gt;45&lt;/sup&gt;</td>
<td>Drugs of choice: Sodium stibogluconate</td>
<td>20 mg Sb/kg/day IV or IM × 20 days&lt;sup&gt;41&lt;/sup&gt;</td>
<td>20 mg Sb/kg/day IV or IM × 20 days&lt;sup&gt;41&lt;/sup&gt;</td>
</tr>
<tr>
<td>or</td>
<td>Meglumine antimonate</td>
<td>20 mg pentavalent antimony/kg/day IV or IM × 20 days&lt;sup&gt;41&lt;/sup&gt;</td>
<td>20 mg pentavalent antimony/kg/day IV or IM × 20 days&lt;sup&gt;41&lt;/sup&gt;</td>
</tr>
<tr>
<td>or</td>
<td>Miltefosine</td>
<td>2.5 mg/kg/day PO (max 150 mg/day) × 28 days</td>
<td>2.5 mg/kg/day PO (max 150 mg/day) × 28 days</td>
</tr>
<tr>
<td>Alternatives&lt;sup&gt;46&lt;/sup&gt;:</td>
<td>Pentamidine&lt;sup&gt;7&lt;/sup&gt;</td>
<td>2-3 mg/kg IV or IM daily or every 2 days × 4-7 doses&lt;sup&gt;47&lt;/sup&gt;</td>
<td>2-3 mg/kg IV or IM daily or every 2 days × 4-7 doses&lt;sup&gt;47&lt;/sup&gt;</td>
</tr>
<tr>
<td>or</td>
<td>Paromomycin&lt;sup&gt;7, 48&lt;/sup&gt;</td>
<td>Topically 2x/day × 10-20 days</td>
<td>Topically 2x/day × 10-20 days</td>
</tr>
</tbody>
</table>

<sup>46</sup>Consultation with physicians experienced in management of this disease is recommended. To maximize effectiveness and minimize toxicity, the choice of drug, dosage and duration of therapy should be individualized based on the region of disease acquisition, likely infecting species, number, significance and location of lesions, and host factors such as immune status (HW Murray, Lancet 2005; 366:1561). Some of the listed drugs and regimens are effective only against certain Leishmania species/strains and only in certain areas of the world (S Sundar and J Chakravarty, Expert Opin Pharmacother 2013; 14:53).

<sup>47</sup>Visceral leishmaniasis is most commonly caused by the Old World species Leishmania donovani (kala-azar) and Leishmania infantum and the New World species. Leishmania chagasi. Treatment duration may vary based on symptoms, host immune status, species, and area of the world where infection was acquired.

<sup>48</sup>May be repeated or continued; a longer duration may be needed for some patients (Henvaldt BL: Lancet 354:1191, 1999).

<sup>49</sup>Three lipid formulations of amphotericin B have been used for treatment of visceral leishmaniasis. Largely based on clinical trials in patients infected with Leishmania infantum, the FDA approved liposomal amphotericin B (AmBisome) for treatment of visceral leishmaniasis (Meyerhoff A, Clin Infect Dis 1999;28:42). Amphotericin B lipid complex (Abelcet) and amphotericin B cholesteryl sulfate (Amphotec) have also been used with good results but are considered investigational for this condition by the FDA.

<sup>50</sup>The FDA-approved dosage regimen for immunocompromised patients (e.g., HIV infected) is 4 mg/kg/day (days 1-5) and 4 mg/kg/day on days 10, 17, 24, 31, and 38. The relapse rate is high, maintenance therapy for immunocompromised patients (e.g., HIV infected) is 4 mg/kg/day (days 1-5) and 4 mg/kg/day on days 10, 17, 24, 31, and 38. The relapse rate is high; maintenance therapy may be indicated, but there is no consensus as to dosage or duration. (Russo R, Nigro LC, Minniti S, et al: Visceral leishmaniasis in HIV infected patients: treatment with high dose liposomal amphotericin B (AmBisome), J Infect Dis 32:133-137, 1996).

<sup>51</sup>For treatment of kala-azar in adults in India, oral miltefosine 100 mg/day (205 mg/kg/day) for 3-4 wk was 97% effective after 6 mo (Jha TK, et al: N Engl J Med 341:1795, 1999; Sangraula H, et al: J Assoc Physicians India 51:686, 2003). Gastrointestinal adverse effects are common, and the drug is contraindicated in pregnancy. The dose of miltefosine in an open-label trial in children in India was 2.5 mg/kg/day × 28 days (Bhattacharya SK, et al: Clin Infect Dis 38:217, 2004). Miltefosine (Impavidol) is available from the manufacturer (Zentaris, Frankfurt, Germany at Impavidol@zentaris.de).

<sup>52</sup>Cutaneous leishmaniasis is most commonly caused by the Old World species Leishmania major and Leishmania tropica and the New World species Leishmania mexicana, Leishmania (Vianna) braziliensis and others. Treatment duration may vary based on symptoms, host immune status, species, and area of the world where infection was acquired.

<sup>53</sup>In a placebo-controlled trial in patients 12 yr old and older, oral miltefosine was effective for the treatment of cutaneous leishmaniasis caused by Leishmania (Vianna) panamensis in Colombia but not L (V) braziliensis in Guatemala at a dosage of about 2.5 mg/kg/day for 28 days. “Motion sickness,” nausea, headache and increased creatinine were the most frequent adverse effects (Soto J, et al: Clin Infect Dis 38:1266, 2004). See footnote 44 regarding miltefosine availability. For treatment of L major cutaneous lesions, a study in Saudi Arabia found that oral fluconazole, 200 mg once/day × 6 wk, appeared to speed healing (Alrajhi AA, et al: N Engl J Med 346:891, 2002).

<sup>54</sup>At this dosage miltefosine has been effective against leishmaniasis in Colombia where the likely organism was L (V) panamensis (Soto-Manipe J, et al: Clin Infect Dis 16:417, 1993; Soto J, et al: Am J Trop Med Hyg 50:107, 1994). Its effect against other species is not well studied.

<sup>55</sup>Topical paromomycin/12% methylbenzenethionim chloride (Leshcunat) in soft white paraffin for topical use has been reported to be partially effective in some patients against cutaneous leishmaniasis due to L major in Israel and against L mexicana and L (V) braziliensis in Guatemala, where mucosal spread is very rare (Arana BA, et al: Am J Trop Med Hyg 65:466, 2001). The methylbenzenethionim is irritating to the skin; lesions may worsen before they improve.

Continued
Table 279-1  Drugs for Parasitic Infections—cont’d

<table>
<thead>
<tr>
<th>INFECTION</th>
<th>DRUG</th>
<th>ADULT DOSAGE</th>
<th>PEDIATRIC DOSAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mucosal49</td>
<td>Sodium stibogluconate</td>
<td>20 mg Sb/kg/day IV or IM × 28 days41</td>
<td>20 mg Sb/kg/day IV or IM × 28 days41</td>
</tr>
<tr>
<td>or</td>
<td>Meglumine antimonate</td>
<td>20 mg pentavalent antimony/kg/day IV or IM × 28 days41</td>
<td>20 mg pentavalent antimony/kg/day IV or IM × 28 days41</td>
</tr>
<tr>
<td>or</td>
<td>Amphotericin B</td>
<td>0.5-1 mg/kg IV daily or every 2 days for up to 8 wk</td>
<td>0.5-1 mg/kg IV daily or every 2 days for up to 8 wk</td>
</tr>
<tr>
<td>or</td>
<td>Miltefosine</td>
<td>2.5 mg/kg/day PO (max 150 mg/day) × 28 days</td>
<td>2.5 mg/kg/day PO (max 150 mg/day) × 28 days</td>
</tr>
</tbody>
</table>

Lice infestation (Pediculus humanus, Pediculus capitis, Phthirus pubis)50

| Drugs of choice: | 0.5% Malathion51 | Topically | Topically |
| or | 1% Permethrin52 | Topically | Topically |
| or | Pyrethrins with piperonyl butoxide52 | Topically | Topically |
| or | 0.5% Ivermectin lotion | Topically, once | Topically, once |
| or | 0.9% Spinosad susp | Topically, 2 × at least 7 days apart | Topically, 2 × at least 7 days apart |
| or | Ivermectin53 | 200 μg/kg PO × 3 doses, on days 1, 2, and 10 | 200 μg/kg PO × 3 doses, on days 1, 2, and 10 |

Loa loa, see Filariasis

Malaria, treatment of (Plasmodium falciparum, Plasmodium ovale, Plasmodium vivax, and Plasmodium malariae)

P. falciparum54 acquired in areas of chloroquine resistance

Oral55

| Drugs of choice: | Atovaquone/proguanil56 | 2 adult tabs PO bid58 or 4 adult tabs PO once daily × 3 days | <5 kg: not indicated |
| or | Quinine sulfate plus doxycycline,7,14 or plus tetracycline,7,14 or plus clindamycin | 650 mg PO every 8 hr × 3-7 days57 | 30 mg/kg/day PO in 3 doses × 3-7 days57 |
| or | | 100 mg PO bid × 7 days | 4 mg/kg/day PO in 2 doses × 7 days |
| or | | 250 mg PO qid × 7 days | 6.25 mg/kg PO qid × 7 days |
| or | | 20 mg/kg/day PO in 3 doses × 7 days60 | 20 mg/kg/day PO in 3 doses × 7 days |

49Mucosal infection is most commonly due to the New World species L. (V.) braziliensis, L. (V.) panamensis, or L. (V.) guyanensis. Treatment duration may vary based on symptoms, host immune status, species, and area of the world where infection was acquired.

50For infestation of eyelashes with Phthirius pubis lice, use petrolatum; TMP-SMX has also been used (Meinking TL: Curr Probl Dermatol 24:157, 1996). For pubic lice, treat with 5% permethrin or ivermectin as for scabies. TMP-SMX has also been effective together with permethrin for head lice (Hipolito RB, et al: Pediatrics 107:E30, 2001).


52A second application is recommended 1 wk later to kill hatching progeny. Some lice are resistant to pyrethrins and permethrin (Meinking et al: Arch Dermatol 2002;138:220).

53Ivermectin is effective against adult lice but has no effect on nits (Jones KN, JC English III: Arch Dermatol 139:994, 2003).

54Chloroquine-resistant P. falciparum occurs in all malarious areas except Central America west of the Panama Canal Zone, Mexico, Haiti, the Dominican Republic, and most of the Middle East (chloroquine resistance has been reported in Yemen, Oman, Saudi Arabia, and Iran). For treatment of multidrug-resistant: P. falciparum in Southeast Asia, especially Thailand, where resistance to mefloquine is frequent, atovaquone/proguanil, artesunate plus mefloquine, or artesether plus mefloquine may be used (Luxemburger JC, et al: Trans R Soc Trop Med Hyg 88:213, 1994; Karbwang J, et al: Trans R Soc Trop Med Hyg 89:296, 1995).

55Uncomplicated or mild malaria may be treated with oral drugs.

56Atovaquone/proguanil is available as a fixed-dose combination tablet: adult tablets (Malarone; atovaquone 250 mg/proguanil 100 mg) and pediatric tablets (Malarone Pediatric; atovaquone 62.5 mg/proguanil 25 mg). To enhance absorption and reduce nausea and vomiting, it should be taken with food or a milky drink. Safety in pregnancy is unknown and use is generally not recommended. In a few small studies outcomes were normal in women treated with the combination in the 2nd and 3rd trimester (B Paternak et al, Arch Intern Med 2011; 171:259; AK Boggild et al, Am J Trop Med Hyg 2007; 76:208). The drug should not be given to patients with severe renal impairment (creatinine clearance <30 mL/min). There have been isolated case reports of resistance in P. falciparum in Africa, but Medical Letter consultants do not believe there is a high risk for acquisition of Malarone-resistant disease (E Schwartz et al, Clin Infect Dis 2003; 37:450; A Farnert et al, BMJ 2003; 326:628; S Kuhn et al, Am J Trop Med Hyg 2005; 72:407; CT Happi et al, Malar J 2006; 5:82).

57In Southeast Asia, relative resistance to quinine has increased and treatment should be continued for 7 days.

58Although approved for once daily dosing, Medical Letter consultants usually divide the dose in 2 to decrease nausea and vomiting.

59For use in pregnancy.

Drugs for Parasitic Infections—cont’d

Table 279-1

<table>
<thead>
<tr>
<th>INFECTION</th>
<th>DRUG</th>
<th>ADULT DOSAGE</th>
<th>PEDIATRIC DOSAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>or</td>
<td>Coartem (Artemether-lumefantrine)</td>
<td>1 tablet = 20 mg artemether and 120 mg lumefantrine. A 3 day treatment schedule with a total of six oral doses is recommended for both adult and pediatric patients based on weight. These six doses should be administered over 3 days (4 tabs/dose at 0, 8, 24, 36, 48, and 60 hr)</td>
<td>5 to &lt;15 kg: 1 tablet PO per dose 15 to &lt;25 kg: 2 tablets PO per dose 25 to &lt;35 kg: 3 tablets per dose ≥35 kg: 4 tablets PO per dose</td>
</tr>
<tr>
<td>Alternative:</td>
<td>Mefloquine61,62</td>
<td>750 mg PO followed 12 hr later by 500 mg</td>
<td>15 mg/kg PO followed 12 hr later by 10 mg/kg</td>
</tr>
</tbody>
</table>

P. vivax63 acquired in areas of chloroquine resistance

Oral55

Drug of choice: Quinine sulfate plus doxycycline7,14 plus primaquine64

650 mg PO every 8 hr × 3-7 days65 | 30 mg/kg/day PO in 3 doses × 3-7 days65 |

100 mg PO bid × 7 days | 4 mg/kg/day PO in 2 doses × 7 days |

30 mg base PO daily × 14 days | 0.5 mg/kg/day PO × 14 days |

or

Mefloquine61

750 mg PO followed 12 hr later by 500 mg PO | 15 mg/kg PO followed 12 hr later by 10 mg/kg PO |

Alternatives: Chloroquine plus primaquine64

25 mg base/kg PO in 3 doses over 48 hr | 25 mg base/kg PO in 3 doses over 48 hr |

30 mg base PO daily × 14 days | 0.5 mg/kg/day PO × 14 days |

All Plasmodium except chloroquine-resistant P. falciparum64 and chloroquine-resistant P. vivax63 (areas without chloroquine resistance)

Oral55

Drug of choice: Chloroquine phosphate65

1 g (600 mg base), then 500 mg (300 mg base) 6 hr later PO, then 500 mg (300 mg base) at 24 and 48 hr | 10 mg base/kg (max 600 mg base), then 5 mg base/kg 6 hr later PO, then 5 mg base/kg at 24 and 48 hr |

All Plasmodium

Parenteral (severe infection; chloroquine-sensitive and resistant)

Drugs of choice64:

Quinidine gluconate67

10 mg/kg IV loading dose (max 600 mg) in normal saline over 1-2 hr, followed by continuous infusion of 0.02 mg/kg/min until PO therapy can be started | 10 mg/kg IV loading dose (max 600 mg) in normal saline over 1-2 hr, followed by continuous infusion of 0.02 mg/kg/min until PO therapy can be started |

Quinine dihydrochloride67

20 mg/kg IV loading dose in 5% dextrose over 4 hr, followed by 10 mg/kg over 2-4 hr every 8 hr (max 1,800 mg/day) until PO therapy can be started | 20 mg/kg IV loading dose in 5% dextrose over 4 hr, followed by 10 mg/kg over 2-4 hr every 8 hr (max 1,800 mg/day) until PO therapy can be started |

61 At this dosage, adverse effects including nausea, vomiting, diarrhea, dizziness, disturbed sense of balance, toxic psychosis, and seizures can occur. Mefloquine should not be used for treatment of malaria in pregnancy unless there is no other treatment option because of increased risk for stillbirth (Nosten F, et al: *Clin Infect Dis* 28:808, 1999). It should be avoided for treatment of malaria in persons with active depression or with a history of psychosis or seizures and should be used with caution in persons with psychiatric illness. Mefloquine can be given to patients taking β blockers if they do not have an underlying arrhythmia; it should not be used in patients with conduction abnormalities. Mefloquine should not be given together with quinine, quinidine, or halofantrine, and caution is required in using quinine, quinidine, or halofantrine to treat patients with malaria who have taken mefloquine for prophylaxis. Resistance to mefloquine has been reported in some areas, such as the Thailand-Myanmar and Thailand-Cambodia borders and in the Amazon basin, where 25 mg/kg should be used. In the United States, a 250 mg tablet of mefloquine contains 228 mg mefloquine base. Outside the United States, each 275 mg tablet contains 250 mg base.

62 P. falciparum with resistance to mefloquine is a significant problem in the malarious areas of Thailand and in areas of Myanmar and Cambodia that border on Thailand. It has also been reported on the borders between Myanmar and China, Laos and Myanmar, and in Southern Vietnam. In the United States, a 250 mg tablet of mefloquine contains 228 mg mefloquine base. Outside the United States, each 275 mg tablet contains 250 mg base.

63 P. vivax with decreased susceptibility to chloroquine is a significant problem in Papua New Guinea and Indonesia. There are also a few reports of resistance from Myanmar, India, the Solomon Islands, Vanuatu, Guyana, Brazil, Columbia, and Peru.

64 Primamaquine phosphate can cause hemolytic anemia, especially in patients whose red cells are deficient in glucose-6-phosphate dehydrogenase (G6PD). This deficiency is most common in African, Asian, and Mediterranean peoples. Patients should be screened for G6PD deficiency before treatment. Primamaquine should not be used during pregnancy.

65 If chloroquine phosphate is not available, hydroxychloroquine sulfate is as effective; 400 mg of hydroxychloroquine sulfate is equivalent to 500 mg of chloroquine phosphate.


67 Continuous ECG, blood pressure, and glucose monitoring are recommended, especially in pregnant women and young children. For problems with quinidine availability, call the manufacturer (Eli Lilly, 800-545-5979) or the CDC Malaria Hotline (770-488-7788). Quinine may have greater antimalarial activity than quinidine. The loading dose should be decreased or omitted in those patients who have received quinidine or mefloquine. If more than 48 hr of parenteral treatment is required, the quinidine or quinine dose should be reduced by 30-50%.
### Table 279-1: Drugs for Parasitic Infections—cont’d

<table>
<thead>
<tr>
<th>INFECTION</th>
<th>DRUG</th>
<th>ADULT DOSAGE</th>
<th>PEDIATRIC DOSAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alternative:</td>
<td>Artesunate*</td>
<td>2.4 mg/kg/dose IV × 3 days, at 0, 12, 24, 48, and 72 hr</td>
<td>2.4 mg/kg/dose IV × 3 days, at 0, 12, 24, 48, and 72 hr</td>
</tr>
</tbody>
</table>

**Prevention of relapses:** *P. vivax* and *P. ovale* only

**Drug of choice:** Primaquine phosphate

- PO once/wk

- 5 mg/kg base once/wk, up to adult dose of 300 mg base

**Chloroquine-sensitive areas**

**Drug of choice:** Chloroquine phosphate

- PO once/wk

- 500 mg (300 mg base), PO once/wk

**Chloroquine-resistant areas**

**Drug of choice:** Atovaquone/proguanil

- 1 adult tab PO q day

- 1-20 kg: 1 pediatric tab PO/day

- 21-30 kg: 2 pediatric tabs PO/day

- 31-40 kg: 3 pediatric tabs PO/day

- >40 kg: 1 adult tab PO/day

**or**

- Mefloquine

- PO once/wk

- 250 mg PO once/wk

- <9 kg: 5 mg/kg salt once/wk

- 9-19 kg: $\frac{1}{2}$ tab once/wk

- 19-30 kg: $\frac{1}{4}$ tab once/wk

- 31-45 kg: $\frac{1}{8}$ tab once/wk

- >45 kg: 1 tab once/wk

**or**

- Doxycycline

- PO once/wk

- 100 mg PO daily

- 2 mg/kg/day, up to 100 mg/day

**Alternatives:** Primaquine

- PO once/wk

- 30 mg base PO daily

- 0.6 mg/kg base daily

**Malaria, self-presumptive treatment**

**Drug of choice:** Atovaquone/proguanil

- 4 adult tabs PO daily × 3 days

**or**

- Mefloquine

- PO once/wk

- 2.4 mg/kg base/kg/day PO

**or**

- Doxycycline

- PO once/wk

- 200 mg PO once/wk

**or**

- Azithromycin

- PO once/wk

- 1000 mg PO once/wk

**Alternative:** Artesunate

- IV

- 2 adult tabs PO once/wk

- 5 mg/kg base once/wk, up to adult dose of 300 mg base

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*Oral artemisinin is not available in the United States; the IV formulation is available through the CDC Malaria branch under an investigational new drug (IND) for patients with severe disease who do not have timely access or cannot tolerate, or fail to respond to IV quinidine.*

*Drugs of choice followed by alternative drugs are recommended. Selection of the drug for prophylaxis is influenced by patient characteristics (e.g., age, pregnancy status, history of drug allergy) and the risk of drug-resistant malaria.*

*Dosages are for adults unless otherwise specified and reflect weight-dependent dosages. For children, refer to the pediatric dosages.*

*In pregnancy, chloroquine prophylaxis has been used extensively and safely.*

*In young children weighing <5 kg, based on dosages in other weight groups, a dose of 5 mg/kg can be used.*

*Beginning 1-2 wk before travel and continuing weekly for the duration of stay and for 4 wk after leaving malarious zone.*

*In pregnant women in endemic areas, chloroquine prophylaxis may be continued.*

*All regimens appropriate for travelers are considered to be prophylactic.*

*Studies have shown that daily primaquine beginning 1 day before departure and continued until 3-7 days after leaving the malaria area provides effective prophylaxis against chloroquine-resistant *P. falciparum,* and in these areas, atovaquone/proguanil or doxycycline should be used for prophylaxis.*

*Beginning 1-2 days before travel and continuing for the duration of stay and for 4 wk after leaving. Use of tetracyclines is contraindicated in pregnancy and in children younger than 8 yr old. Doxycycline can cause gastrointestinal disturbances, vaginal moniliasis, and photosensitivity reactions.*

*Studies have shown that chloroquine prophylaxis, primaquine, and doxycycline are effective prophylaxis agents.*

*The protective efficacy of malaria is variable ranging from 84% in Indonesian New Guinea (J Ling et al., *Clin Infect Dis* 2002; 35:825) to 100% in Colombia (J Soto et al., *Am J Trop Med Hyg* 2006; 75:430). Some Medical Letter consultants prefer alternate drugs if traveling to areas where *P. vivax* predominates.*
Table 279-1 Drugs for Parasitic Infections—cont’d

<table>
<thead>
<tr>
<th>INFECTION</th>
<th>DRUG</th>
<th>ADULT DOSAGE</th>
<th>PEDIATRIC DOSAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>or</td>
<td>Quinine sulfate plus</td>
<td>650 mg PO every 8 hr x 3-7 days</td>
<td>30 mg/kg/day PO in 3 doses x 3-7 days</td>
</tr>
<tr>
<td>or</td>
<td>doxycycline</td>
<td>100 mg bid PO x 7 days</td>
<td>4 mg/kg/day in 2 PO doses x 7 days</td>
</tr>
<tr>
<td>or</td>
<td>Mefloquine</td>
<td>750 mg PO followed 12 hr later by</td>
<td>15 mg/kg followed 12 hr later by 10 mg/kg</td>
</tr>
<tr>
<td>Microsporidiosis</td>
<td></td>
<td>500 mg</td>
<td></td>
</tr>
<tr>
<td>Ocular (Encephalitozoon</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>E. bieneusi</td>
<td>Albenzazole</td>
<td>400 mg PO bid</td>
<td></td>
</tr>
<tr>
<td>Intestinal (Enterocytozoon</td>
<td>Fumagillin</td>
<td>60 mg/day PO x 14 days in 3 divided</td>
<td></td>
</tr>
<tr>
<td>E. intestinalis</td>
<td></td>
<td>doses</td>
<td></td>
</tr>
<tr>
<td>Disseminated (E. hellem,</td>
<td>Albenzole plus fumagillin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>E. cuniculi, E. intestinalis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug of choice:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mites, see Scabies</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moniliformis moniliformis</td>
<td>Pyrantel pamoate</td>
<td>11 mg/kg PO once, repeat twice, 2 wk</td>
<td>11 mg/kg PO once, repeat twice, 2 wk apart</td>
</tr>
<tr>
<td>Naegleria species, see</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amebic meningoencephalitis,</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Necator americanus, see</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HOOKWORM INFECTION</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oesophagostomum bifurcum</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug of choice:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Onchocerca volvulus, see</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Filarial infection</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Opisthorchis viverrini, see</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluke infection</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paragonimus westermani, see</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluke infection</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pediculus capitis, Pediculus</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>humanus, Phthirus pubis, see</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lice</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pinworm, see Enterobius</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumocystis jiuroveci (formerly Pneumocystis carinii) pneumonia (PCP)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate to severe disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug of choice:</td>
<td>Trimethoprim-sulfamethoxazole (TMP-SMX)</td>
<td>TMP 15-20 mg/kg/day, SMX 75-100 mg/kg/day, PO or IV (change to PO after clinical improvement) in 3 or 4 doses x 21 days</td>
<td></td>
</tr>
<tr>
<td>Alternatives:</td>
<td>Pentamidine or Primaquine plus clindamycin</td>
<td>3-4 mg IV daily x 21 days</td>
<td>3-4 mg IV daily x 21 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>30 mg base PO daily x 21 days</td>
<td>0.3 mg/kg base PO (max 30 mg) daily x 21 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>600-900 mg IV tid or qid x 21 days, or 300-450 mg PO tid or qid x 21 days (change to PO after clinical improvement)</td>
<td>15-25 mg/kg IV tid or qid x 21 days, or 10 mg/kg PO tid or qid (max 300-450 mg/dose) x 21 days (change to PO after clinical improvement)</td>
</tr>
</tbody>
</table>

57Ocular lesions caused by E. hellemin HIV-infected patients have responded to fumagillin eyedrops prepared from Fumidil-B (bicyclohexyl ammonium fumagillin) used to control a microsporidial disease of honey bees (Diesenhouse MC, Am J Ophthalmol 115:293, 1993), available from Leiter’s Park Avenue Pharmacy (see footnote 1). For lesions caused by V. corneae, topical therapy is generally not effective and keratoplasty may be required (Davis RM, et al: Ophthalmology 101:579, 1993).

58Oral fumagillin (Sanofi Recherche, Gentilly, France) has been effective in treating E. bieneusi (Molina JM, et al: N Engl J Med 346:1963, 2002), but has been associated with thrombocytopenia. HAART may lead to microbiologic and clinical response in HIV-infected patients with microsporidial diarrhea (Benson CA, Kaplan JE, Masur H, et al: Treating opportunistic infections among HIV-infected adults and adolescents: recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association/Infectious Diseases Society of America, MMWR Recomm Rep 53([RR-15]:1-112, 2004). Octreotide (Sandostatin) has provided symptomatic relief in some patients with large-volume diarrhea.


61Pneumocystis has been reclassified as a fungus. In severe disease with room air Po2 ≤70 mm Hg or a-Ao2 gradient ≥35 mm Hg, prednisone should also be used (Gagnon S, et al: N Engl J Med 323:1444, 1990; Caumes E, et al: Clin Infect Dis 18:319, 1994).
### Table 279-1  
Drugs for Parasitic Infections—cont’d

<table>
<thead>
<tr>
<th>INFECTION</th>
<th>DRUG</th>
<th>ADULT DOSAGE</th>
<th>PEDIATRIC DOSAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mild to moderate disease</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug of choice:</td>
<td>Trimethoprim-sulfamethoxazole (TMP-SMX)</td>
<td>2 DS tablets (160 mg/800 mg each) PO tid x 21 days</td>
<td>TMP 15-20 mg/kg/day SMX 75-100 mg/kg/day PO in 3 or 4 doses x 21 days</td>
</tr>
<tr>
<td>Alternative:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dapsone plus trimethoprim or primaquine plus clindamycin or atovaquone</td>
<td>100 mg PO daily x 21 days</td>
<td>2 mg/kg/day (max 100 mg) PO x 21 days</td>
<td>15 mg/kg/day in 3 doses</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dapsone plus trimethoprim or primaquine plus clindamycin or atovaquone</td>
<td>30 mg base PO daily x 21 days</td>
<td>0.3 mg/kg base PO daily (max 30 mg) x 21 days</td>
<td>10 mg/kg PO tid or qd (max 300-450 mg/dose) x 21 days</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Dapsone plus trimethoprim or primaquine plus clindamycin or atovaquone</td>
<td>300-450 mg PO tid or qid x 21 days</td>
<td>1-3 mo: 30 mg/kg/day PO in 2 doses x 21 days</td>
<td>4-24 mo: 45 mg/kg/day PO in 2 doses x 21 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>&gt;24 mo: 30 mg/kg/day PO in 2 doses x 21 days</td>
</tr>
</tbody>
</table>

#### Primary and secondary prophylaxis

<table>
<thead>
<tr>
<th>INFECTION</th>
<th>DRUG</th>
<th>ADULT DOSAGE</th>
<th>PEDIATRIC DOSAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug of choice:</td>
<td>Trimethoprim-sulfamethoxazole (TMP-SMX)</td>
<td>1 tab (single or double strength) PO daily or 1 DS tab PO 3 doses/wk</td>
<td>TMP 150 mg/m², SMX 750 mg/m² PO in 2 doses on 3 consecutive days per wk</td>
</tr>
<tr>
<td>Alternative:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dapsone or Dapsone plus pyrimethamine</td>
<td>50 mg PO bid, or 100 mg PO daily</td>
<td>2 mg/kg/day (max 100 mg) PO or 4 mg/kg (max 200 mg) PO each wk</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pentamidine aerosol</td>
<td>300 mg inhaled monthly via Respirgard II nebulizer</td>
<td>≥5 yr: 300 mg inhaled monthly via Respirgard II nebulizer</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atovaquone</td>
<td>1,500 mg/d PO in 1 or 2 doses</td>
<td>1-3 mo: 30 mg/kg/day PO</td>
<td>4-24 mo: 45 mg/kg/day PO</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>&gt;24 mo: 30 mg/kg/day PO</td>
</tr>
</tbody>
</table>

#### Scabies (Sarcoptes scabiei)

**Sappinia diploidea**, see Amecic meningocerephalitis, primary

**Scabias** (Sarcoptes scabiei)

<table>
<thead>
<tr>
<th>INFECTION</th>
<th>DRUG</th>
<th>ADULT DOSAGE</th>
<th>PEDIATRIC DOSAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug of choice:</td>
<td>5% Permethrin</td>
<td>Topically, 2x at least 7 days apart</td>
<td>Topically, 2x at least 7 days apart</td>
</tr>
<tr>
<td>Alternative:</td>
<td>Ivermectin and 10% Crotamiton</td>
<td>200 µg/kg PO 2x at least 7 days apart</td>
<td>200 µg/kg PO 2x at least 7 days apart</td>
</tr>
<tr>
<td></td>
<td>Topically overnight on days 1, 2, 3, 8</td>
<td></td>
<td>Topically overnight on days 1, 2, 3, 8</td>
</tr>
</tbody>
</table>

#### Schistosomiasis (Bilharziasis)

**Schistosoma haematobium**

<table>
<thead>
<tr>
<th>INFECTION</th>
<th>DRUG</th>
<th>ADULT DOSAGE</th>
<th>PEDIATRIC DOSAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug of choice:</td>
<td>Praziquantel</td>
<td>40 mg/kg/day PO in 1 or 2 doses x 1 day</td>
<td>40 mg/kg/day PO in 1 or 2 doses x 1 day</td>
</tr>
<tr>
<td>Schistosoma intercalatum</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug of choice:</td>
<td>Praziquantel</td>
<td>40 mg/kg/day PO in 1 or 2 doses x 1 day</td>
<td>40 mg/kg/day PO in 1 or 2 doses x 1 day</td>
</tr>
<tr>
<td>Schistosoma japonicum</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug of choice:</td>
<td>Praziquantel</td>
<td>60 mg/kg PO in 2 or 3 doses x 1 day</td>
<td>60 mg/kg/day PO in 3 doses x 1 day</td>
</tr>
</tbody>
</table>

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68Primary/secondary prophylaxis in patients with HIV can be discontinued after CD4 count increases to >200 x 10^9/L for longer than 3 mo.

69An alternative trimethoprim-sulfamethoxazole regimen is 1 DS tab 3x/wk. Weekly therapy with sulfadoxine 500 mg/pyrimethamine 25 mg/leucovorin 25 mg was effective Pneumocystis carinii pneumonia (PCP) prophylaxis in liver transplant patients (Torre-Cisneros J, et al: Clin Infect Dis 29:771, 1999).

70Plus leucovorin 25 mg with each dose of pyrimethamine.

71In some cases, treatment may need to be repeated in 10-14 days. BJ Currie and JS McCarthy, N Engl J Med 2010; 362:717. A second ivermectin dose taken 2 wk later increased the cure rate to 95%, which is equivalent to that of 5% permethrin (V Usha et al., J Am Acad Dermatol 2000; 42:236). Ivermectin, either alone or in combination with a topical scabicide, is the drug of choice for crusted scabies in immunocompromised patients (P del Giudice, Curr Opin Infect Dis 2004; 15:123).

72Lindane (γ-benzene hexachloride; Kwell) should be reserved as a second-line agent. The FDA has recommended it should not be used for immunocompromised patients, young children, the elderly, and patients who weigh <50 kg.

73Ivermectin, either alone or in combination with a topical scabicide, is the drug of choice for crusted scabies in immunocompromised patients (del Giudice P: Curr Opin Infect Dis 15:123, 2004). The safety of oral ivermectin in pregnancy and young children has not been established.
Drugs for Parasitic Infections—cont’d

<table>
<thead>
<tr>
<th>INFECTION</th>
<th>DRUG</th>
<th>ADULT DOSAGE</th>
<th>PEDIATRIC DOSAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schistosoma mansoni</td>
<td>Praziquantel</td>
<td>40 mg/kg/day PO in 1 or 2 doses × 1 day</td>
<td>40 mg/kg/day PO in 1 or 2 doses × 1 day</td>
</tr>
<tr>
<td>Alternative:</td>
<td>Oxamniquine</td>
<td>15 mg/kg PO once</td>
<td>20 mg/kg/day PO in 2 doses × 1 day</td>
</tr>
<tr>
<td>Schistosoma mekongi</td>
<td>Praziquantel</td>
<td>60 mg/kg/day PO in 2 or 3 doses × 1 day</td>
<td>60 mg/kg/day PO in 3 doses × 1 day</td>
</tr>
<tr>
<td>Sleeping sickness, see</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Strongyloidiasis (Strongyloides</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug of choice</td>
<td>Ivermectin</td>
<td>200 µg/kg/day PO × 2 days</td>
<td>200 µg/kg/day PO × 2 days</td>
</tr>
<tr>
<td>Alternative:</td>
<td>Albendazole</td>
<td>400 mg PO bid × 7 days</td>
<td>400 mg bid PO × 7 days</td>
</tr>
<tr>
<td>Tapeworm infection</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adult (intestinal stage)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diphyllobothrium latum (fish),</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug of choice</td>
<td>Praziquantel</td>
<td>5-10 mg/kg PO once</td>
<td>5-10 mg/kg PO once</td>
</tr>
<tr>
<td>Alternative:</td>
<td>Niclosamide</td>
<td>2 g PO once</td>
<td>50 mg/kg PO once</td>
</tr>
<tr>
<td>Hymenolepis nana (dwarf tapeworm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug of choice</td>
<td>Praziquantel</td>
<td>25 mg/kg PO once</td>
<td>25 mg/kg PO once</td>
</tr>
<tr>
<td>Alternative:</td>
<td>Niclosamide</td>
<td>2 g PO daily × 7 days</td>
<td>11-34 kg; 1 g PO on day 1 then 500 mg/day PO × 6 days* &gt;34 kg; 1.5 g PO on day 1 then 1 g/d PO × 6 days*</td>
</tr>
<tr>
<td>Larval (tissue stage)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Echinococcus granulosus (hydatid cyst)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug of choice</td>
<td>Albendazole</td>
<td>400 mg PO bid × 1-6 mo</td>
<td>15 mg/kg/day PO (max 800 mg) × 1-6 mo</td>
</tr>
<tr>
<td>Echinococcus multilocularis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment of choice:</td>
<td>See footnote 96</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Taenia solium (cysticercosis)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment of choice:</td>
<td>See footnote 97</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alternative:</td>
<td>Albendazole</td>
<td>400 mg PO bid × 8-30 days; can be repeated as necessary</td>
<td>15 mg/kg/day PO (max 800 mg) in 2 doses × 8-30 days; can be repeated as necessary</td>
</tr>
<tr>
<td>or Praziquantel</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Toxocariasis, see Visceral larva migrans</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

*Oxamniquine has been effective in some areas in which praziquantel is less effective (Stelma FF, et al: J Infect Dis 176:304, 1997). Oxamniquine is contraindicated in pregnancy.
*In East Africa, the dose should be increased to 30 mg/kg, and in Egypt and South Africa to 30 mg/kg/day × 2 days. Some experts recommend 40-60 mg/kg over 2-3 days in all of Africa (Shekhar KC: Drugs 42:379, 1991).
*In immunocompromised patients or disseminated disease, it may be necessary to prolong or repeat therapy, or to use other agents. Veterinary parenteral and enema formulations of ivermectin have been used in severely ill patients unable to take oral medications (Chiiodini PL, et al: Lancet 355:43, 2000; Orem J, et al: Clin Infect Dis 37:152, 2003; Tarr PE: Am J Trop Med Hyg 68:453, 2003).
*Albendazole must be taken with food, a fatty meal increases oral bioavailability.
*Patients may benefit from surgical resection or percutaneous drainage of cysts. Praziquantel is useful preoperatively or in case of spillage of cyst contents during surgery. Percutaneous aspiration-injection-reaspiration (PAIR) with ultrasound guidance plus albendazole therapy has been effective for management of hepatic hydatid cyst disease (Smego RA Jr, et al: Clin Infect Dis 37:1073, 2003).
*Surgical excision is the only reliable means of cure. Reports have suggested that in nonresectable cases use of albendazole or mebendazole can stabilize and sometimes cure infection (Craig P: Curr Opin Infect Dis 16:437, 2003).
*Initial therapy for patients with inflamed parenchymal cysticercosis should focus on symptomatic treatment with antiseizure medication. Treatment of parenchymal cysticerci with albendazole or praziquantel is controversial (Maguire JM: N Engl J Med 350:215, 2004). Patients with live parenchymal cysts who have seizures should be treated with albendazole together with steroids (6 mg dexamethasone or 40-60 mg prednisone daily) and an antiseizure medication (García HH, et al: N Engl J Med 350:249, 2004). Patients with subarachnoid cysts or giant cysts in the tissues should be treated for at least 30 days (Praoño JV, et al: N Engl J Med 345:879, 2001). Surgical intervention or CSF diversion is indicated for obstructive hydrocephalus; prednisone 40 mg/day may be given with surgery. Achromoïdiasis, vascuilitis, or cerebral edema is treated with prednisone 60 mg/day or dexamethasone 4-6 mg/day together with albendazole or praziquantel (White Jr AC: Annu Rev Med 51:187, 2000). Any cysticercocidal drug may cause irreparable damage when used to treat ocular or spinal cysts, even when corticosteroids are used. An ophthalmic exam should always precede treatment to rule out intraocular cysts.
Table 279-1  Drugs for Parasitic Infections—cont’d

<table>
<thead>
<tr>
<th>INFECTION</th>
<th>DRUG</th>
<th>ADULT DOSAGE</th>
<th>PEDIATRIC DOSAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toxoplasmosis (Toxoplasma gondii)⁹⁸</td>
<td>Pyrimethamine⁹⁹,¹⁰⁰ plus Sulfadiazine or plus Clindamycin or plus Atovaquone</td>
<td>200 mg PO x 1, then 50-75 mg/day x 3-6 wk</td>
<td>2 mg/kg/d x 3 days, then 1 mg/kg/day (max 25 mg/day) x 4 wk¹⁰¹</td>
</tr>
<tr>
<td></td>
<td>1-1.5 g PO qid x 3-6 wk</td>
<td>100-200 mg/kg/day x 3-4 wk</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.8-2.4 g/day IV or PO in 3 or 4 doses</td>
<td>5-7.5 mg/kg/day IV or PO in 3 or 4 doses (max 600 mg/day)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1,500 mg PO bid</td>
<td>1,500 mg PO bid</td>
<td></td>
</tr>
<tr>
<td>Alternative:</td>
<td>Trimethoprim-sulfamethoxazole (TMP-SMX)</td>
<td>TMP 15-20 mg/kg/day; SFX 75-100 mg/kg/day PO or IV in 3 or 4 doses</td>
<td></td>
</tr>
<tr>
<td>Trichinosis (Trichinella spiralis)</td>
<td>Steroids for severe symptoms plus Albendazole¹</td>
<td>Prednisone 30-60 mg PO daily x 10-15 days</td>
<td></td>
</tr>
<tr>
<td></td>
<td>400 mg PO bid x 8-14 days</td>
<td>400 mg PO bid x 8-14 days</td>
<td></td>
</tr>
<tr>
<td>Alternative:</td>
<td>Mebendazole⁷</td>
<td>200-400 mg PO tid x 3 days, then 400-500 mg PO tid x 10 days</td>
<td></td>
</tr>
<tr>
<td>Trichomoniasis (Trichomonas vaginalis)</td>
<td>Metronidazole or Tinidazole⁷</td>
<td>2 g PO once or 500 mg PO bid x 7 days</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2 g PO</td>
<td>15 mg/kg/day PO in 3 doses x 7 days</td>
<td></td>
</tr>
<tr>
<td>Alternative:</td>
<td>Mebendazole⁷</td>
<td>400 mg PO once</td>
<td></td>
</tr>
<tr>
<td></td>
<td>400 mg PO bid x 8-14 days</td>
<td>400 mg PO bid x 8-14 days</td>
<td></td>
</tr>
<tr>
<td>Alternative:</td>
<td>Albendazole¹</td>
<td>100 mg PO bid x 3 days</td>
<td></td>
</tr>
<tr>
<td>Trichuriasis (Trichuris trichiura, whipworm)</td>
<td>Mebendazole</td>
<td>100 mg PO bid x 3 days</td>
<td></td>
</tr>
<tr>
<td></td>
<td>400 mg PO</td>
<td>100 mg PO bid x 3 days</td>
<td></td>
</tr>
<tr>
<td>Alternative:</td>
<td>Albendazole⁷ or Ivermectin¹</td>
<td>400 mg PO x 3 days</td>
<td></td>
</tr>
<tr>
<td></td>
<td>200 µg/kg PO x 3 days</td>
<td>400 mg PO x 3 days</td>
<td></td>
</tr>
<tr>
<td></td>
<td>400 µg/kg PO x 3 days</td>
<td>200 µg/kg PO x 3 days</td>
<td></td>
</tr>
<tr>
<td>Trypanosomiasis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trypanosoma cruzi</td>
<td>Benznidazole or Nifurtimox</td>
<td>5-7 mg/kg/day PO in 2 divided doses x 60 days</td>
<td>≤12 yr: 10 mg/kg/day PO in 2 or 3 doses x 60 days</td>
</tr>
<tr>
<td>(American trypanosomiasis, Chagas disease)</td>
<td></td>
<td></td>
<td>1-10 yr: 15-20 mg/kg/day PO in 4 doses x 90 days</td>
</tr>
<tr>
<td></td>
<td>8-10 mg/kg/day PO in 3-4 doses x 90 days</td>
<td>11-16 yr: 12.5-15 mg/kg/day in 4 doses x 90 days</td>
<td></td>
</tr>
</tbody>
</table>

⁹⁸In ocular toxoplasmosis with macular involvement, corticosteroids are recommended in addition to antiparasitic therapy for an antiinflammatory effect.

¹⁰⁰To treat CNS toxoplasmosis in HIV-infected patients, some clinicians have used pyrimethamine 50-100 mg/day (after a loading dose of 200 mg) with sulfadiazine and, when sulfonamide sensitivity developed, have given clindamycin 1.8-2.4 g/day in divided doses instead of the sulfonamide. Atovaquone plus pyrimethamine appears to be an effective alternative in sulfa-intolerant patients (Chirgwin K, et al: Clin Infect Dis 34:1243, 2002). Treatment is followed by chronic suppression with lower-dosage regimens of the same drugs. For primary prophylaxis in HIV patients with <100 x 10⁹/L CD4 cells, either trimethoprim-sulfamethoxazole, pyrimethamine with dapsone, or atovaquone with or without pyrimethamine can be used. Primary or secondary prophylaxis may be discontinued when the CD4 count increases to 200 x 10⁹/L for more than 3 mo (Benson CA, Kaplan JE, Masur H, et al: Treating opportunistic infections among HIV-infected adults and adolescents: recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association/Infectious Diseases Society of America, MMWR Recomm Rep 53[RR-15]:1-112, 2004).

¹⁰¹Women who develop toxoplasmosis during the 1st trimester of pregnancy can be treated with spiramycin (3-4 g/day). After the 1st trimester, if there is no documented transmission to the fetus, spiramycin can be continued until term. If transmission has occurred in utero, therapy with pyrimethamine and sulfadiazine should be started (Montoya JG, Liesenfeld O: Lancet 363:1965, 2004). Pyrimethamine is a potential teratogen and should be used only after the 1st trimester.

¹⁰²Congenitally infected newborns should be treated with pyrimethamine every 2 or 3 days and a sulfonamide daily for about 1 yr (Remington JS, Klein JO, editors: Infectious disease of the fetus and newborn infant, ed 5, Philadelphia, 2001, WB Saunders, p. 290).

¹⁰³Sexual partners should be treated simultaneously. Metronidazole-resistant strains have been reported and can be treated with higher doses of metronidazole (2-4 g/day x 7-14 days) or with tinidazole (Hager WD: Sex Transm Dis 31:343, 2004).


¹⁰⁵The addition of γ-interferon to nifurtimox for 20 days in experimental animals and in a limited number of patients appears to shorten the acute phase of Chagas disease (McCabe RE, et al: J Infect Dis 163:912, 1991).
Table 279-1  Drugs for Parasitic Infections—cont’d

<table>
<thead>
<tr>
<th>INFECTION</th>
<th>DRUG</th>
<th>ADULT DOSAGE</th>
<th>PEDIATRIC DOSAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Trypanosoma brucei gambiense</strong> (West African trypanosomiasis, sleeping sickness)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Hemolymphatic stage</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug of choice&lt;sup&gt;106&lt;/sup&gt;:</td>
<td>Pentamidine isethionate&lt;sup&gt;7&lt;/sup&gt;</td>
<td>4 mg/kg/day IM × 7 days</td>
<td>4 mg/kg/day IM or IV × 7 days</td>
</tr>
<tr>
<td>Alternative:</td>
<td>Suramin</td>
<td>100-200 mg (test dose) IV, then 1 g IV on days 1, 3, 5, 14, and 21</td>
<td>2 mg/kg (test dose) IV, then 20 mg/kg IV on days 1, 3, 5, 14, and 21</td>
</tr>
<tr>
<td>Late disease with CNS involvement</td>
<td>Drug of choice:</td>
<td>2.2 mg/kg/day IV × 10 days</td>
<td>2.2 mg/kg/day IV × 10 days</td>
</tr>
<tr>
<td>or Eflornithine&lt;sup&gt;108&lt;/sup&gt;</td>
<td></td>
<td>400 mg/kg/day IV in 4 doses × 14 d</td>
<td>400 mg/kg/day in 4 doses × 14 days</td>
</tr>
<tr>
<td><strong>Trypanosoma brucei rhodesiense</strong> (East African trypanosomiasis, sleeping sickness)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Hemolymphatic stage</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug of choice:</td>
<td>Suramin</td>
<td>100-200 mg (test dose) IV, then 1 g IV on days 1, 3, 5, 14, and 21</td>
<td>2 mg/kg (test dose), then 20 mg/kg IV on days 1, 3, 5, 14, and 21</td>
</tr>
<tr>
<td>Late disease with CNS involvement</td>
<td>Drug of choice:</td>
<td>2.2 mg/kg/day × 10 days</td>
<td></td>
</tr>
<tr>
<td>or Melarsoprol&lt;sup&gt;107&lt;/sup&gt;</td>
<td></td>
<td>2.2 mg/kg/day × 10 days</td>
<td></td>
</tr>
<tr>
<td><strong>Visceral larva migrans</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug of choice:</td>
<td>Albenzazole&lt;sup&gt;7&lt;/sup&gt;,</td>
<td>400 mg PO bid × 5 days</td>
<td>400 mg PO bid × 5 days</td>
</tr>
<tr>
<td>Mebendazole&lt;sup&gt;7&lt;/sup&gt;</td>
<td></td>
<td>100-200 mg PO bid × 5 days</td>
<td></td>
</tr>
<tr>
<td><strong>Whipworm</strong></td>
<td></td>
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</tr>
</tbody>
</table>

<sup>7</sup>For treatment of T. b. gambiense, pentamidine and suramin have equal efficacy but pentamidine is better tolerated.

<sup>106</sup>In frail patients, begin with as little as 18 mg and increase the dose progressively. Pretreatment with suramin has been advocated for debilitated patients.


<sup>108</sup>Eflornithine is highly effective in T. b. gambiense but not against T. b. rhodesiense infections. It is available in limited supply only from the WHO and the CDC. Eflornithine dose may be reduced to 400 mg/kg IV in 2 doses for 7 d when used in conjunction with nifurtimox at a dose of 15 mg/kg/d PO in 3 doses × 10 d.

<sup>109</sup>Optimum duration of therapy is not known; some Medical Letter consultants would treat for 20 days. For severe symptoms or eye involvement, corticosteroids can be used in addition.

CDC, Centers for Disease Control and Prevention; CNS, central nervous system; CSF, cerebrospinal fluid; DS, double strength; ECG, electrocardiography; FDA, U.S. Food and Drug Administration; GI, gastrointestinal; HAART, highly active antiretroviral therapy; SMX, sulfamethoxazole; TMP, trimethoprim; WHO, World Health Organization.


**SELECTED ANTIPARASITIC DRUGS FOR HELMINTHS**

**Albenzazole (Albenza)**

Albenzazole is a benzimidazole carbamate structurally related to mebendazole and has similar anthelmintic activity. Its absorption from the gastrointestinal tract is poor but improved with a concomitant high-fat meal. Albenzazole sulfoxide, the principal metabolite with anthelmintic activity, has a plasma half-life of 8.5 hr. It is widely distributed in the body, including the bile and cerebrospinal fluid. It is eliminated by bile. Albenzazole is FDA approved for treatment of neurocysticercosis and hydatid diseases (*Echinococcus granulosus*). It is not FDA approved but is used for *Ankylostoma caninum*, ascariasis, Chinese liver fluke, cutaneous larva migrans, pinworms, filariasis, gnathostomiasis, hookworms, microsporidiosis, and visceral larva migrans. Albenzazole is generally well tolerated. Common adverse effects include headache, nausea, vomiting, and abdominal pain. Serious adverse effects include elevated liver enzymes and leukopenia, which have occurred in a few patients with treatment of hydatid disease. Rare adverse effects include acute renal failure, pancytopenia, granulocytopenia, and thrombocytopenia.

**Ivermectin (Stromectol, Mectizan)**

Ivermectin is a semisynthetic derivative of 1 of the avermectins, which is a group of macrocyclic lactones produced by *Streptomyces avermitilis*. After oral administration, ivermectin has peak plasma concentrations after approximately 4 hr and a plasma elimination half-life of approximately 12 hr. It is excreted as metabolites over a 2 wk period via feces. It is FDA approved for treatment of onchocerciasis and intestinal strongyloidiasis. It may have some effect in treating cutaneous larva migrans, intestinal nematode infections, loiasis, lymphatic filariasis, *Mansoniella* infections, and scabies. Combination therapies of ivermectin with albenzazole or diethylcarbamazine are being used to treat lymphatic filariasis. Common adverse events include dizziness, headache, pruritus, and gastrointestinal effects. Serious adverse events include Mazzotti reactions, including arthralgia, synovitis, enlarged lymph nodes, rash, and fever secondary to microfilaria death in patients with onchocerciasis.

**Praziquantel (Biltricide)**

Praziquantel achieves its antiparasitic activity via the pyrazino isoquinoline ring system and was originally synthesized as a potential tranquilizer. After oral administration, praziquantel is rapidly absorbed with peak levels in 1-2 hr and plasma half-life of about 1-3 hr. Elimination via the urine and feces is >80% complete after 24 hr. Praziquantel is metabolized in the liver by the microsomal cytochrome P450 (especially 2B1 and 3A). Bioavailability of praziquantel is increased with concomitant administration of agents that inhibit cytochrome P450. Praziquantel is FDA approved for treatment of Chinese liver fluke, Southeast Asian liver fluke, and schistosomiasis. It is used for treatment of intestinal flukes, North American liver fluke, *Nanophyetus salmincola*, lung fluke, and tapeworm infections but is not FDA approved for these indications. Adverse effects can be seen in 30-60% of patients.
although most are mild and disappear within 24 hr. Common adverse effects include headache, abdominal pain, dizziness, and malaise. Serious but rare adverse effects include arrhythmias, heart block, and convulsions.
Protozoan Diseases

Chapter 280
Primary Amebic Meningoencephalitis
Matthew D. Eberly and Martin E. Weisse

Naegleria, Acanthamoeba, Balamuthia, and Sappinia are small, free-living amebas that cause human amebic meningoencephalitis, which has 2 distinct clinical presentations. The more common is an acute, fulminant, and usually fatal amebic meningitis caused by Naegleria that occurs in previously healthy children and young adults. Granulomatous amebic meningoencephalitis, which is caused by Acanthamoeba, Balamuthia, and Sappinia, is a more indolent infection that typically occurs in immunocompromised hosts.

ETIOLOGY
Naegleria is an ameboflagellate that can exist as cysts, trophozoites, and transient flagellate forms. Temperature and environmental nutrient and ion concentrations are the major factors that determine the stage of the ameba. Trophozoites are the only stages that are invasive, although cysts are potentially infective, because they can convert to the vegetative form very quickly under the proper environmental stimuli. Although there are some 30 species of Naegleria, only Naegleria fowleri has been shown to be pathogenic for humans.

Acanthamoeba exist in cyst and motile trophozoite forms; only the trophozoite form is invasive. Cases of Acanthamoeba keratitis usually follow incidents of trivial corneal trauma followed by flushing with contaminated tap water. Infections can also occur among contact lens wearers who come in contact with contaminated water during swimming or using contact lenses cleaned or stored in contaminated tap water. Granulomatous amebic encephalitis from Acanthamoeba occurs worldwide and is associated with an immunocompromising condition such as HIV infection, diabetes mellitus, chronic liver disease, renal failure, immunosuppressive therapy, or radiation therapy.

Balamuthia mandrillaris has been implicated as an etiology of granulomatous amebic encephalitis. Although the clinical presentation is similar to infection with Acanthamoeba, most patients are not immunocompromised.

Other free-living amebas can also cause infection, as illustrated by case reports of Sappinia diploidea granulomatous encephalitis.

EPIDEMIOLOGY
The free-living amebas have a worldwide distribution. Naegleria species have been isolated from a variety of freshwater sources, including ponds and lakes, domestic water supplies, hot springs and spas, thermal discharge of power plants, groundwater, and, occasionally, from the nasal passages of healthy children. Acanthamoeba species have been isolated from soil, mushrooms, vegetables, brackish water, and seawater, as well as most of the freshwater sources for Naegleria. It can also be found in tap water, as chlorination does not kill Acanthamoeba. Balamuthia is present in soil and may be transmitted by inhalation or contamination of preexisting skin lesions.

Naegleria meningoencephalitis has been reported from every continent. Most of the cases occur during the summer months in previously healthy individuals who have a history of swimming in or contact with freshwater before their illness. Only 1-2 cases are reported in the United States per year, but 8 cases were reported in 2001-2002, and 6 cases were reported in 2007. Most of the reports have come from the southern and southwestern states, particularly Florida and Texas, with occasional infections occurring in the Midwest and East. Of note, 2 cases from Louisiana in 2011 were linked to sinus irrigation with neti pots, which contained contaminated tap water.

PATHOGENESIS
The free-living amebas enter the nasal cavity by inhalation or aspiration of dust or water contaminated with trophozoites or cysts. Naegleria gains access to the central nervous system through the olfactory epithelium and migrates via the olfactory nerve to the olfactory bulbs located in the subarachnoid space and bathed by the cerebrospinal fluid (CSF). This space is richly vascularized and is the route of spread to other areas of the central nervous system. Grossly, there is widespread cerebral edema and hyperemia of the meninges. The olfactory bulbs are necrotic, hemorrhagic, and surrounded by a purulent exudate. Microscopically, the gray matter is the most severely affected, with severe involvement in all cases. Fibrinopurulent exudate may be found throughout the cerebral hemispheres, brainstem, cerebellum, and upper portions of the spinal cord. Pockets of trophozoites may be seen in necrotic neural tissue, usually in the perivascular spaces of arteries and arterioles.

The route of invasion and penetration in cases of granulomatous amebic meningoencephalitis caused by Acanthamoeba and Balamuthia may be by direct spread through olfactory epithelium or hematomagenous from a primary focus in the skin or lungs. Pathologic examination reveals granulomatous encephalitis, with multinucleated giant cells mainly in the posterior fossa structures, basal ganglia, bases of the cerebral hemispheres, and cerebellum. Both trophozoites and cysts may be found in the central nervous system lesions, primarily located in the perivascular spaces and invading blood vessel walls. The olfactory bulbs and spinal cord are usually spared. The single case of Sappinia encephalitis followed a sinus infection, and evaluation revealed a solitary 2 cm temporal lobe mass with mild ring enhancement.

CLINICAL MANIFESTATIONS
The incubation of Naegleria infection may be as short as 2 days or as long as 15 days. Symptoms have an acute onset and progress rapidly. Infection is characterized by a sudden onset of severe headache, fever, pharyngitis, nasal congestion or discharge, and nausea and vomiting, followed by altered mental status, confusion, somnolence, seizures, and ultimately coma. Most cases end in death within 3-10 days after onset of symptoms.

Granulomatous amebic meningoencephalitis may occur weeks to months after initial infection. The presenting signs and symptoms are often those of a single or multiple central nervous system space-occupying lesions and include hemiparesis, ataxia, personality changes, seizures, and drowsiness. Altered mental status is often a prominent symptom. Headache and fever occur only sporadically, but stiff neck is seen in a majority of cases. Cranial nerve palsies, especially of cranial nerves III and VI, may be present. There is also 1 report of acute hydrocephalus and fever with Balamuthia. Granulomatous amebic meningoencephalitis is usually fatal after 4-6 wk of illness. Results of neuroimaging studies of the brain usually demonstrate multiple low-density lesions resembling infarcts or enhancing lesions of granulomas (Fig. 280-1).

DIAGNOSIS
The CSF in Naegleria infection may mimic that of herpes simplex encephalitis early in the disease and that of acute bacterial meningitis later in the disease, with a neutrophilic pleocytosis, elevated protein level, and hypoglycorrhachia. Motile amebas may be visualized on a wet mount of freshly drawn CSF using Wright or Giemsa stains, but are often mistaken for lymphocytes or macrophages. Because Naegleria are the only amebas that differentiate into the flagellate state in a
hypotonic environment, placing a drop of fresh CSF in 1 mL of distilled water and watching for development of swimming flagellates after 1-2 hr can confirm the diagnosis of *Naegleria*. *Naegleria* can also be grown on a nonnutrient agar plate coated with *Escherichia coli*, on which they feed.

The diagnosis of granulomatous amebic meningoencephalitis relies on the isolation or histologic identification of *Acanthamoeba* trophozoites or cysts from brain tissue specimens. The CSF findings of granulomatous meningoencephalitis reveal lymphocytic pleocytosis, moderately elevated protein, and low glucose concentrations. Motile trophozoites of *Acanthamoeba*, however, are more difficult to isolate than *Naegleria* and the CSF is typically sterile. *Acanthamoeba* may be cultured from the same agar used for growing *Naegleria*, but *Balamuthia* must be grown on mammalian cell cultures. Pediatric cases of *Balamuthia* meningoencephalitis have been diagnosed antemortem by brain biopsy as well as postmortem. Immunofluorescence staining of brain tissue can differentiate *Acanthamoeba* and *Balamuthia*.

**TREATMENT**

*Naegleria* infection is nearly always fatal, and early recognition and early treatment are crucial to successful therapy. There are several reports of treatment survivors, most of whom recovered fully. *Naegleria* infections have been successfully treated using amphotericin B, either alone or in combination with rifampin, chloramphenicol, fluconazole, or ketoconazole. The early use of dexamethasone may be considered, as steroid treatment was used in the few cases of survivors (as well as nonsurvivors). The optimal duration of treatment is unknown, but at least 10 days of therapy has been used in survivors. In 2013, the U.S. Centers for Disease Control and Prevention made available miltefosine for the treatment of primary amebic meningoencephalitis. In 2013, two children with *Naegleria* infection survived; both received miltefosine as part of their treatment; one received therapeutic hypothermia.

The optimal therapy for granulomatous amebic meningoencephalitis is also uncertain. Miltefosine has been used to successfully treat patients with *Balamuthia* and disseminated *Acanthamoeba* infections. Strains of *Acanthamoeba* isolated from fatal cases are usually susceptible in vitro to pentamidine, ketoconazole, fluconazole, and less so to amphotericin B. One patient was successfully treated with sulfadiazine and fluconazole, and another was successfully treated with intravenous pentamidine followed by oral itraconazole. *Acanthamoeba* keratitis responds to long courses of topical propamidine–polymyxin B sulfate or topical polyhexamethylene biguanide or chlorhexidine gluconate, and antifungal azoles plus topical steroids. Limited success has been demonstrated in *Balamuthia* infection with systemic azole therapy combined with fluconazole. More recently, the combination of fluconazole, pentamidine, fluconazole, sulfadiazine, a macrolide, and phenothiazines resulted in the survival of 2 patients with *Balamuthia* meningoencephalitis, although both were left with mild neuromotor and cognitive impairment. Corticosteroids prior to initiating effective therapy appear to have a detrimental effect, contributing to rapid progression of disease.

*Bibliography is available at Expert Consult.*
Bibliography


Entamoeba species infects or colonizes up to 10% of the world’s population, particularly in resource-limited settings. In most infected individuals, Entamoeba histolytica or a related species parasitizes the lumen of the gastrointestinal tract and causes few symptoms or sequelae. *E. histolytica* is the only invasive species and can cause amebic colitis with parasitic invasion of the intestinal mucosa and amebic liver abscess with dissemination of the parasite to the liver.

**ETIOLOGY**

Three morphologically identical but genetically distinct species of *Entamoeba* commonly infect humans. *Entamoeba dispar*, the most prevalent species, does not cause symptomatic disease. *Entamoeba moshkovskii*, previously thought to be nonpathogenic, has been shown to cause diarrhea in infants. *E. histolytica*, the main pathogenic species, causes a spectrum of disease and can become invasive in 4-10% of infected patients. Patients previously described as asymptomatic carriers of *E. histolytica* based on microscopy findings were likely harboring *E. dispar*. Four other species of nonpathogenic *Entamoeba* are known to colonize the human gastrointestinal tract: *E. coli*, *E. hartmanni*, *E. gingivalis*, and *E. polecki*.

Infection is acquired through the ingestion of parasite cysts, which measure 10-18 µm in diameter and contain 4 nuclei. Cysts are resistant to harsh environmental conditions, including chlorine concentrations commonly used in water purification, but can be killed by heating to 55°C (131°F). After ingestion, cysts are resistant to gastric acidity and digestive enzymes and germinate in the small intestine to form trophozoites. These large, actively motile organisms colonize the lumen of the large intestine and may invade the mucosal lining. Infection is not
usually transmitted by trophozoites, as these rapidly degenerate outside the body and are unable to survive the low pH of the stomach if swallowed.

EPIDEMIOLOGY
Prevalence of infection with *E. histolytica* varies greatly depending on region and socioeconomic status. Most prevalence studies have not distinguished between *E. histolytica* and *E. dispar*, and thus the true prevalence of *E. histolytica* infection is not known. It is estimated that infection with *E. histolytica* leads to 50 million cases of symptomatic disease and 40,000-110,000 deaths annually. Amebiasis is the second leading parasitic cause of death worldwide, after malaria. Prospective studies show that 4-10% of infected individuals develop *E. histolytica* and that <1% of infected individuals develop disseminated disease, including amebic liver abscesses. These numbers vary by region; for example, in South Africa and Vietnam, liver abscesses form a disproportionately large number of the cases of invasive disease caused by *E. histolytica*. Amebic liver abscesses are rare in children and occur equally in male and female children; in adults, amebic liver abscesses occur predominantly in men.

Amebiasis is endemic to Africa, Latin America, India, and Southeast Asia. In the United States, amebiasis is seen most frequently in immigrants from and in travelers to developing countries. Residents of mental health institutions and men who have sex with men are also at increased risk for invasive amebiasis. Food or drink contaminated with *Entamoeba* cysts and oral-anogenital sex are the most common means of infection. Untreated water and night soil (human feces used as fertilizer) are important sources of infection. Food handlers shedding amebic cysts play a role in spreading infection. Direct contact with infected feces can also result in person-to-person transmission.

PATHOGENESIS
Trophozoites are responsible for tissue invasion and destruction. These attach to colonial epithelial cells by a galactose and N-acetyl-D-galactosamine–specific lectin. This lectin is also thought to be responsible for resistance to complement-mediated lysis. Once attached to the colonial mucosa, amebas release proteases that allow for penetration through the epithelial layer. Host cells are destroyed by cytolysis and apoptosis. Cytolysis is mediated by trophozoite release of *amoebapores* (pore-forming proteins), phospholipases, and hemolysins. Amoebapores, which cause a massive influx of extracellular calcium, may also be partially responsible for the induction of apoptosis that occurs with amebic liver disease and colitis. Once host cells are partially digested by amebic proteases, the degraded material is internalized through phagocytosis. Early invasive amebiasis produces significant inflammation, due in part to parasite-mediated activation of nuclear factor-κB. Once *E. histolytica* trophozoites invade the intestinal mucosa, the organisms multiply and spread laterally underneath the intestinal epithelium to produce the characteristic *flask-shaped ulcers*. Amebas produce similar lytic lesions if they reach the liver. Changes at the base of the right lung, such as elevation of the diaphragm and atelectasis or effusion, may also occur.

Immunity to infection is associated with a mucosal secretory IgA response against the galactose/N-acetyl-D-galactosamine lectin. Neutrophils appear to be important in initial host defense, but *E. histolytica*–induced epithelial cell damage releases neutrophil chemoattractants, and *E. histolytica* is able to kill neutrophils, which then release mediators that further damage epithelial cells. The disparity between the extent of tissue destruction by amebas and the absence of a local host inflammatory response in the presence of systemic humoral (antibody) and cell-mediated responses may reflect both parasite-mediated apoptosis and the ability of the trophozoite to kill not only epithelial cells but neutrophils, monocyes, and macrophages. Studies show a protective role of the hormone leptin in mucosal resistance. A malnourished state, in which leptin levels are low, and a genetic polymorphism in the leptin receptor can increase susceptibility to invasive disease.

The sequencing of the *E. histolytica* genome has led to further insights into the pathogenesis of *E. histolytica* disease. The genome is functionally tetraploid and contains evidence of lateral gene transfer from bacteria. It has been demonstrated that the *amoebapore-A* (*Ap-A*) gene, along with other important genes, can be epigenetically silenced using plasmids with specifically engineered sequences or short hairpin RNAs. Transcriptional profiling using proteomics and microarrays has likewise identified several candidate virulence factors. Several classes of proteases that may be associated with pathogenesis have been identified, including the cysteine proteases binding family proteins (CPBF8), which modulate lysosome and phagosome function, and M8 metalloprotease EhMSP-1, which likely has a key role in amebic invasion and is notably absent in *E. dispar*.

CLINICAL MANIFESTATIONS
Clinical presentations range from asymptomatic cyst passage to amebic colitis, amebic dysentery, ameboma, and extraintestinal disease. Up to 10% of infected persons develop invasive disease within a year. Thus, asymptomatic carriers should be treated. Severe disease is common in young children, pregnant women, malnourished individuals, and persons taking corticosteroids, and invasive disease is more common in men. Extraintestinal disease usually involves the liver, but less common extraintestinal manifestations include amebic brain abscess, pleuropulmonary disease, ulcerative skin, and genitourinary lesions.

Amebic Colitis
Amebic colitis may occur within 2 wk of infection or may be delayed for months. The onset is usually gradual, with colicky abdominal pains and frequent bowel movements (6-8/day). Diarrhea is frequently associated with tenesmus. Almost all stool is heme-positive, but most patients do not present with grossly bloody stools. Generalized constitutional symptoms and signs are characteristically absent, with fever documented in only one third of patients. Amebic colitis affects all age groups but is strikingly common in children 1-5 yr of age. Severe amebic colitis in infants and young children tends to be rapidly progressive with more frequent extraintestinal involvement and high mortality rates, particularly in tropical countries. Amebic dysentery can result in dehydration and electrolyte disturbances.

Amebic Liver Abscess
Amebic liver abscess, a serious manifestation of disseminated infection, is uncommon in children. Although diffuse liver enlargement has been associated with intestinal amebiasis, liver abscesses occur in <1% of infected individuals and may appear in patients with no clear history of intestinal disease. Amebic liver abscess may occur months to years after exposure, so obtaining a careful travel history is critical. In children, fever is the hallmark of amebic liver abscess and is frequently associated with abdominal pain, abdominal distention, and enlargement and tenderness of the liver. Changes at the base of the right lung, such as elevation of the diaphragm and atelectasis or effusion, may also occur.

Men Who Have Sex with Men and HIV Coinfection
Epidemiologic studies from both developed and developing countries have shown an increased risk for *E. histolytica* infection among men who have sex with men. This risk is further increased in HIV because of increased host susceptibility and is particularly pronounced in men who have sex with men with HIV infection.

LABORATORY FINDINGS
Laboratory examination findings are often unremarkable in uncomplicated amebic colitis. Laboratory findings in amebic liver abscesses are a slight leukocytosis, moderate anemia, high erythrocyte sedimentation rate, and elevations of hepatic enzyme (particularly alkaline phosphatase) levels. Stool examination for amebas is negative in more than half of patients with documented amebic liver abscess. Ultrasonography, CT, or MRI can localize and delineate the size of the abscess cavity (Fig. 281-1). The most common finding is a single abscess in the right hepatic lobe in about one half of these cases. Higher-resolution
ultrasound and CT studies show that left lobe abscess and multiple abscesses occur more often than previously recognized.

**DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS**

A diagnosis of amebic colitis is made in the presence of compatible symptoms with detection of *E. histolytica* antigens in stool. This approach has a >95% sensitivity and specificity and coupled with a positive serology test is the most accurate means of diagnosis in developed countries. The *E. histolytica* II stool antigen detection test (TechLab, Blacksburg, VA) is able to distinguish *E. histolytica* from *E. dispar* infection. Microscopic examination of stool samples has a sensitivity of 60%. Sensitivity can be increased to 85-95% by examining 3 stools, as excretion of cysts can be intermittent. However, microscopy cannot differentiate between *E. histolytica* and *E. dispar* unless phagocytosed erythrocytes (specific for *E. histolytica*) are seen. In highly endemic areas, trophozoites without phagocytosed erythrocytes may reflect coinfection with *E. dispar*. In highly endemic areas, trophozoites without phagocytosed erythrocytes may reflect coinfection with *E. dispar* in a patient with another cause of colitis, such as shigellosis. Endoscopy and biopsies of suspicious areas should be performed when stool sample results are negative and suspicion for amebiasis remains high.

Various serum antiamebic antibody tests are available. Serologic results are positive in 70-80% of patients with invasive disease (colitis or liver abscess) at presentation and in >90% of patients after 7 days of disease symptoms. The most sensitive serologic test, indirect hemagglutination, yields a positive result even years after invasive infection. Therefore, many uninfected adults and children in highly endemic areas demonstrate antibodies to *E. histolytica*. Polymerase chain reaction detection in stool of *E. histolytica* is also able to distinguish *E. histolytica* from *E. dispar* but is less sensitive (72%) than the stool antigen test. Rapid antigen and antibody tests for bedside diagnosis in the developing world have been developed and are currently being tested. A high-throughput Luminex technique for simultaneous detection and differentiation of *Entamoeba* species has also been developed. In addition, a loop-mediated isothermal amplification assay that can be optimized for field use is under development.

The **differential diagnosis** for amebic colitis includes colitis caused by bacterial (*Shigella, Salmonella*, enteropathogenic *Escherichia coli*, *Campylobacter, Verrucaria, Clostridium difficile*), mycobacterial (tuberculosis and atypical mycobacteria), and viral (cytomegalovirus) pathogens, as well as noninfectious causes such as inflammatory bowel disease. Pyogenic liver abscess from bacterial infection, hepatoma, and echinococcal cysts are in the differential diagnosis for amebic liver abscess. However, echinococcal cysts are rarely associated with systemic symptoms such as fever unless there is cyst rupture or leakage.

**COMPLICATIONS**

Complications of amebic colitis include acute necrotizing colitis, ameboma, toxic megacolon, extraintestinal extension, or local perforation and peritonitis. Less commonly, a chronic form of amebic colitis develops, often recurring over several years. Amebomas are nodular foci of proliferative inflammation that sometimes develop in the wall of the colon. Chronic amebiasis should be excluded before initiating corticosteroid treatment for inflammatory bowel disease, as corticosteroid therapy given during active amebic colitis is associated with high mortality rates.

An amebic liver abscess may rupture into the peritoneum, pleural cavity, skin, and pericardium. Cases of amebic abscesses in extrahepatic sites, including the lung and brain, have been reported.

**TREATMENT**

Invasive amebiasis is treated with a nitroimidazole such as **metronidazole** or **tinidazole** and then a **luminal amebicide** (Table 281-1).

**Table 281-1 Drug Treatment for Amebiasis**

<table>
<thead>
<tr>
<th>MEDICATION</th>
<th>ADULT DOSAGE (ORAL)</th>
<th>PEDIATRIC DOSAGE (ORAL)*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>INVASIVE</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metronidazole</td>
<td>Colitis or liver abscess: 750 mg tid for 7-10 days</td>
<td>Colitis or liver abscess: 35-50 mg/kg/day in 3 divided doses for 7-10 days</td>
</tr>
<tr>
<td>or</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tinidazole</td>
<td>Colitis: 2 g once daily for 3 days</td>
<td>Liver abscess: 50 mg/kg/day once daily for 3 days</td>
</tr>
<tr>
<td>or</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Followed by: Paromomycin (preferred)</td>
<td>Liver abscess: 2 g once daily for 3-5 days</td>
<td>Liver abscess: 50 mg/kg/day once daily for 3-5 days</td>
</tr>
<tr>
<td>or</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diloxanide furoate</td>
<td>500 mg tid for 7 days</td>
<td>25-35 mg/kg/day in 3 divided doses for 7 days</td>
</tr>
<tr>
<td>or</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Iodoquinol</td>
<td>650 mg tid for 20 days</td>
<td>20 mg/kg/day in 3 divided doses for 7 days</td>
</tr>
<tr>
<td><strong>ASYMPTOMATIC INTESTINAL COLONIZATION</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paromomycin (preferred)</td>
<td>As for invasive disease</td>
<td>As for invasive disease</td>
</tr>
<tr>
<td>or</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diloxanide furoate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>or</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Iodoquinol</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*All pediatric dosages are up to a maximum of the adult dose.

*Not available in the United States.
Tinidazole has similar efficacy to metronidazole with shorter and simpler dosing and less-frequent adverse effects. These adverse effects include nausea, abdominal discomfort, and a metallic taste that disappears after completion of therapy. Therapy with a nitroimidazole should be followed by treatment with a luminal agent, such as paromomycin (which is preferred) or iodoquinol. Diloxanide furoate can also be used in children older than 2 yr of age, but it is no longer available in the United States. Paromomycin should not be given concurrently with metronidazole or tinidazole, because diarrhea is a common side effect of paromomycin and may confuse the clinical picture. Asymptomatic intestinal infection with *E. histolytica* should be treated preferably with paromomycin or alternatively with either iodoquinol or diloxanide furoate. For fulminant cases of amebic colitis, some experts suggest adding dehydroemetine (1 mg/kg/day subcutaneously or IM, never IV), available only through the Centers for Disease Control and Prevention. Patients should be hospitalized for monitoring if dehydroemetine is administered. Dehydroemetine should be discontinued if tachycardia, T-wave depression, arrhythmia, or proteinuria develops.

Broad-spectrum antibiotic therapy may be indicated in fulminant colitis to cover possible spillage of intestinal bacteria into the peritoneum and translocation into the bloodstream. Intestinal perforation and toxic megacolon are indications for surgery. In amebic liver abscess, image-guided aspiration of large lesions or left lobe abscesses may be necessary if rupture is imminent or if the patient shows a poor clinical response 4-6 days after administration of amebicidal drugs. A Cochrane metaanalysis comparing metronidazole and metronidazole plus aspiration in uncomplicated amebic liver abscess showed that there is insufficient evidence to make any recommendation for or against this approach. Chloroquine, which concentrates in the liver, may also be a useful adjunct to nitroimidazoles in the treatment of amebic liver abscess. To confirm cure, stool examination should be repeated every 2 wk following completion of therapy until clear.

**PROGNOSIS**

Most infections evolve to either an asymptomatic carrier state or eradication. Extraintestinal infection carries about a 5% mortality rate.

**PREVENTION**

Control of amebiasis can be achieved by exercising proper sanitation and avoiding fecal-oral transmission. Regular examination of food handlers and thorough investigation of diarrheal episodes may help identify the source of infection. No prophylactic drug or vaccine is currently available for amebiasis. Immunization with a combination of galactose/N-acetyl-d-galactosamine lectin and CpG oligodeoxynucleotides is protective against amebic trophozoite challenge in animals, and an intranasal galactose-lectin subunit vaccine is protective in baboons.

*Bibliography is available at Expert Consult.*
Bibliography


Giardiasis and Balantidiasis

282.1 Giardia lamblia

Chandy C. John

*Giardia lamblia* is a flagellated protozoan that infects the duodenum and small intestine. Infection results in clinical manifestations that range from asymptomatic colonization to acute or chronic diarrhea and malabsorption. Infection is more prevalent in children than in adults. *Giardia* is endemic in areas of the world with poor levels of sanitation. It is also an important cause of morbidity in developed countries, where it is associated with urban childcare centers, residential institutions for the developmentally delayed, and waterborne and foodborne outbreaks. *Giardia* is a particularly significant pathogen in people with malnutrition, certain immunodeficiencies, and cystic fibrosis.

**ETIOLOGY**

The life cycle of *G. lamblia* (also known as *Giardia intestinalis* or *Giardia duodenalis*) is composed of 2 stages: trophozoites and cysts. *Giardia* infects humans after ingestion of as few as 10-100 cysts (which measure 8-10 µm in diameter). Each ingested cyst produces 2 trophozoites in the duodenum. After excystation, trophozoites colonize the lumen of the duodenum and proximal jejunum, where they attach to the brush border of the intestinal epithelial cells and multiply by binary fission. The body of the trophozoite is teardrop shaped, measuring 10-20 µm in length and 5-15 µm in width. *Giardia* trophozoites contain 2 oval nuclei anteriorly, a large ventral disk, a curved median body posteriorly, and 4 pairs of flagella. As detached trophozoites pass down the intestinal tract, they encyst to form oval cysts that contain 4 nuclei. Cysts are passed in stools of infected individuals and may remain viable in water for as long as 2 mo. Their viability is often not affected by the usual concentrations of chlorine used to purify water for drinking.

*Giardia* strains that infect humans are diverse biologically, as shown by differences in antigens, restriction endonuclease patterns, DNA fingerprinting, isoenzyme patterns, and pulsed-field gel electrophoresis. Studies suggest that different *Giardia* genotypes may cause unique clinical manifestations, but these findings appear to vary according to the geographic region tested.

**EPIDEMIOLOGY**

*Giardia* occurs worldwide and is the most common intestinal parasite identified in public health laboratories in the United States, where it is estimated that up to 2 million cases of giardiasis occur annually. *Giardia* infection usually occurs sporadically, but *Giardia* is a frequently identified etiologic agent of outbreaks associated with drinking water. The age-specific prevalence of giardiasis is high during childhood and begins to decline after adolescence. The asymptomatic carrier rate of *G. lamblia* in the United States is as high as 20-30% in children younger than 36 mo of age attending childcare centers. Asymptomatic carriage may persist for several months.

Transmission of *Giardia* is common in certain high-risk groups, including children and employees in childcare centers, consumers of contaminated water, travelers to certain areas of the world, men who have sex with men, and persons exposed to certain animals. The major reservoir and vehicle for spread of *Giardia* appears to be water contaminated with *Giardia* cysts, but foodborne transmission occurs. The seasonal peak in age-specific case reports coincides with the summer recreational water season and might be a result of the extensive use of communal swimming venues by young children, the low infectious dose, and the extended periods of cyst shedding that can occur. In addition, *Giardia* cysts are relatively resistant to chlorination and to ultraviolet light irradiation. Boiling is effective for inactivating cysts.

Person-to-person spread also occurs, particularly in areas of low hygiene standards, frequent fecal-oral contact, and crowding. Individual susceptibility, lack of toilet training, crowding, and fecal contamination of the environment all predispose to transmission of enteropathogens, including *Giardia*, in childcare centers. Childcare centers play an important role in transmission of urban giardiasis, with secondary attack rates in families as high as 17-30%. Children in childcare centers may pass cysts for several months. Campers who drink untreated stream or river water, particularly in the western United States, and residents of institutions for the developmentally delayed are also at increased risk for infection.

Humoral immunodeficiencies, including common variable hypogammaglobulinemia and X-linked agammaglobulinemia, predispose...
humans to chronic symptomatic *Giardia* infection, suggesting the importance of humoral immunity in controlling giardiasis. Selective immunoglobulin A deficiency is also associated with *Giardia* infection. Although many individuals with AIDS have relatively mild *Giardia* infections, some reports suggest that severe *Giardia* infection, often refractory to treatment, may occur in a subset of individuals with AIDS. There is a higher incidence of *Giardia* infection in patients with cystic fibrosis, probably owing to local factors such as the increased amount of mucus, which may protect the organism against host factors in the duodenum. Human milk contains glycoconjugates and secretory immunoglobulin A antibodies that may provide protection to nursing infants against *Giardia*.

**CLINICAL MANIFESTATIONS**

The incubation period of *Giardia* infection usually is 1-2 wk but may be longer. A broad spectrum of clinical manifestations occurs, depending on the interaction between *G. lambia* and the host. Children who are exposed to *G. lambia* may experience asymptomatic excretion of the organism, acute infectious diarrhea, or chronic diarrhea with persistent gastrointestinal tract signs and symptoms, including failure to thrive and abdominal pain or cramping. *Giardia* was the cause of 15% of nondysenteric diarrhea illnesses in children examined in U.S. outpatient clinics in 1 study. Most infections in both children and adults are asymptomatic. There usually is no extraintestinal spread, but occasionally trophozoites may migrate into bile or pancreatic ducts.

Symptomatic infections occur more frequently in children than in adults. Most symptomatic patients usually have a limited period of acute diarrheal disease with or without low-grade fever, nausea, and anorexia; in a small proportion of patients, an intermittent or more protracted course characterized by diarrhea, abdominal distention and cramps, bloating, malaise, flatulence, nausea, anorexia, and weight loss develops (Table 282-1). Stools initially may be profuse and watery and later become greasy and foul smelling and may float. Stools do not contain blood, mucus, or fecal leukocytes. Varying degrees of malabsorption may occur. Abnormal stool patterns may alternate with periods of constipation and normal bowel movements. Malabsorption of sugars, fats, and fat-soluble vitamins is well documented and may be responsible for substantial weight loss. *Giardia* has been associated with iron deficiency in internationally adopted children. Giardiasis has been associated with growth stunting, and repeated *Giardia* infections correlate with a decrease in cognitive function in children in endemic areas.

**DIAGNOSIS**

Giardiasis should be considered in children who have acute non-dysenteric diarrhea, persistent diarrhea, intermittent diarrhea and constipation, malabsorption, chronic crampy abdominal pain and bloating, failure to thrive, or weight loss. It should be particularly high in the differential diagnosis of children in child care, children in contact with an index case, children with a history of recent travel to an endemic area, and children with humoral immunodeficiencies. Testing for giardiasis should be standard for internationally adopted children from *Giardia*-endemic areas, and screening for iron deficiency should be considered in internationally adopted children with giardiasis.

Stool enzyme immunoassay (EIA) or direct fluorescent antibody tests for *Giardia* antigens are the tests of choice for giardiasis in most situations. EIA is less reader dependent and more sensitive for detection of *Giardia* than microscopy. Some studies report that a single stool is sufficiently sensitive for detection of *Giardia* by EIA, whereas others suggest that sensitivity is increased with testing of 2 samples. A diagnosis of giardiasis was traditionally established by microscopy documentation of trophozoites or cysts in stool specimens, but 3 stool specimens are required to achieve a sensitivity of >90% using this approach. In patients in whom other parasitic intestinal infections are in the differential diagnosis, microscopy examination of stool allows evaluation for these infections in addition to *Giardia*. Laboratories can reduce reagent and personnel costs by pooling specimens submitted for detection of *Giardia* before evaluation by microscopy or EIA. Polymerase chain reaction and gene probe–based detection systems specific for *Giardia* have been used in environmental monitoring but at present remain research tools. Multiplex polymerase chain reaction testing for multiple parasitic pathogens may become a viable option for testing in the future.

In patients with chronic symptoms in whom giardiasis is suspected but in whom testing of stool specimens for *Giardia* yields a negative result, aspiration or biopsy of the duodenum or upper jejunum should be considered. In a fresh specimen, trophozoites usually can be visualized by direct wet mount. An alternate method of directly obtaining duodenal fluid is the commercially available Entero-Test (Hedeco Corp, Mountain View, CA), but this method is less sensitive than aspiration or biopsy. The biopsy can be used to make touch preparations and tissue sections for identification of *Giardia* and other enteric pathogens and also to visualize changes in histology. Biopsy of the small intestine should be considered in patients with characteristic clinical symptoms, negative stool and duodenal fluid specimen findings, and 1 or more of the following: abnormal radiographic findings (such as edema and segmentation in the small intestine); abnormal lactose tolerance test result; absent secretory immunoglobulin A level; hypogammaglobulinemia; and achlorhydria. Duodenal biopsy may show findings consistent with chronic inflammation, including eosinophilic infiltration of the lamina propria.

Radiographic contrast studies of the small intestine may show nonspecific findings such as irregular thickening of the mucosal folds. Blood cell counts usually are normal. Giardiasis is not tissue invasive and is not associated with peripheral blood eosinophilia.

**TREATMENT**

Children with acute diarrhea in whom *Giardia* organisms are identified should receive therapy. In addition, children who manifest failure to thrive or exhibit malabsorption or gastrointestinal tract symptoms such as chronic diarrhea should be treated.

Asymptomatic excreters generally are not treated except in specific instances such as outbreak control, prevention of household transmission by toddlers to pregnant women and patients with hypogammaglobulinemia or cystic fibrosis, and situations requiring oral antibiotic treatment where *Giardia* may produce malabsorption of the antibiotic.

The FDA has approved tinidazole and nitazoxanide for the treatment of *Giardia* in the United States. Both medications have been used to treat *Giardia* in thousands of patients in other countries and have excellent safety and efficacy against *Giardia* (Table 282-2). Tinidazole

<table>
<thead>
<tr>
<th>SYMPTOM</th>
<th>FREQUENCY (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>64-100</td>
</tr>
<tr>
<td>Malaise, weakness</td>
<td>72-97</td>
</tr>
<tr>
<td>Abdominal distention</td>
<td>42-97</td>
</tr>
<tr>
<td>Flatulence</td>
<td>35-97</td>
</tr>
<tr>
<td>Abdominal cramps</td>
<td>44-81</td>
</tr>
<tr>
<td>Nausea</td>
<td>14-79</td>
</tr>
<tr>
<td>Foul-smelling, greasy stools</td>
<td>15-79</td>
</tr>
<tr>
<td>Anorexia</td>
<td>41-73</td>
</tr>
<tr>
<td>Weight loss</td>
<td>53-73</td>
</tr>
<tr>
<td>Vomiting</td>
<td>14-35</td>
</tr>
<tr>
<td>Fever</td>
<td>0-28</td>
</tr>
<tr>
<td>Constipation</td>
<td>0-27</td>
</tr>
</tbody>
</table>

*Table 282-1 Clinical Signs and Symptoms of Giardiasis*
has the advantage of single-dose treatment and very high efficacy (>90%), while nitazoxanide has the advantage of a suspension form, high efficacy (80-90%), and very few adverse effects. Metronidazole, though never approved by the FDA for treatment of *Giardia*, is also highly effective (80-90% cure rate), and the generic form is considerably less expensive than tinidazole or nitazoxanide. Frequent adverse effects are seen with metronidazole therapy, and it requires 3 times a day dosing for 5-7 days. Suspension forms of tinidazole and metronidazole must be compounded by a pharmacy; neither drug is sold in suspension form.

**Second-line alternatives** for the treatment of patients with giardiasis include albendazole, paromomycin, and quinacrine (see Table 282-2). Albendazole may be of similar efficacy to metronidazole. Albendazole has few adverse effects and is effective against many helminths, making it useful for treatment when multiple intestinal parasites are identified or suspected. Paromomycin is a nonabsorbable aminoglycoside and is less effective than other agents but is recommended for treatment of pregnant women with giardiasis because of potential teratogenic effects of other agents. Quinacrine is effective and inexpensive but is not available commercially and must be obtained from compounding pharmacies (see Table 282-2). Quinacrine can also rarely have serious side effects, including hallucinations and psychosis. Refractory cases of giardiasis have been successfully treated with nitazoxanide, prolonged courses of tinidazole, or a 3 wk course of metronidazole and quinacrine.

**PROGNOSIS**

Symptoms recur in some patients in whom reinfection cannot be documented and in whom an immune deficiency such as an immunoglobulin abnormality is not present, despite use of appropriate therapy. Several studies have demonstrated that variability in antimicrobial susceptibility exists among strains of *Giardia*, and in some instances resistant strains have been demonstrated. Combined therapy may be useful for infection that persists after single-drug therapy, assuming reinfection has not occurred and the medication was taken as prescribed.

**PREVENTION**

Infected persons and persons at risk should practice strict handwashing after any contact with feces. This point is especially important for caregivers of diapered infants in childcare centers, where diarrhea is common and *Giardia* organism carriage rates are high.

Methods to purify public water supplies adequately include chlorination, sedimentation, and filtration. Inactivation of *Giardia* cysts by chlorine requires the coordination of multiple variables such as chlorine concentration, water pH, turbidity, temperature, and contact time. These variables cannot be appropriately controlled in all municipalities and are difficult to control in swimming pools. Individuals, especially children in diapers, should avoid swimming if they have diarrhea.

Individuals should also avoid swallowing recreational water and drinking untreated water from shallow wells, lakes, springs, ponds, streams, and rivers.

Travelers to endemic areas are advised to avoid uncooked foods that might have been grown, washed, or prepared with water that was potentially contaminated. Purification of drinking water can be achieved by a filter with a pore size of <1 µm or that has been National Sanitation Foundation rated for cyst removal, or by brisk boiling of water for at least 1 min. Treatment of water with chlorine or iodine is less effective but may be used as an alternate method when boiling or filtration is not possible.

**Bibliography is available at Expert Consult.**

### Table 282-2 Drug Treatment for Giardiasis

<table>
<thead>
<tr>
<th>MEDICATION</th>
<th>ADULT DOSAGE (ORAL)</th>
<th>PEDIATRIC DOSAGE (ORAL)*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RECOMMENDED</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tinidazole</td>
<td>2 g once</td>
<td>&gt;3 yr: 50 mg/kg once</td>
</tr>
<tr>
<td>Nitazoxanide</td>
<td>500 mg bid for 3 days</td>
<td>1-3 yr: 100 mg (5 mL) bid for 3 days</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>250 mg tid for 5-7 days</td>
<td>4-11 yr: 200 mg (10 mL) bid for 3 days</td>
</tr>
<tr>
<td><strong>ALTERNATIVE</strong></td>
<td></td>
<td>&gt;12 yr: 500 mg bid for 3 days</td>
</tr>
<tr>
<td>Albendazole</td>
<td>400 mg once a day for 5 days</td>
<td>15 mg/kg/day in 3 divided doses for 5-7 days</td>
</tr>
<tr>
<td>Paromomycin</td>
<td>25-35 mg/kg/day in 3 divided doses for 5-10 days</td>
<td></td>
</tr>
<tr>
<td>Quinacrine†</td>
<td>100 mg tid for 5-7 days</td>
<td>Not recommended</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6 mg/kg/day in 3 divided doses for 5 days</td>
</tr>
</tbody>
</table>

*All pediatric dosages are up to a maximum of the adult dose.
†Not commercially available. Can be compounded by Medical Center Pharmacy in New Haven, CT (203-688-6816) or Panorama Compounding Pharmacy in Van Nuys, CA (800-247-9767).

**282.2 Balantidiasis**

*Chandy C. John*

*Balantidium coli* is a ciliated protozoan and is the largest protozoan that parasitizes humans. Both trophozoites and cysts may be identified in feces. Disease caused by this organism is uncommon in the United States and generally is reported where there is a close association of humans with pigs, which are the natural hosts of *B. coli*. Because the organism infects the large intestine, symptoms are consistent with large bowel disease, similar to those associated with amebiasis and trichuriasis, and include nausea, vomiting, lower abdominal pain, tenesmus, and bloody diarrhea. Symptoms associated with chronic infection include abdominal cramps, watery diarrhea with mucus, occasionally bloody diarrhea, and colonic ulcers similar to those associated with *Entamoeba histolytica*. Extraintestinal spread of *B. coli* is rare and usually occurs only in immunocompromised patients. Most infections are asymptomatic.

Diagnosis using direct saline mounts is established by identification of trophozoites (50-100 µm long) or spherical or oval cysts (50-70 µm in diameter) in stool specimens. Trophozoites usually are more numerous than cysts. The recommended treatment regimen is metronidazole (45 mg/kg/day divided tid PO; maximum: 750 mg/dose) for 5 days, or tetracycline (40 mg/kg/day divided qid PO; maximum: 500 mg/dose) for 10 days for persons older than 8 yr of age. An alternative is iodoquinol (40 mg/kg/day divided tid PO; maximum: 650 mg/dose) for 20 days. Prevention of contamination of the environment by pig feces is the most important means for control.

**Bibliography is available at Expert Consult.**
Bibliography


Bibliography


Chapter 283
Cryptosporidium, Isospora, Cyclospora, and Microsporidia
Patricia M. Flynn

The spore-forming intestinal protozoa Cryptosporidium, Isospora, and Cyclospora are important intestinal pathogens in both immunocompetent and immunocompromised hosts. Cryptosporidium, Isospora, and Cyclospora are coccidian parasites that predominantly infect the epithelial cells lining the digestive tract. Microsporidia were formerly considered spore-forming protozoa but have been reclassified as fungi. Microsporidia are ubiquitous, obligate intracellular parasites that infect many other organ systems in addition to the gastrointestinal tract and cause a broader spectrum of disease.

CRYPTOSPORIDIUM
Cryptosporidium is recognized as a leading protozoal cause of diarrhea in children worldwide and is a common cause of outbreaks in childcare centers; it is also a significant pathogen in immunocompromised patients.

Etiology
Cryptosporidium hominis and Cryptosporidium parvum cause most cases of cryptosporidiosis in humans. Disease is initiated by ingestion of infectious oocysts that release 4 sporozoites that invade enterocytes, primarily in the small intestine. The cysts are immediately infectious to other hosts or can reinfect the same host.

Epidemiology
Cryptosporidiosis is associated with diarrheal illness worldwide and is more prevalent in developing countries and among children younger than 2 yr of age. It has been implicated as an etiologic agent of persistent diarrhea in the developing world and as a cause of significant morbidity and mortality from malnutrition, including permanent effects on growth.

Transmission of Cryptosporidium to humans can occur by close association with infected animals, via person-to-person transmission, or from environmentally contaminated water. Although zoonotic transmission, especially from cows, occurs in persons in close association with animals, person-to-person transmission is probably responsible for cryptosporidiosis outbreaks within hospitals and childcare centers where transmission rates as high as 67% have been reported. Recommendations to prevent outbreaks in childcare centers include strict handwashing, use of protective clothes or diapers capable of retaining liquid diarrhea, and separation of diapering and food-handling areas and responsibilities.

Outbreaks of cryptosporidial infection are associated with contaminated community water supplies and recreational waters, including lakes and chlorinated swimming pools. Wastewater in the form of raw sewage and runoff from dairies and grazing lands can contaminate both drinking and recreational water sources. It is estimated that Cryptosporidium oocysts are present in 65-97% of the surface water in the United States. The organism's small size (4-6 µm in diameter), resistance to chlorination, and ability to survive for long periods outside a host creates problems in public water supplies.

Clinical Manifestations
The incubation period is 2-14 days. Infection with Cryptosporidium is associated with profuse, watery, nonbloody diarrhea that can be accompanied by diffuse crampy abdominal pain, nausea, vomiting, and anorexia. Although less common in adults, vomiting occurs in more than 80% of children with cryptosporidiosis. Nonspecific symptoms such as myalgia, weakness, and headache also may occur. Fever occurs in 30-50% of cases. Malabsorption, lactose intolerance, dehydration, weight loss, and malnutrition often occur in severe cases. Recently, the clinical spectrum and disease severity has been linked with both the infecting species and host human leukocyte antigen class I and class II alleles.

In immunocompetent persons, the disease is usually self-limited, typically 5-10 days, although diarrhea may persist for several weeks and oocyst shedding may persist many weeks after symptoms resolve. Chronic diarrhea is common in individuals with immunodeficiency, such as congenital hypogammaglobulinemia or HIV infection. Symptoms and oocyst shedding can continue indefinitely and may lead to severe malnutrition, wasting, anorexia, and even death.

Cryptosporidiosis in immunocompromised hosts is often associated with biliary tract disease, characterized by fever, right upper quadrant pain, nausea, vomiting, and diarrhea. It also is associated with pancreatitis. Respiratory tract disease, with symptoms of cough, shortness of breath, wheezing, croup, and hoarseness, is very rare.

Diagnosis
Infection can be diagnosed by microscopy using modified acid-fast stain or polymerase chain reaction, but immunodetection of antigens on the surface of the organism in stool samples using monoclonal antibody–based assays is the current diagnostic method of choice. In stool, oocysts appear as small, spherical bodies (2-6 µm) and stain red with modified acid-fast staining. Because Cryptosporidium does not invade below the epithelial layer of the mucosa, fecal leukocytes are not found in stool specimens. Oocyst shedding in feces can be intermittent, and several fecal specimens (at least 3 for an immunocompetent host) should be collected for microscopic examination. Serologic diagnosis is not helpful in acute cryptosporidiosis.

In tissue sections, Cryptosporidium organisms can be found along the microvillus region of the epithelia that line the gastrointestinal tract. The highest concentration usually is detected in the jejunal. Histologic section results reveal villus atrophy and blunting, epithelial flattening, and inflammation of the lamina propria.

Treatment
Often the diarrheal illness attributable to cryptosporidiosis is self-limited in immunocompetent patients and requires no specific antimicrobial therapy. Treatment should focus on supportive care, including rehydration orally or, if fluid losses are severe, intravenously. Nitazoxanide (100 mg bid PO for 3 days for children 1-3 yr of age; 200 mg bid PO for children 4-11 yr of age; 500 mg bid PO for children ≥12 yr of age) is approved for treatment of diarrhea caused by Cryptosporidium. Clinical studies have not definitively demonstrated that nitazoxanide is superior to placebo in trials of HIV-infected (with low CD4 counts) or immunocompromised patients. However, given the severity of the infection in these populations, nitazoxanide treatment is usually initiated. In patients with HIV infection, treatment with combination antiretroviral therapy should also be administered to improve immune function. Other agents that have been suggested for treatment in clinical reports or small studies include orally administered human serum immunoglobulin or bovine colostrum, paromomycin, spiramycin, azithromycin, and roxithromycin or a combination of antibiotics.

ISOSPORA
Like Cryptosporidium, Isospora belli (also called Cystoisospora) is implicated as a cause of diarrhea in institutional outbreaks and in travelers and has also been linked with contaminated water and food. Isospora appears to be more common in tropical and subtropical climates and in developing areas, including South America, Africa, and Southeast Asia. Isospora has not been associated with animal contact. It is also an infrequent cause of diarrhea in patients with AIDS in the United States but may infect up to 15% of AIDS patients in Haiti.
The life cycle and pathogenesis of infection with Isospora species are similar to those of Cryptosporidium organisms except that oocysts excreted in the stool are not immediately infectious and must undergo further maturation at temperatures below 37°C (98.6°F). Thus, direct person-to-person transmission is unlikely. The most common clinical manifestation is watery, nonbloody diarrhea. Symptoms of infection are indistinguishable from those of cryptosporidiosis, although fever may be a more common finding. Eosinophilia may be present in up to 50% of cases, contrasting with other enteric protozoan infections. The diagnosis is established by detecting the oval, 22-33 µm long by 10-19 µm wide, oocysts by using modified acid-fast staining of the stool. Each oocyst contains 2 sporozoites with 4 sporozoites in each. Fecal leukocytes are not detected. Oocysts are shed in low number, underscoring the need for repeated stool examinations. Presence of oocysts in the gastrointestinal tract is almost always associated with clinical symptoms. Histologic appearance of gastrointestinal epithelium reveals blunting and atrophy of the villi, acute and chronic inflammation, and crypt hyperplasia.

Isosporiasis responds promptly to treatment with oral trimethoprim-sulfamethoxazole (TMP-SMZ) (5 mg TMP and 25 mg SMZ/kg/dose; maximum: 160 mg TMP and 800 mg SMZ/dose bid for 10 days). In patients with AIDS, relapses are common and often necessitate higher doses of trimethoprim-sulfamethoxazole and/or maintenance therapy. Combination antiretroviral therapy associated with immune recovery may also result in improved symptoms. Ciprofloxacin, nitazoxanide, or a regimen of pyrimethamine alone or with folinic acid is effective in patients intolerant of sulfonamide drugs.

**CYCLOSPORA**

Cyclospora cayetanensis is a coccidian parasite similar to but larger than Cryptosporidium. The organism infects both immunocompromised and immunocompetent individuals and is more common in children younger than 18 mo of age. The pathogenesis and pathologic findings of cyclosporiasis are similar to those of isosporiasis. Asymptomatic carriage of the organism has been found, but travelers who harbor the organism almost always have diarrhea. Outbreaks of cyclosporiasis are linked with contaminated food and water. Implicated foods include raspberries, lettuce, snow peas, basil, and other fresh food items. After fecal excretion, the oocysts must sporulate outside the host to become infectious. This finding explains the lack of person-to-person transmission.

The clinical manifestations of cyclosporiasis are similar to those of cryptosporidiosis and isosporiasis and follow an incubation period of approximately 7 days. Moderate Cyclospora illness is characterized by a median of 6 stools/day with a median duration of 10 days (range: 3-25 days). The duration of diarrhea in immunocompetent persons is characteristically longer in cyclosporiasis than in the other intestinal protozoan illnesses. Associated symptoms frequently include anorexia; fatigue; abdominal bloating or gas; abdominal cramps or pain; nausea; muscle, joint, or body aches; low-grade fever; chills; headache; and weight loss. Vomiting may occur. Bloody stools are uncommon. Biliary disease has been reported. Intestinal pathology includes inflammation with villus blunting.

The diagnosis is established by identification of oocysts in the stool. Oocysts are wrinkled spheres, measure 8-10 µm in diameter, and resemble large Cryptosporidium organisms. Each oocyst contains 2 sporozoites, each with 2 sporozoites. The organisms can be seen by using modified acid-fast, auramine-phenol, or modified trichrome staining, but stain less consistently than Cryptosporidium. They can also be detected with phososafranin stain and by autofluorescence using strong green or intense blue under ultraviolet epifluorescence. Multiple stool samples enhance identification of the pathogen. New molecular diagnostic testing, including real-time polymerase chain reaction, is currently under investigation. Fecal leukocytes are not present.

The treatment of choice for cyclosporiasis is TMP-SMZ (5 mg TMP and 25 mg SMZ/kg/dose bid PO for 7 days; maximum: 160 mg TMP and 800 mg SMZ/dose). Ciprofloxacin or nitazoxanide is effective in patients intolerant of sulfonamide drugs.

**MICROSPORIDIA**

Microsporidia are ubiquitous and infect most animal groups, including humans. They are classified as fungi and multiple species of the phylum Microsporidia have been linked with human disease in both immunocompetent and immunocompromised hosts. The species most commonly associated with gastrointestinal disease are Enterocytozoon bieneusi and Encephalitozoon intestinalis. Although still not definitive, the source of human infections is likely zoonotic. Like Cryptosporidium, there is concern for waterborne transmission through occupational and recreational contact with contaminated water sources. There is also the potential for foodborne outbreaks; the organisms have been identified on vegetables as a consequence of contaminated irrigation water. Vector-borne transmission is hypothesized because 1 species, Brachiola algerae, typically infects mosquitoes. Finally, transplacental transmission has been reported in animals but not in humans. Once infected, intracellular division produces new spores that can spread to nearby cells, disseminate to other host tissues, or be passed into the environment via feces. Spores also have been detected in urine and respiratory epithelium, suggesting that some body fluids may also be infectious. Once in the environment, microsporidial spores remain infectious for up to 4 mo.

Initially, microsporidial intestinal infection had been almost exclusively reported in patients with AIDS, but there is increasing evidence that immunocompetent individuals are also commonly infected. Microsporidia-associated diarrhea is intermittent, copious, watery, and nonbloody. Abdominal cramping and weight loss may be present; fever is unusual. Stromal keratitis and encephalitis may also be associated with microsporidia infections. Disseminated disease involving most organs, including liver, heart, kidney, bladder, biliary tract, lung, bone, skeletal muscle, and sinuses, has been reported.

Microsporidia stain with modified trichrome, hematoxylin-eosin, Giemsa, Gram, periodic acid–Schiff, and acid-fast stains, but are often overlooked because of their small size (1-5 µm) and the absence of associated inflammation in surrounding tissues. Electron microscopy remains the reference method of detection. Multiple research laboratories report success with polymerase chain reaction technology in detecting microsporidia, both in human and environmental samples.

There is no proven therapy for microsporidial intestinal infections. Albendazole (adult dose 400 mg bid PO for 3 wk) is usually effective against *E. intestinalis* infection, but is ineffective against infection caused by some microsporidial species. Fumagillin (adult dose 20 mg tid PO for 2 wk) was effective in a small controlled study of adults with *E. bieneusi* infection and topical therapy with this agent was also demonstrated to be effective in HIV-infected adults with keratoconjunctivitis. Supportive care with hydration, correction of electrolyte imbalances, and nutrition should be used in gastrointestinal infection when clinically indicated. Improvement in underlying HIV infection with combination antiretroviral therapy also improves microsporidiosis symptoms.

**Bibliography** is available at Expert Consult.
Bibliography
Trichomoniasis, caused by the protozoan parasite *Trichomonas vaginalis*, is the most common nonviral sexually transmitted disease worldwide. It primarily causes vulvovaginitis in women but has been implicated in pelvic inflammatory disease, adverse outcomes in pregnancy, chronic prostatitis, and an increased risk of transmission of HIV.

**Epidemiology**

More than 170 million new cases of trichomoniasis occur yearly, the majority in resource-limited settings. Prevalence and incidence rates are likely underestimated, as most men and up to 30% of women are asymptomatic. Diagnostic accuracy using wet mount microscopy, the mainstay of diagnosis, is less sensitive than previously assumed. While the disease is easily treated, sequelae of untreated infection remain a significant cause of morbidity as a result of high reinfection rates from untreated partners, underrecognition of asymptomatic cases, and insensitive diagnostics.

Trichomoniasis is the most common parasitic infection in the United States, with approximately 7.4 million cases occurring each year. A population-based study conducted in 2005 showed a prevalence of 2.8% in women and 1.7% in men, and an overall prevalence of 2.3%. The incidence of trichomoniasis is highest among females with multiple sexual partners and in groups with the highest rates of other sexually transmitted infections. *T. vaginalis* is recovered from more than 60% of female partners of infected men and 70% of male sexual partners of infected women. Vaginal trichomoniasis is rare until menarche. Its presence in a younger child should raise the possibility of sexual abuse.

Trichomoniasis may be transmitted to neonates during passage through an infected birth canal. Infection in this setting is usually self-limited, but rare cases of neonatal vaginitis and respiratory infection have been reported.

**Pathogenesis**

*T. vaginalis* is an anaerobic, flagellated protozoan parasite. Infected vaginal secretions contain 10^4 to 10^7 more protozoa/mL. *T. vaginalis* is pear shaped and exhibits characteristic twitching motility in wet mount (Fig. 284-1). Reproduction is by binary fission. It exists only as vegetative cells; cyst forms have not been described. *T. vaginalis* damages host cells and tissues by a number of mechanisms. Adhesion molecules allow attachment of *T. vaginalis* to host cells, and hydrolases, proteases, and cytotoxic molecules act to destroy or impair the integrity of host cells. An iron-upregulated cysteine proteinase legumain-1 (TvLEGU-1) has been characterized as a major factor in cytadherence. There is increasing evidence that *T. vaginalis* is associated with low levels of *Lactobacillus* spp. and high levels of *Mycoplasma* spp. in the vaginal microbiota. However, whether trichomoniasis alters the bacterial flora or whether altered bacterial flora predisposes to trichomoniasis is uncertain. Parasite-specific antibodies and lymphocyte priming occur in response to infection, but durable protective immunity does not occur.

**Clinical Manifestations**

The incubation period in females is 5-28 days. Symptoms may begin or exacerbate with menses. Most infected women eventually develop symptoms, although up to one third remain asymptomatic. Common signs and symptoms include a copious malodorous gray, frothy vaginal discharge, vulvovaginal irritation, dysuria, and dyspareunia. Physical examination may reveal a frothy discharge with vaginal erythema and cervical hemorrhages ("strawberry cervix"). The discharge usually has a pH of >4.5. Abdominal discomfort is unusual and should prompt evaluation for pelvic inflammatory disease (see Chapter 120).

Most infections in males are asymptomatic. Symptomatic males usually have dysuria and scant urethral discharge. Trichomonads occasionally cause epididymitis, prostatic involvement, and superficial penile ulceration. Infection is often self-limited, spontaneously resolving in 36% of men. *Trichomonas* has been implicated as a cause of recurrent or relapsing urethritis and can be isolated in 3-20% of men with nongonococcal urethritis. Treatment failures with standard therapy for gonorrhea and *Chlamydia* are frequently treated with anti-trichomonal therapy.

**Diagnosis**

Trichomonads may be recognized in vaginal secretions by using the wet mount technique. This technique has been estimated to have a sensitivity of 60-70%; studies using more sensitive assays with nucleic acid probes and polymerase chain reaction suggest that this is closer to 35-60%. Although *Trichomonas* is sometimes seen on Papanicolaou smears and in urine, these methods are not considered reliable tests for disease. Wet mount examination of material obtained by platinum loop from the anterior urethra may reveal the organism in 3-20% of infected men. Microscopic examination of urine sediment after prostate massage is also useful in infected men. Culture of the organism is the gold standard for detection, and commercial culture media are available. Enzyme-linked immunosorbent assay and direct fluorescent antigen testing of vaginal secretions are more sensitive than wet mount testing but less sensitive than culture for detection of *T. vaginalis* infection. In women, DNA immunoblot and polymerase chain reaction testing of vaginal secretions have similar sensitivity and specificity to culture. In men, these methods appear to be more sensitive at detection of infection than culture. Nucleic acid amplification testing and immunologic diagnostic kits for diagnosis of *Trichomonas* alone and in combination with other gynecologic diseases, such as *Candida* and *Gardnerella*, have been evaluated by multiple studies and have been found to be accurate and easy to use. The APTIMA TV (Gen-Probe Incorporated, CA) assay is an FDA-approved commercial nucleic acid amplification test that is highly sensitive and specific, particularly in asymptomatic patients. Two point-of-care kits for rapid testing, Affirm VP III (BD Diagnostic Systems, Sparks, MD) and OSOM *Trichomonas* Rapid Test (Genzyme Diagnostics, Cambridge, MA), have received approval by the FDA but are less sensitive than the APTIMA TV. Patients with *T. vaginalis* should be screened for other sexually transmitted infections, including *Chlamydia* and gonorrhea.
COMPLICATIONS
Untreated trichomoniasis is associated with pelvic inflammatory disease, premature delivery, low birthweight, tubal infertility, and vaginal cuff cellulitis. *T. vaginalis* infection increases the risk of acquisition and transmission of HIV. *Trichomonas*-induced inflammation of the genital mucosa recruits greater numbers of CD4+ cells in the epithelium and provides greater access to the bloodstream for HIV. In HIV-infected individuals, trichomoniasis is associated with higher viral loads in cervical secretions and semen, as well as higher levels of infected lymphocytes in urogenital fluids. HIV-1 shedding in vaginal fluids decreases following treatment for trichomoniasis.

TREATMENT
In the United States, metronidazole and tinidazole are used; in other countries ornidazole is also used. Both metronidazole (single-dose regimen of 2 g orally as a single dose for adolescents and adults; alternative regimen, 500 mg orally bid for 7 days) and tinidazole (single 2 g dose orally in adolescents and adults) are used as first-line treatment. For children infected prior to adolescence, the recommended regimen is metronidazole 15 mg/kg/day divided in 3 doses orally for 7 days; tinidazole is not approved for dosing in younger children. Topical metronidazole gel is not efficacious when used as the sole therapy for *T. vaginalis* infection, but it may decrease symptoms in individuals with severe infection when used in conjunction with oral therapy. Sexual partners should be treated simultaneously to prevent reinfection. Multiple head-to-head trials comparing the efficacy between single-dose/short courses of metronidazole and single-dose tinidazole have shown either noninferiority or superior efficacy for tinidazole. A Cochrane metaanalysis demonstrated that single dose tinidazole was superior compared to short-course metronidazole in clinical efficacy and parasitologic cure rates and had significantly fewer side effects. Tinidazole is more expensive than metronidazole and is generally reserved for treatment failures or metronidazole intolerance.

Treatment failures have been reported with metronidazole, although poor response can usually be overcome by higher doses of drugs. Second-line treatment recommendations include either a 7-day course of metronidazole 500 mg twice daily or a single dose of tinidazole. If this treatment fails, either metronidazole or tinidazole at 2 g daily for 5 days is recommended. Further treatment failure should be referred to an infectious diseases specialist and may require susceptibility testing, which is available from the Centers for Disease Control and Prevention. Metronidazole has not been shown to be teratogenic during pregnancy in humans but is currently classified as a category C drug. A Cochrane metaanalysis showed an association (RR = 1.78 [1.19, 2.66]) between premature births with metronidazole treatment of asymptomatic *T. vaginalis* infection in pregnancy. Further studies are needed to confirm this finding. Treatment of asymptomatic trichomoniasis in pregnancy should be weighed against possible risks, while treatment of asymptomatic disease should be delayed as much as possible to near term.

PREVENTION
Prevention of *T. vaginalis* infection is best accomplished by treatment of all sexual partners of an infected person and by programs aimed at prevention of all sexually transmitted infections (see Chapter 120). No vaccine is available, and drug prophylaxis is not recommended.

Bibliography is available at Expert Consult.
Bibliography


Martin DH, Zozaya M, Lillis RA, et al: Unique vaginal microbiota which include an unknown Mycoplasma-like organism are associated with Trichomonas vaginalis infection, J Infect Dis 2013.


The leishmaniases are a diverse group of diseases caused by intracellular protozoan parasites of the genus *Leishmania*, which are transmitted by phlebotomine sand flies. Multiple species of *Leishmania* are known to cause human disease involving the skin and mucosal surfaces and the visceral reticuloendothelial organs. Cutaneous disease is generally mild but may cause cosmetic disfigurement. Mucosal and visceral leishmaniasis is associated with significant morbidity and mortality.

**ETIOLOGY**  
*Leishmania* organisms are members of the Trypanosomatidae family and include 2 subgenera, *Leishmania (Leishmania)* and *Leishmania (Viannia)*. The parasite is dimorphic, existing as a flagellate promastigote in the insect vector and as an aflagellate amastigote that resides and replicates within mononuclear phagocytes of the vertebrate host. Within the sandfly vector, the promastigote changes from a noninfective procyclic form to an infective metacyclic stage. Fundamental to this transition are changes that take place in the terminal polysaccharides of the surface lipophosphoglycan, which allow forward migration of the infective parasites from the sandfly midgut to the mouth parts and inoculation of the host during a blood meal. Metacyclic lipophosphoglycan also plays an important role in the entry and survival of *Leishmania* in the mammalian host by conferring complement resistance and by facilitating entry into the macrophage by way of multiple receptors, including complement receptors 1 and 3. Once within the macrophage, the promastigote transforms to an amastigote and resides and replicates within a phagolysosome. The parasite is resistant to the acidic, hostile environment of the macrophage and eventually ruptures the cell and goes on to infect other macrophages. Infected macrophages have a diminished capacity to initiate and respond to an inflammatory response, thus providing a safe haven for the intracellular parasite.

**EPIDEMIOLOGY**  
The leishmaniases are estimated to affect 10–20 million people in endemic tropical and subtropical regions on all continents except Australia and Antarctica. The different forms of the disease are distinct in their causes, epidemiologic characteristics, transmission, and geographic distribution. The leishmaniases may occur sporadically throughout an endemic region or may occur in epidemic focuses. With only rare exceptions, the *Leishmania* organisms that primarily cause cutaneous disease do not cause visceral disease.

**Localized cutaneous leishmaniasis (LCL)** in the Old World is caused by *L. (Leishmania) major* and *L. (L.) tropica* in North Africa, the Middle East, central Asia, and the Indian subcontinent. *L. (L.) aethiopica* is a cause of LCL and diffuse cutaneous leishmaniasis (DCL) in Kenya and Ethiopia. **Visceral leishmaniasis (VL)** in the Old World is caused by *L. (L.) donovani* in Kenya, Sudan, India, Pakistan, and China and by *L. (L.) infantum* in the Mediterranean basin, Middle East, and central Asia. *L. infantum* is also a cause of LCL (without visceral disease) in this same geographic distribution. *L. tropica* also has been recognized as an uncommon cause of visceral disease in the Middle East and India. In the New World, *L. (L.) mexicana* causes LCL in a region stretching from southern Texas through Central America. *L. (L.) amazonensis, L. (L.) pifanoi, L. (L.) garinami, and L. (L.) venezuelensis* cause LCL in South America, the Amazon basin, and northward. Members of the *Viannia* subgenus (*L. [V.] braziliensis, L. [V.] panamensis, L. [V.] guyanensis, and L. [V.] peruviana*) cause LCL from the northern highlands of Argentina northward to Central America.
Members of the Viannia subgenus also cause mucosal leishmaniasis (ML) in a similar geographic distribution. VL in the New World is caused by L. (L.) chagasi (now considered to be the same organism as L. infantum), which is distributed from Mexico (rare) through Central and South America. L. infantum/chagasi can also cause LCL in the absence of visceral disease.

The maintenance of Leishmania in most endemic areas is through a zoonotic transmission cycle. In general, the dermotropic strains in both the Old and New Worlds are maintained in rodent reservoirs, and the domestic dog is the usual reservoir for L. infantum/chagasi. The transmission between reservoir and sandfly is highly adapted to the specific ecologic characteristics of the endemic region. Human infections occur when human activities bring them in contact with the zoonotic cycle. Anthroponotic transmission, in which humans are the presumed reservoir, occurs with L. tropica in some urban areas of the Middle East and Central Asia, and with L. donovani in India and Sudan. Congenital transmission of L. donovani or L. infantum/chagasi has been reported.

There is a resurgence of leishmaniasis in long-standing endemic areas as well as in new foci. Tens of thousands of cases of LCL occurred in an outbreak in Kabul, Afghanistan, and severe epidemics with more than 100,000 deaths from VL have occurred in India and Sudan. VL is most prevalent among the poorest of the poor, with substandard housing contributing to the vector-borne transmission and undernutrition leading to increased host susceptibility. The emergence of the leishmaniasis in new areas is the result of (1) movement of a susceptible population into existing endemic areas, usually because of agricultural or industrial development or timber harvesting; (2) increase in vector and/or reservoir populations as a result of agriculture development projects; (3) increase in anthropogenic transmission owing to rapid urbanization in some focuses; and (4) increase in sandfly density resulting from a reduction in vector control programs.

PATHOLOGY
Histopathologic analysis of the LCL lesion shows intense chronic granulomatous inflammation involving the epidermis and dermis. Occasionally, neutrophils and even microabscesses can be seen. The lesions of DCL are characterized by dense infiltration with vacuolated macrophages containing abundant amastigotes. ML is characterized by an intense granulomatous reaction with prominent tissue necrosis, which may include adjacent cartilage or bone. In VL there is prominent reticuloendothelial cell hyperplasia in the liver, spleen, bone marrow, and lymph nodes. Amastigotes are abundant in the histiocytes and Kupffer cells. Late in the course of disease, splenic infarcts are common, centrilobular necrosis and fatty infiltration of the liver occur, the normal normal elements are replaced by parasitized histiocytes, and erythrophagocytosis is present.

PATHOGENESIS
Cellular immune mechanisms determine resistance or susceptibility to infection with Leishmania. Resistance is mediated by interleukin (IL)-12-driven generation of a T helper 1 cell response, with interferon-γ inducing classical macrophage (M1) activation and parasite killing. Susceptibility is associated with expansion of IL-4–producing Th2 cells and/or the production of IL-10 and transforming growth factor-β, which are inhibitors of macrophage-mediated parasite killing, and the generation of regulatory T cells and alternatively activated (M2) macrophages. Patients with ML exhibit a hyperresponsive cellular immune reaction that may contribute to the prominent tissue destruction seen in this form of the disease. Patients with DCL or active VL demonstrate reduced or altered Leishmania–specific cellular immune responses, with prominent generation of IL-10, but these responses recover after successful therapy.

Within endemic areas, people who have had a subclinical infection can be identified by a positive delayed-type hypersensitivity skin response to leishmanial antigens (Montenegro skin test) or by antigen-induced production of interferon-γ in a whole blood assay. Subclinical infection occurs considerably more frequently than does active cutaneous or visceral disease. Host factors (genetic background, concomitant disease, nutritional status), parasite factors (virulence, size of the inoculum), and possibly vector-specific factors (vector genotype, immunomodulatory salivary constituents) influence the expression as either subclinical infection or active disease. Within endemic areas the prevalence of skin test result positivity increases with age and the incidence of clinical disease decreases with age, indicating that immunity is acquired in the population over time. Individuals with prior active disease or subclinical infection are usually immune to a subsequent clinical infection; however, latent infection can lead to active disease if the patient is immunosuppressed.

CLINICAL MANIFESTATIONS
The different forms of the disease are distinct in their causes, epidemiologic features, transmission, and geographic distribution.

Localized Cutaneous Leishmaniasis
LCL (Oriental sore) can affect individuals of any age, but children are the primary victims in many endemic regions. It may present as 1 or a few papular, nodular, plaquelike, or ulcerative lesions that are usually located on exposed skin, such as the face and extremities (Fig. 285-1). Rarely, more than 100 lesions have been recorded. The lesions typically begin as a small papule at the site of the sandfly bite, which enlarges to 1–3 cm in diameter and may ulcerate over the course of several weeks to months. The shallow ulcer is usually without and surrounded by a sharp, indurated, erythematous margin. There is no drainage unless a bacterial superinfection develops. Lesions caused by L. major and L. mexicana usually heal spontaneously after 3–6 mo, leaving a depressed scar. Lesions on the ear pinna caused by L. mexicana, called chichero ulcer because they were common in chile harvesters in Mexico and Central America, often follow a chronic, destructive course. In general, lesions caused by L. (Viannia) species tend to be larger and more chronic. Regional lymphadenopathy and palpable subcutaneous nodules or lymphatic cords, the so-called sporotrichoid appearance, are also more common when the patient is infected with organisms of the Viannia subgenus. If lesions do not become secondarily infected, there are usually no complications aside from the residual cutaneous scar.

Diffuse Cutaneous Leishmaniasis
DCL is a rare form of leishmaniasis caused by organisms of the L. mexicana complex in the New World and L. aethiopica in the Old World. DCL manifests as large nonulcerating macules, papules,
nODULES, OR PLAQUES THAT OFTEN INVOLVE LARGE AREAS OF SKIN AND MAY RESEMBLE LEPROMATOUS LEPROSY. THE FACE AND EXTREMITIES ARE MOST COMMONLY INVOLVED. DISSEMINATION FROM THE INITIAL LESION USUALLY TAKES PLACE OVER SEVERAL YEARS. IT IS THOUGHT THAT AN IMMUNOLOGIC DEFECT UNDERLIES THIS SEVERE FORM OF CUTANEOUS LEISHMANIASIS.

**Mucosal Leishmaniasis**

ML (**espundia**) is an uncommon but serious manifestation of leishmanial infection resulting from hematogenous metastases to the nasal or oropharyngeal mucosa from a cutaneous infection. It is usually caused by parasites in the *L. (Viannia)* complex. Approximately half of the patients with mucosal lesions have had active cutaneous lesions within the preceding 2 yr, but ML may not develop until many years after resolution of the primary lesion. ML occurs in <5% of individuals who have, or have had, LCL caused by *L. (V.) braziliensis*. Patients with ML most commonly have nasal mucosal involvement and present with nasal congestion, discharge, and recurrent epistaxis. Oropharyngeal and laryngeal involvement is less common but associated with severe morbidity. Marked soft tissue, cartilage, and even bone destruction occurs late in the course of disease and may lead to visible deformity of the nose or mouth, nasal septal perforation, and tracheal narrowing with airway obstruction.

**Visceral Leishmaniasis**

VL (**kala-azar**) typically affects children younger than 5 yr of age in the New World and Mediterranean region (*L. infantum/chagasi*) and older children and young adults in Africa and Asia (*L. donovani*). After inoculation of the organism into the skin by the sandfly, the child may have a completely asymptomatic infection or an oligosymptomatic illness that either resolves spontaneously or evolves into active kala-azar. Children with asymptomatic infection are transiently seropositive but show no clinical evidence of disease. Children who are oligosymptomatic have mild constitutional symptoms (malaise, intermittent diarrhea, poor activity tolerance) and intermittent fever; most will have a mildly enlarged liver. In most of these children the illness will resolve without therapy, but in approximately 25% it will evolve to active kala-azar within 2–8 mo. Extreme incubation periods of several years have rarely been described. During the first few wk to months of disease evolution the fever is intermittent, there is weakness and loss of energy, and the spleen begins to enlarge. The classic clinical features of high fever, marked splenomegaly, hepatomegaly, and severe cachexia typically develop approximately 6 mo after the onset of the illness, but a rapid clinical course over 1 mo has been noted in up to 20% of patients in some series (Fig. 285–2). At the terminal stages of kala-azar the hepatosplenomegaly is massive, there is gross wasting, the pancytopenia is profound, and jaundice, edema, and ascites may be present. Anemia may be severe enough to precipitate heart failure. Bleeding episodes, especially epistaxis, are frequent. The late stage of the illness is often complicated by secondary bacterial infections, which frequently are a cause of death. A younger age at the time of infection and underlying malnutrition may be risk factors for the development and more rapid evolution of active VL. Death occurs in more than 90% of patients without specific antileishmanial treatment.

VL is an opportunistic infection associated with HIV infection. Most cases have occurred in southern Europe and Brazil, often as a result of needle sharing associated with illicit drug use, with the potential for many more cases as the endemic regions for HIV and VL converge. Leishmaniasis may also result from reactivation of a long-standing subclinical infection. Frequently there is an atypical clinical presentation of VL in HIV-infected individuals with prominent involvement of the gastrointestinal tract and absence of the typical hepatosplenomegaly.

A small percentage of patients previously treated for VL develop diffuse skin lesions, a condition known as post-kala-azar dermal leishmaniasis. These lesions may appear during or shortly after therapy (Africa) or up to several years later (India). The lesions of post-kala-azar dermal leishmaniasis are hypopigmented, erythematous, or nodular and commonly involve the face and torso. They may persist for several months or for many years.

**LABORATORY FINDINGS**

Patients with cutaneous leishmaniasis or ML generally do not have abnormal laboratory results unless the lesions are secondarily infected with bacteria. Laboratory findings associated with classic kala-azar include anemia (hemoglobin <5 mg/dL), thrombocytopenia, leukopenia (2,000–3,000 cells/μL), elevated hepatic transaminase levels, and hypergammaglobulinemia (>5 g/dL) that is mostly immunoglobulin G.

**DIFFERENTIAL DIAGNOSIS**

Diseases that should be considered in the differential diagnosis of LCL include sporotrichosis, blastomycosis, chromomycosis, lobomycosis, cutaneous tuberculosis, atypical mycobacterial infection, leprosy, echyma, syphilis, yaws, and neoplasms. Infections such as syphilis, tertiary yaws, histoplasmosis, paracoccidioidomycosis, as well as sarcoidosis, Wegener granulomatosis, midline granuloma, and carcinoma may have clinical features similar to those of ML. VL should be strongly suspected in the patient with prolonged fever, weakness, cachexia, marked splenomegaly, hepatomegaly, cytopenias, and hypergamma-globulinemia who has had potential exposure in an endemic area. The clinical picture may also be consistent with that of malaria, typhoid

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fever, miliary tuberculosis, schistosomiasis, brucellosis, amebic liver abscess, infectious mononucleosis, lymphoma, and leukemia.

**DIAGNOSIS**

The development of 1 or several slowly progressive, nontender, nodular, or ulcerative lesions in a patient who had potential exposure in an endemic area should raise suspicion of LCL.

Serologic tests for diagnosis of ML or LCL generally have low sensitivity and specificity and offer little for diagnosis. Serologic testing by enzyme immunoassay, indirect fluorescence assay, or direct agglutination is very useful in VL because of the very high level of antileishmanial antibodies. An immunochromatographic strip test using a recombinant antigen (K39) has a diagnostic sensitivity and specificity for VL of 80-90% and 95%, respectively. Serodiagnostic tests have positive findings in only about half of the patients who are coinfected with HIV.

Definitive diagnosis of leishmaniasis is established by the demonstration of amastigotes in tissue specimens or isolation of the organism by culture. Amastigotes can be identified in Giemsa-stained tissue sections, aspirates, or impression smears in about half of the cases of LCL but only rarely in the lesions of ML. Culture of a tissue biopsy or aspirate, best performed by using Novy-McNeal-Nicolle biphasic bacthot agar medium, yields a positive finding in only approximately 65% of cases of cutaneous leishmaniasis. Identification of parasites in impression smears, histopathologic sections, or culture medium is usually diagnostic. In experienced hands, splenic aspersion has a higher diagnostic sensitivity, but it is rarely performed in the United States because of the risk for bleeding complications. A positive culture result allows speciation of the parasite, usually by isoenzyme analysis by a reference laboratory, which may have therapeutic and prognostic significance.

**TREATMENT**

Specific antileishmanial therapy is not routinely indicated for uncomplicated LCL caused by strains that have a high rate of spontaneous resolution and self-healing (*L. major*, *L. mexicana*). Lesions that are extensive, severely inflamed, or located where a scar would result in disability (near a joint) or cosmetic disfigurement (face or ear), that involve the lymphatics, or that do not begin healing within 3-4 mo should be treated. Cutaneous lesions suspected or known to be caused by members of the *Viannia* subgenus (*New World*) should be treated because of the low rate of spontaneous healing and the potential risk for development of mucosal disease. Similarly, patients with lesions caused by *L. tropica* (*Old World*), which are typically chronic and nonhealing, should be treated. All patients with VL or ML should receive therapy.

The pentavalent antimony compounds (sodium stibogluconate [Pentostam, GlaxoSmithKline, Uxbridge, UK] and meglumine antimoniate [Glucantime, Aventis, Strasbourg, France]) have been the mainstay of antileishmanial chemotherapy for more than 40 yr. These drugs have similar efficacies, toxicities, and treatment regimens. Currently, for sodium stibogluconate (available in the United States from the Centers for Disease Control and Prevention, Atlanta, Georgia), the recommended regimen is 20 mg/kg/day intravenously or intramuscularly for 20 days (for LCL and DCL) or 28 days (for ML and VL). Repeated courses of therapy may be necessary in patients with severe cutaneous lesions, ML, or VL. An initial clinical response to therapy usually occurs in the 1st wk of therapy, but complete clinical healing (reepithelialization and scarring for LCL and ML, and regression of splenomegaly and normalization of cytopenias for VL) is usually not evident for weeks to a few months after completion of therapy. Cure rates with this regimen of 90-100% for LCL, 50-70% for ML, and 80-100% for VL were common in the 1990s, but treatment failures, especially in children, have become common in parts of India, East Africa, and Latin America. Relapses are common in patients who do not have an effective antileishmanial cellular immune response (DCL or HIV coinfection). Adverse effects of antimony therapy are dose and duration dependent and commonly include fatigue, arthralgias and myalgias (50%), abdominal discomfort (30%), elevated hepatic transaminase level (30-80%), elevated amylase and lipase levels (almost 100%), mild hematologic changes (slightly decreased leukocyte count, hemoglobin level, and platelet count) (10-30%), and nonspecific T-wave changes on electrocardiography (50%). Sudden death from cardiac toxicity has rarely been reported with use of very high doses of pentavalent antimony.

Amphotericin B desoxycholate and the amphotericin lipid formulations are very useful in the treatment of VL or ML and in some regions have replaced antimony as first-line therapy. However, the prohibitively high cost of these drugs precludes their use in many resource-poor regions of the world. Amphotericin B desoxycholate at doses of 0.5-1.0 mg/kg every day or every other day for 14-20 doses achieved a cure rate for VL of close to 100%, but the renal toxicity associated with amphotericin B was common. The lipid formulations of amphotericin B are especially attractive for treatment of leishmaniasis because the drugs are concentrated in the reticuloendothelial system and are less nephrotoxic. Liposomal amphotericin B is highly effective, with a 90-100% cure rate for VL in immunocompetent children, some of whom were refractory to antimony therapy. Liposomal amphotericin B (AmBisome, Gilead Sciences, Foster City, CA) is approved by the U.S. Food and Drug Administration for treatment of VL at a recommended dose for immunocompetent patients of 3 mg/kg on days 1-5, 14, and 21 and should be considered for first-line therapy in the United States. Therapy for immunocompromised patients may need to be prolonged. A single high dose of liposomal amphotericin B (10 mg/kg) was found to be noninferior to conventional amphotericin (15 doses of 1 mg/kg) in India and offers a less-cost-prohibitive approach. Parenteral treatment of VL with the aminoglycoside paromomycin (aminosidine) has efficacy (~95%) similar to that of amphotericin B in India. Miltefosine, a membrane-activating alkylphospholipid, has been approved as the first oral treatment for VL and has a cure rate of 80-90% in Indian patients with VL when administered orally at 50-100 mg/day (or 2.5 mg/kg for children younger than 12 yr of age) for 28 days. Miltefosine is indicated for cutaneous infection caused by *L. braziliensis*, *L. guyanensis*, and *L. panamensis*; mucosal disease caused by *L. braziliensis*; and visceral disease caused by *L. donovani*. Gastrointestinal adverse effects were frequent but did not require discontinuation of the drug. An increased rate of relapse (up to 20%) has been seen in children treated with miltefosine. Dose-sparing combination regimens are being actively investigated for treatment of VL. Treatment of LCL with oral drugs has had only modest success. Ketoconazole has been effective in treating adults with LCL caused by *L. major*, *L. mexicana*, and *L. panamensis*, but not *L. tropica* or *L. braziliensis*. Fluconazole in high doses (up to 8 mg/kg/day) for 4-8 wk was demonstrated to be effective in treating LCL in studies in both the Old and New World; however, the experience in young children is limited. Miltefosine 2.5 mg/kg/day orally for 20-28 days was effective in 70-90% of patients with LCL in the Americas. Topical treatment of LCL with paromomycin ointment has been effective in selected areas in the both Old and New World. Enhanced drug development efforts and clinical trials of new drugs are clearly needed, especially in children.

**PREVENTION**

Personal protective measures should include avoidance of exposure to the nocturnal sandflies and, when necessary, the use of insect repellent and permethrin-impregnated mosquito netting. Where peridomestic or anthroponotic transmission is present, community-based residual insecticide spraying has had some success in reducing the prevalence of leishmaniasis, but long-term effects are difficult to maintain. Control or elimination of infected reservoir hosts (e.g., seropositive domestic dogs) has had limited success. Where anthroponotic transmission is thought to occur, early recognition and treatment of cases are essential. Several vaccines have been demonstrated to have efficacy in experimental models, and vaccination of humans or domestic dogs may have a role in the control of the leishmaniasis in the future.

**Bibliography is available at Expert Consult.**
**Bibliography**


Chapter 286
African Trypanosomiasis (Sleeping Sickness; Trypanosoma brucei Complex)
Edsel Maurice T. Salvana and Robert A. Salata

Seventy million people in 36 countries are at risk for infection with Trypanosoma brucei complex, the causative agent of sleeping sickness. Also known as human African trypanosomiasis (HAT), this disease is restricted to sub-Saharan Africa, the range of the tsetse fly vector. It is a disease of extreme poverty, with an increased burden observed in remote rural areas. HAT comes in 2 geographically and clinically distinct forms. T. brucei gambiense causes a chronic infection lasting years and mostly affects people who live in Western and Central Africa (West African sleeping sickness, Gambian trypanosomiasis). T. brucei rhodesiense is a zoonosis that presents as an acute illness lasting several weeks and usually occurs in residents of eastern and southern Africa (East African sleeping sickness, Rhodesian trypanosomiasis).

ETIOLOGY
HAT is a vector-borne disease caused by parasitic, flagellated kinetoplastid protozoans of 2 subspecies of T. brucei. It is transmitted to humans through the bite of Glossina, commonly known as the tsetse fly. The vector feeds on the blood of humans and wild game animals and penetrates intact mucous membranes and skin. Humans usually contract East African HAT when they venture from towns to rural areas to visit woodlands or livestock, highlighting the importance of zoonotic reservoirs in this disease. West African HAT is contracted closer to settlements and only requires a small vector population, which makes it difficult to eradicate. Low rates of infection in tsetse flies of this form necessitates close and repeated contact between humans and insects to permit frequent biting. While animal reservoirs occur, these are less important than for East African HAT, and the main source of infection remains chronically infected human hosts.

LIFE CYCLE
T. brucei undergoes several stages of development in the insect and mammalian host. Upon ingestion with a blood meal, nonproliferative stumpy forms of the parasite, which are optimally adapted to maintain its life cycle. The insect vector is able to transmit disease for at least 5-7 wk. The vector feeds on the blood of humans and wild game animals and penetrates intact mucous membranes and skin. Humans usually contract East African HAT when they venture from towns to rural areas to visit woodlands or livestock, highlighting the importance of zoonotic reservoirs in this disease. West African HAT is contracted closer to settlements and only requires a small vector population, which makes it difficult to eradicate. Low rates of infection in tsetse flies of this form necessitates close and repeated contact between humans and insects to permit frequent biting. While animal reservoirs occur, these are less important than for East African HAT, and the main source of infection remains chronically infected human hosts.

EPIDEMIOLOGY
HAT is a major public health problem in sub-Saharan Africa. It occurs in the region between latitudes 14 degrees north and 29 degrees south, corresponding roughly to the area where the annual rainfall creates optimal climatic conditions for Glossina flies to thrive. More than 70% of reported cases are from the Democratic Republic of Congo. In 2009, as a result of intensive control efforts spearheaded by the World Health Organization (WHO), the number of new HAT cases annually fell below 10,000 for the first time in 50 yr. In 2011, this further fell to 6,743 cases. As a result, the disease has been targeted by the international community for elimination as a public health problem.

T. brucei rhodesiense infection is restricted to the eastern third of the endemic area in tropical Africa, stretching from Ethiopia to the northern boundaries of South Africa. T. brucei gambiense, which accounts for 97% of HAT cases, occurs mainly in the western half of the continent’s endemic region. Glossina captured in endemic foci show a low rate of infection, usually <5%. Rhodesian HAT, which has an acute and often fatal course, greatly reduces chances of transmission to tsetse flies. The ability of T. brucei rhodesiense to multiply rapidly in the bloodstream and infect other species of mammals helps maintain its life cycle. The insect vector is able to transmit disease for up to 6 mo.

PATHOGENESIS
The initial entry site of the organisms develops a hard, painful, red nodule known as a trypanosomal chancre. It contains long, thin trypanosomes multiplying beneath the dermis and is surrounded by a lymphocytic cellular infiltrate. Dissemination into the blood and lymphatic systems follows, with subsequent localization to the central nervous system (CNS). Histopathologic findings in the brain are consistent with meningoencephalitis, with lymphocytic infiltration and perivascular cuffing of the membranes. The appearance of morular cells (large, strawberry-like cells, supposedly derived from plasma cells) is a characteristic finding in chronic disease.

Antigenic variation of variant surface glycoproteins on the trypanosome’s surface enables evasion of acquired immunity during infection. Both T. brucei gambiense and T. brucei rhodesiense have acquired resistance to trypanolytic factors in human serum, the most well-studied of which is apolipoprotein L-1 (APOL1), through the expression of a protein known as serum resistance-associated protein (SRAp). A frameshift mutation in the APOL1 gene in 1 patient enabled infection with a nonhuman trypanosome, Trypanosoma evansi, and treatment with recombinant APOL1 restored trypanolytic activity. Mechanisms underlying virulence in HAT are still incompletely understood, although severity of disease seems to be dependent on the host inflammatory response, particularly interferon-γ production in the CNS and blood.

CLINICAL MANIFESTATIONS
Clinical presentations vary not only because of the 2 subspecies of organisms but also because of differences in host response in the indigenous population of endemic areas and in newcomers or visitors. Visitors usually suffer more from the acute symptoms, but in untreated cases death is inevitable for natives and visitors alike. Symptoms usually occur within 1-4 wk of infection. The clinical syndromes of HAT are trypanosomal chancre, hemolymphatic stage, and meningoencephalitic stage.

Trypanosomal Chancre
The site of the tsetse fly bite may be the first presenting feature. A nodule or chancre develops in 2-3 days and becomes a painful, hard, red nodule surrounded by an area of erythema and swelling within 1 wk. Nodules are commonly seen on the lower limbs and sometimes also on the head. They subside spontaneously in about 2 wk, leaving no permanent scar.

Hemolymphatic Stage (Stage 1)
The most common presenting features of acute HAT occur at the time of invasion of the bloodstream by the parasites, 2-3 wk after infection.
Patients usually present with irregular episodes of fever, each lasting up to 7 days, accompanied by headache, sweating, and generalized lymphadenopathy. Attacks may be separated by symptom-free intervals of days or even weeks. Painless, nonmatted lymphadenopathy, most commonly of the posterior cervical and supraclavicular nodes, is one of the most constant signs, particularly in the Gambian form. A common feature of trypanosomiasis in Caucasians is the presence of blotty, irregular, nonpruritic, erythematous macules, which may appear any time after the first febrile episode, usually within 6-8 wk. The majority of macules have a normal central area, giving the rash a circinate outline. This rash is seen mainly on the trunk and is evanescent, fading in 1 place only to appear at another site. Examination of the blood during this stage may show anemia, leukopenia with relative monocyteosis, and elevated levels of immunoglobulin M. Cardiac manifestations of HAT have also been reported but are generally limited to nonspecific ST-T wave electrocardiographic abnormalities. Histopathologic characterization shows a lymphomonohistiocytic infiltrate in the interstitium and no penetration of the myocardial cells, unlike that for American trypanosomiasis (see Chapter 287). Progression of cardiac pathology to congestive heart failure has not been reported, and the perimyocarditis is usually self-limited and/or readily resolves with treatment.

**Meningoencephalitic Stage (Stage 2)**

Neurologic symptoms and signs are nonspecific, including irritability, insomnia, and irrational and inexplicable anxieties with frequent changes in mood and personality. Neurologic symptoms may precede invasion of the CNS by the organisms. In untreated *T. brucei rhodesiense* infections, CNS invasion occurs within 3-6 wk and is associated with recurrent bouts of headache, fever, weakness, and signs of acute toxemia. Tachycardia may be evidence of myocarditis. Death occurs in 6-9 mo as a result of secondary infection or cardiac failure.

In Gambian HAT, cerebral symptoms appear within 2 yr after the acute symptoms. An increase in drowsiness during the day and insomnia at night reflect the continuous progression of infection and may be accompanied by anemia, leukopenia, and muscle wasting. Patients are also at increased risk for infection.

The chronic, diffuse meningoencephalitis without localizing symptoms is the form referred to as sleeping sickness. Drowsiness and an uncontrollable urge to sleep are the major features of this stage of the disease and become almost continuous in the terminal stages. Tremor or rigidity with stiff and ataxic gait, suggest involvement of the basal ganglia. Psychotic changes occur in almost one third of untreated patients. Although untreated disease has been thought to be uniformly fatal, there is prospective evidence that, in rare cases, some individuals remain asymptomatic, are able to clear parasitemia, and occasionally become seronegative.

**DIAGNOSIS**

Definitive diagnosis can be established during the early stages by examination of a fresh, thick blood smear, which permits visualization of the motile active forms (Fig. 286-1). HAT can also be detected from blood using a variety of sensitive techniques: quantitative buffy coat smears and mini anion exchange resins are common examples. The card agglutination trypanosomiasis test is of value for epidemiologic purposes and in screening for *T. brucei gambiense*. Dried, Giemsa-stained smears should be examined for the detailed morphologic features of the organisms. If a thick blood or buffy coat smear is negative, concentration techniques may help. Aspiration of an enlarged lymph node can also be used to obtain material for parasitologic examination. If positive, cerebrospinal fluid should also be examined for the organisms. The presence of trypanosomes, or 5 white blood cells/µL, or both, is indicative of stage 2 disease. If trypanosomes are absent in the cerebrospinal fluid, some authorities use a count of 20 white blood cells/µL as a cutoff for diagnosing late-stage disease. Because the white blood cell count in the cerebrospinal fluid is critical in making treatment decisions, methods for improving cell counting, such as the use of disposable cell counters and combining multiple counts, have been proposed.

Figure 286-1 Trypanosoma brucei sp. trypomastigotes in thick blood smear stained with Giemsa (left) and thin blood smear stained with Wright-Giemsa (right). (From the Centers for Disease Control and Prevention [CDC]. Laboratory identification of parasites of public health concern. Trypanosomiasis, African. Available at: http://www.dpd.cdc.gov/dpdx/HTML/ImageLibrary/TrypanosomiasisAfrican_il.htm)

Polymerase chain reaction–based tests have been shown to be highly sensitive and specific, but these require advanced laboratory facilities. Field-based loop-mediated isothermal amplification tests have been developed but need further validation. Low cost, stable, but highly specific rapid tests such as the HAT Sero-Strip and HAT Sero-K-SeT that detect trypanosome-specific antibodies have been developed, and may prove to be useful for point-of-care diagnosis as the focus shifts from control to elimination.

**TREATMENT**

The choice of chemotherapeutic agents for treatment is dependent upon the stage of the infection and the causative organisms.

**Stage 1 Treatment**

Hematogenous forms of both Rhodesian and Gambian HAT can be treated with either suramin or pentamidine, which are better tolerated than drugs for stage 2 or CNS disease but are associated with substantial risks of toxicity. **Suramin** is a polysulphonated symmetrical naphthalene derivative given as a 10% solution for intravenous administration. A **test dose** (10 mg for children; 100-200 mg for adults) is initially administered to detect rare idiosyncratic reactions of shock and collapse. The dose for subsequent IV injections is 20 mg/kg (maximum: 1 g) administered on days 1, 3, 7, 14, and 21. Suramin is nephrotoxic, and thus a urolysis should be performed before each dose. Marked proteinuria, blood, or casts is a contraindication to continuation of suramin. Resistance is rare but has been reported.

**Pentamidine isethionate** (4 mg/kg/day IM for 7-10 days daily or on alternate days) concentrates to high levels in trypanosomes and is highly trypanocidal. It is better tolerated than suramin but carries significant risk of hypoglycemia, nephrotoxicity, hypotension, leukopenia, and liver enzyme elevation. Because of its potency, long half-life, and toxicity, short course treatment is desirable and is being investigated.

**Stage 2 Treatment**

The treatment of late stage *T. brucei gambiense* has substantially changed as a result of programmatic efforts of the WHO and the donation of large quantities of trypanosomicidal drugs, including eflornithine, pentamidine, suramin, and nifurtimox. **Combination eflornithine and nifurtimox** is the treatment of choice for *T. brucei gambiense* CNS infection. This regimen is noninferior to eflornithine monotherapy, and the duration of treatment is shorter. For combination therapy eflornithine is given at 400 mg/kg/day every 12 hr IV for 7 days, along with nifurtimox 15 mg/kg/day every 8 hr PO for 10 days. If nifurtimox is unavailable, eflornithine monotherapy can be given at a dose of 400 mg/kg/day, every 6 hr IV for 14 days. Adverse reactions to these regimens include fever, hypotension and seizures, with combination eflornithine and nifurtimox having less-frequent events.
**Melarsoprol** is an arsenical compound and is the only effective treatment for late *T. brucei rhodesiense* disease. Treatment of children is initiated at 0.36 mg/kg once daily IV, with gradually escalating doses every 1-5 days to 3.6 mg/kg once daily IV; treatment is usually 10 doses (18-25 mg/kg total dose). Treatment of adults is with melarsoprol 2-3.6 mg/kg once daily IV for 3 days; and after 1 wk, 3.6 mg/kg once daily IV for 3 days, which is repeated after 10-21 days. An alternative regimen is 2.2 mg/kg once daily for 10 days. Guidelines recommend 18-25 mg/kg total over 1 mo. Reactions such as fever, abdominal pain, and chest pain are rare but may occur during or shortly after administration. Serious toxic effects include encephalopathy and exfoliative dermatitis.

Because of the inherent logistic difficulties in administering intravenous therapy for late stage HAT, an active area of research is finding effective oral agents for late-stage HAT. Several promising agents are due to enter phase 2 trials. Efforts to decrease the toxicity of melarsoprol by making it more water soluble are also underway.

**PREVENTION**

A vaccine or consistently effective prophylactic therapy is not available and is particularly challenging because of the antigenic variation resulting from variant surface glycoproteins. A single injection of pentamidine (3-4 mg/kg IM) provides protection against Gambian trypanosomiasis for at least 6 mo, but the effectiveness against the Rhodesian form is uncertain.

While the progress in controlling HAT has been impressive, the increasing cost of treatment per case as the overall number of patients decline may lead to premature termination of intensive control efforts. Underreporting of cases remains a challenge. Vector control programs to control *Glossina* have been essential in controlling disease, coupled with the use of screens, traps, and sanitary measures. Encouraging neutral-colored clothing that is not attractive to the tsetse fly may reduce bites.

Using serology and parasitologic methods, mobile medical surveillance of the population at risk by specialized staff has been done, and strong collaboration between WHO, Medecins sans Frontieres, and African governments has shifted the burden of treatment to well-organized and funded national control programs. Ground spraying of insecticides, aerial spraying, and the use of cloth and live animal baits have proven successful. Transgenic techniques to restrict the ability of the tsetse fly to survive and transmit pathogens are also being developed.

The full genome of *T. brucei* with approximately 9,000 genes has been sequenced. Approximately 10% of these genes encode variant surface glycoproteins. This advance has helped identify genes relevant to the disease and its possible prevention, as well as the design of new antitrypanosomal drugs, including those that target specific metabolic pathways.

*Bibliography is available at Expert Consult.*
Bibliography
American trypanosomiasis or Chagas disease is a vector-borne disease caused by the protozoan Trypanosoma cruzi. Its natural vectors are the bloodsucking insects of the family Reduviidae. It can also be transmitted orally from contaminated food, vertically from mother to child, and through blood transfusion and organ transplantation. While acute American trypanosomiasis usually manifests as a nonspecific febrile illness, chronic Chagas disease is associated with cardiomyopathy and severe gastrointestinal abnormalities.

**ETIOLOGY**

American trypanosomiasis is caused by *T. cruzi*, a parasitic, flagellated kinetoplastid protozoan (Fig. 287-1). The main vectors for *T. cruzi* are insects of the order Triatominae, which includes *Triatoma infestans* (free roaming kissing bugs), *Rhodnius prolixus*, and *Panstrongylus megistus*.

**LIFE CYCLE**

*T. cruzi* has 3 recognizable morphogenetic phases: amastigotes, trypomastigotes, and epimastigotes (see Figs. 287-1 and 287-2). Amastigotes are intracellular forms found in mammalian tissues that are spherical and have a short flagellum but form clusters of oval shapes (pseudocysts) within infected tissues. Trypomastigotes are spindle-shaped, extracellular, nondividing forms that are found in blood and are responsible for both transmission of infection to the insect vector and cell-to-cell spread of infection. Epimastigotes are found in the midgut of the vector insect and multiply in the midgut and rectum of arthropods, differentiating into metacyclic trypomastigotes. Metacyclic trypomastigotes are the infectious form for humans and are released onto the skin of a human when the insect defecates close to the site of a bite, entering via the damaged skin or mucous membranes. Once in the host, these multiply intracellularly as amastigotes and are

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**Figure 287-1 Stages of Trypanosoma cruzi.** From left to right: amastigote, trypomastigote, and epimastigote. (From the Centers for Disease Control and Prevention [CDC]: Laboratory identification of parasites of public health concern. Trypanosomiasis, American. Available at: http://www.dpd.cdc.gov/dpdx/HTML/ImageLibrary/TrypanosomiasisAmerican_il.htm)
Chronic positive antibody titer. Up to 30% of infected persons proceed to terminate, and chronic. Acute infection is the most amenable to treatment. Indeterminate infection is asymptomatic but associated with a positive antibody titer. Up to 30% of infected persons proceed to chronic T. cruzi infection and develop symptoms. While it was initially believed that chronic infection without treatment does not clear, at least 3 well-documented cases of spontaneous resolution without treatment have been reported. It is still unclear how this parasitic protozoan escapes the immune system because, unlike African trypanosomiasis (see Chapter 286), antigenic variation is not observed. The T. cruzi genome has been fully sequenced and contains 12,000 genes, the most widely expanded among trypanosomatids, possibly reflect the ability of T. cruzi to invade a wide variety of host tissues. Significant strain-to-strain genome variability and extensive epigenetic modification of surface proteins have been found, likely contributing to immune evasion.

T. cruzi infection is primarily a zoonosis, and humans are incidental hosts. T. cruzi has a large sylvan reservoir and has been isolated from numerous animal species. The presence of reservoirs and vectors of T. cruzi and the socioeconomic and educational levels of the population are the most important risk factors for vector-borne transmission to humans. The arthropod vectors for T. cruzi are the reduviid insects or triatomines, variously known as wild bedbugs, assassin bugs, or kissing bugs. Insect vectors are found in rural, wooded areas and acquire infection through ingestion of blood from humans or animals with circulating trypomastigotes. Free roaming kissing bugs in the southwestern United States have been found to have fed on humans; some bugs contained T. cruzi.

Housing conditions are very important in the transmission chain. Incidence and prevalence of infection depends on the adaptation of the triatomines to human dwellings as well as the vector capacity of the species. Animal reservoirs of reduviid bugs include dogs, cats, rats, opossums, guinea pigs, monkeys, bats, and raccoons. Humans often released into the circulation when the cell dies. Bloodborne trypomastigotes circulate until they enter another host cell or are taken up by the bite of another insect, completing the life cycle.

**EPIDEMIOLOGY**
Chagas disease is found only in the Western hemisphere, specifically the Americas, particularly in southern Patagonia (Fig. 287-3). Natural transmission only occurs within this region, but the disease may arise elsewhere as a consequence of migration and transmission through contaminated blood. Multilateral efforts coordinated by the World Health Organization and the Pan-American Health Organization in large-scale vector control, blood donor screening to prevent transmission through transfusion, and case-finding and treatment of chronically infected mothers and newborn infants have effectively halted transmission in a number of areas around South America. In the Brazilian Amazon, vectorial transmission from T. infestans has been effectively interrupted through multicountry programs involving vector control, housing design improvements, and health education. The number of cases has dropped from a peak of 24 million in 1984 to a current estimate of 8-10 million. Vectorial transmission continues to drop in other regions, although challenges remain, including the emergence of disease in new areas thought to be Chagas-free, along with occasional re-emergence in previously controlled areas.

Infection is divided into 3 main phases: acute (Table 287-1), indeterminate, and chronic. Acute infection is the most amenable to treatment. Indeterminate infection is asymptomatic but associated with a positive antibody titer. Up to 30% of infected persons proceed to chronic T. cruzi infection and develop symptoms. While it was initially
Infectious and replicate. A local tissue reaction, the panosomes lyse the phagosomal membrane, escape into the cytoplasm, macrophages and are sequestered in membrane-bound vacuoles. Trypanosomes lyse the phagosomal membrane, escape into the cytoplasm, macrophages and are sequestered in membrane-bound vacuoles.

At the site of entry or puncture site, neutrophils, lymphocytes, macrophages and monocytes infiltrate. Trypanosomes lyse the phagosomal membrane, escape into the cytoplasm, macrophages and are sequestered in membrane-bound vacuoles. Trypanosomes lyse the phagosomal membrane, escape into the cytoplasm, macrophages and are sequestered in membrane-bound vacuoles. Trypanosomes lyse the phagosomal membrane, escape into the cytoplasm, macrophages and are sequestered in membrane-bound vacuoles. Trypanosomes lyse the phagosomal membrane, escape into the cytoplasm, macrophages and are sequestered in membrane-bound vacuoles. Trypanosomes lyse the phagosomal membrane, escape into the cytoplasm, macrophages and are sequestered in membrane-bound vacuoles. Trypanosomes lyse the phagosomal membrane, escape into the cytoplasm, macrophages and are sequestered in membrane-bound vacuoles.

Acute Disease

PATHOGENESIS

Acute Disease

At the site of entry or puncture site, neutrophils, lymphocytes, macrophages, and monocytes infiltrate. T. cruzi organisms are engulfed by macrophages and are sequestered in membrane-bound vacuoles. Trypanosomes lyse the phagosomal membrane, escape into the cytoplasm, and replicate. A local tissue reaction, the chagoma, develops, and the process extends to a local lymph node (see Fig. 287-2). Blood forms appear, and the process disseminates. Initial immune recognition of parasites is through innate pathways involving activation of multiple Toll-like receptors (TLRs) by different parasite substrates, including TLR 2/6, TLR 4, and TLR 9. Adaptive immunity is mediated by interferon-γ and interleukin-12 activation of T-cells and is modulated by interleukin-10 and transforming growth factor-β, which downregulates macrophage activity. The interplay of these cytokines is probably responsible, in part, for the variability in disease manifestations and the progression to chronic disease. Acute myocarditis likely occurs in all patients with acute disease but is frequently asymptomatic and may only be apparent on biopsy.

Chronic Disease

The pathophysiology of chronic Chagas disease is incompletely understood. Two main mechanisms are likely involved, although other factors may come into play. The first mechanism involves direct tissue destruction by low-level parasite persistence mediated by lymphocytic infiltration and fibrosis. The second mechanism involves molecular mimicry of host antigens by the parasite, resulting in autoantibodies that produce (1) an inflammatory reaction associated with direct damage to host tissue, and/or (2) direct stimulation of adrenergic and muscarinic cholinergic receptors associated with dysautonomia and increased risk of arrhythmia.

T. cruzi strains demonstrate selective parasitism for certain tissues. Most strains are myotropic and invade smooth, skeletal, and heart muscle cells. Attachment is mediated by specific receptors on the trypanosomes that attach to complementary glycoconjugates on the host cell surface. Attachment to cardiac muscle results in inflammation of the endocardium and myocardium, edema, focal necrosis in the contractile and conducting systems, perigangliitis, and lymphocytic inflammation. The heart becomes enlarged, and endocardial thrombosis or aneurysm may result. Right bundle-branch block is also common. Trypanosome parasites also attach to neural cells and reticuloendothelial cells. In patients with gastrointestinal tract involvement, myenteric plexus destruction leads to pathologic organ dilatation. Immunologic mechanisms for control of parasitism and resistance are not fully understood.

Figure 287-3 Estimated number of immigrants with Trypanosoma cruzi infection living in nonendemic countries. Data are supplied for Canada, Australia, and Japan in 2006; the United States in 2005; Spain in 2008; and other European countries in 2004–2006. (From Rassi A Jr, Rassi A, Marin-Neto JA: Chagas disease, Lancet 375:1388–1400, 2010, Fig. 2, p. 1391.)
understood. Despite strong acquired immunity, parasitologic cure in chronic infection is exceedingly rare. Antibodies involved with resistance to T. cruzi are related to the phase of infection. Immunoglobulin G antibodies, probably to several major surface antigens, mediate immunoprophagocytosis of T. cruzi by macrophages. Conditions that depress cell-mediated immunity increase the severity of T. cruzi infection. There is increasing evidence that host genetic factors play a significant role in progression and severity of chronic disease.

**CLINICAL MANIFESTATIONS**

**Acute Chagas disease** in children is usually asymptomatic or is associated with a mild febrile illness characterized by malaise, facial edema, and lymphadenopathy (see Table 287-1). Infants often demonstrate local signs of inflammation at the site of parasite entry, which is then referred to as a *chagoma*. Approximately 50% of children come to medical attention with the *Romaña sign* (unilateral, painless eye swelling), conjunctivitis, and preauricular lymphadenitis. Patients complain of fatigue and headache. Fever can persist for 4-5 wk. More severe systemic presentations can occur in children younger than 2 yr old and may include lymphadenopathy, hepatosplenomegaly, and meningoencephalitis. A cutaneous morbilliform eruption can accompany the acute syndrome. Anemia, lymphocytosis, hepatitis, and thrombocytopenia have also been described.

The heart, central nervous system, peripheral nerve ganglia, and reticuloendothelial system are often heavily parasitized. The heart is the primary target organ. The intense parasitism can result in acute inflammation and in 4-chamber cardiac dilation. Diffuse myocarditis and inflammation of the conduction system can lead to the development of fibrosis. Histologic examination reveals the characteristic *pseudocysts*, which are the intracellular aggregates of amastigotes.

**Intrauterine infection** in pregnant women can cause spontaneous abortion or premature birth. In children with congenital infection, severe anemia, hepatosplenomegaly, jaundice, and convulsions can mimic congenital cytomegalovirus infection, toxoplasmosis, and erythroblastosis fetalis. *T. cruzi* can be visualized in the cerebrospinal fluid in meningoencephalitis. Children usually undergo spontaneous remission in 8-12 wk and enter an indeterminate phase with lifelong low-grade parasitemia and development of antibodies to many *T. cruzi* cell

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**Table 287-1 Vector-Borne Transmission and Life Cycle of Trypanosoma Cruzi**

<table>
<thead>
<tr>
<th>Geographical Distribution</th>
<th>Predominant Population</th>
<th>Incubation Time</th>
<th>Clinical Presentation</th>
<th>Diagnosis</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vectorial</td>
<td>Endemic countries</td>
<td>Children and adolescents</td>
<td>1-2 wk</td>
<td>Asymptomatic; fever, malaise, lymphadenopathy, hepatosplenomegaly, subcutaneous edema; signs of portal of entry (<em>Romaña sign</em>, chagoma); myocarditis, meningoencephalitis</td>
<td>Parasite detection by microscopy; fresh blood specimen; stained blood smears; buffy coat preparation (microhematocrit technique); or serum precipitate (Strout technique)</td>
</tr>
<tr>
<td>Transfusion-based</td>
<td>Endemic and nonendemic countries</td>
<td>Adults</td>
<td>8-120 days</td>
<td>Same as for vectorial but excluding signs of portal of entry</td>
<td>Same as for vectorial</td>
</tr>
<tr>
<td>Congenital</td>
<td>Endemic and nonendemic countries</td>
<td>Neonates and children younger than 1 yr</td>
<td>Up to a few weeks</td>
<td>Asymptomatic; abortion, neonatal death, prematurity, low birthweight, low Apgar score; hypotonicity, fever, hepatosplenomegaly, respiratory distress, anemia; myocarditis, meningoencephalitis, megaviscera, edema</td>
<td>Microhematocrit with cord blood or peripheral blood from neonate; 2 or more samples in the 1st mo of life; immunoglobulin G serology</td>
</tr>
<tr>
<td>Oral</td>
<td>Amazon basin and regional outbreaks</td>
<td>Individuals of any age from the same family or community</td>
<td>3-22 days</td>
<td>Same as for transfusion-based plus headache, myalgia, vomiting, abdominal pain, jaundice, diarrhea, and digestive hemorrhage</td>
<td>Same as for vectorial</td>
</tr>
<tr>
<td>Reactivation-based</td>
<td>Endemic and nonendemic countries</td>
<td>Patients with associated immunosuppressive states</td>
<td>Variable</td>
<td>Same as for transfusion-based plus panniculitis, subcutaneous parasite-containing nodules, and skin ulcers</td>
<td>Same as for vectorial, and parasites can also be detected in tissues by microscopy or polymerase chain reaction</td>
</tr>
</tbody>
</table>

*Refers to symptomatic cases; because 95% of acute infections from vectorial transmission are asymptomatic and 5-10% of patients with acute symptoms die, estimated mortality in this phase of infection is between 1 in 200 and 1 in 400.

†Depends on the underlying disease and the patient's clinical condition.

Chronic Chagas disease may be asymptomatic or symptomatic. The most common presentation of chronic *T. cruzi* infection is cardiomyopathy, manifested by congestive heart failure, arrhythmia, and thromboembolic events. Electrocardiographic abnormalities include partial or complete atrioventricular block and right bundle-branch block. Left bundle-branch block is unusual. Pathologic examination of infected heart muscle reveals muscle atrophy, myonecrosis, myocytolysis, fibrosis, and lymphocytic infiltration. Myocardial infarction has been reported and may be secondary to left apical aneurysm embolization or necrotizing arteriolitis of the microvasculature. Left ventricular apical aneurysms are pathognomonic of chronic chagasic cardiomyopathy.

Gastrointestinal manifestations of chronic Chagas disease occur in 8-10% of patients and involve a diminution in the Auerbach plexus and Meissner plexus. There are also preganglionic lesions and a reduction in the number of dorsal motor nuclear cells of the vagus nerve. Characteristically, this involvement presents clinically as megaaesophagus and megacolon. Sigmoid dilation, volvulus, and fecalomas are often found in megacolon. Loss of ganglia in the esophagus results in abnormal dilation; the esophagus can reach up to 26 times its normal weight and hold up to 2 L of excess fluid. Megaaesophagus presents as dysphagia, odynophagia, and cough. Esophageal body abnormalities occur independently of lower esophageal dysfunction. Megaaesophagus can lead to esophagitis and cancer of the esophagus. Aspiration pneumonia and pulmonary tuberculosis are also more common in patients with megaaesophagus.

**Immunocompromised Persons**

*T. cruzi* infections in immunocompromised persons may be caused by transmission from an asymptomatic donor of blood products or reactivation of prior infection. Organ donation to allograft recipients can result in a devastating form of the illness. Cardiac transplantation for Chagas cardiomyopathy has resulted in reactivation, despite prophylaxis and postoperative treatment with benznidazole. HIV infection also leads to reactivation in approximately 20% of cases; cerebral lesions are more common in these patients and can mimic those of toxoplastic encephalitis. Myocarditis is also commonly observed, and secondarily, tremors and seizures (hemolysis in patients with glucose-6-phosphate dehydrogenase deficiency) may be of benefit in some HIV coinfected patients. In immunocompromised patients at risk for reactivation, serologic testing and close monitoring are necessary.

**DIAGNOSIS**

A careful history with attention to geographic origin and travel is important. A peripheral blood smear or a Giemsa-stained smear during the acute phase of illness may show motile trypanosomes, which is diagnostic for Chagas disease (see Fig. 287-1). These are only seen in the 1st 6-12 wk of illness. Buffy coat smears may improve yield.

Most persons seek medical attention during the chronic phase of the disease, when parasites are not found in the bloodstream and clinical symptoms are not diagnostic. Serologic testing is used for diagnosis, most commonly enzyme-linked immunosorbent assay, indirect hemagglutination, and indirect fluorescent antibody testing. No single serology test is sufficiently reliable to make the diagnosis, so repeat or parallel testing using a different method or antigen is required to confirm the result of an initial positive serologic test. In the case of discordant results, a third test may be employed. Confirmatory tests used typically include the radiologic immunoprecipitation assay (used as a confirmatory test in blood donors in the United States) and Western blot assays based on trypanomastigote excreted-secreted antigens. Nonimmunologic methods of diagnosis are also available. Mouse inoculation and xenodiagnosis (allowing uninfected reduviid bugs to feed on a patient's blood and examining the intestinal contents of those bugs 30 days after the meal) are quite sensitive. Parasites may also be cultured in Novy-MacNeal-Nicolle media. Polymerase chain reaction of nuclear and kinetoplast DNA sequences have been developed and can be highly sensitive in acute disease, but are less reliable for the detection of chronic disease. Polymerase chain reaction is not sufficiently sensitive for blood screening and was only positive in 1 of 22 radiologic immunoprecipitation assay--confirmed donors in the United States. Moreover, there is significant variability among methods and parasite strains. An international collaborative study has validated 4 methods that have the best performance characteristics for widespread use. Diagnosis of congenital transmission in newborns cannot be made at birth with serology because of the presence of maternal antibodies in the 1st 6 mo of life. Microscopic examination, parasite culture, or polymerase chain reaction can be used. However, a serologic test at 6-12 mo is recommended to completely exclude infection.

**TREATMENT**

Biochemical differences between the metabolism of American trypanosomes and that of mammalian hosts have been exploited for chemotherapy. Trypanosomes are very sensitive to oxidative radicals and do not possess catalase or glutathione reductase/glutathione peroxidase, which are key enzymes in scavenging free radicals. All trypanosomes also have an unusual reduced nicotinamide adenine dinucleotide phosphate--dependent disulfide reductase. Drugs that stimulate H2O2 generation or prevent its use are potential trypanosomicidal agents. Other biochemical pathways that have been targeted include ergosterol synthesis using azole compounds and the hypoxanthine-guanine phosphoribosyltransferase pathway using allopurinol.

Drug treatment for *T. cruzi* infection is currently limited to nifurtimox and benznidazole. Both are effective against trypanomastigotes and amastigotes and have been used to eradicate parasites in the acute stages of infection. Treatment responses vary according to the phase of Chagas disease, duration of treatment, dose, age of the patient, and geographic origin of the patient. For acute disease, the average cure rate is approximately 60-80%, while for chronic cases, the cure rate is less than 20%. Neither drug is safe in pregnancy.

Benznidazole is a nitroimidazole derivative that may be slightly more effective than nifurtimox. Although benznidazole is capable of inducing the production of free oxide radicals, the dose at which it is given is not effective for this mode of action. Instead, its nitro reduction intermediates may form covalent bonds or interact in other ways with parasitic DNA, lipids, and proteins and cause damage to parasite components. The recommended treatment regimen for children younger than 12 yr of age is 10 mg/kg/day divided twice daily PO for 60 days, and for those older than 12 yr of age, it is 5-7 mg/kg/day divided twice daily PO for 60 days. This drug is associated with significant toxicity, including rash, photosensitivity, peripheral neuritis, granulocytopenia, and thrombocytopenia.

Nifurtimox generates highly toxic oxygen metabolites through the action of nitroreductases, which produce unstable nitro anion radicals, which, in turn, react with oxygen to produce peroxide and superoxide free radicals. The treatment regimen for children 1-10 yr of age is 15-20 mg/kg/day divided 4 times a day PO for 90 days; for children 11-16 yr of age, 12.5-15 mg/kg/day divided 4 times a day PO for 90 days; and for children older than 16 yr of age, 8-10 mg/kg/day divided 3 or 4 times a day PO for 90-120 days. Nifurtimox is associated with weakness, anorexia, gastrointestinal disturbances, toxic hepatitis, tremors, and seizures (hemolysis in patients with glucose-6-phosphate dehydrogenase deficiency).

Although treatment is generally recommended for acute Chagas disease and is effective in the early stages of infection, the treatment of asymptomatic (or indeterminate) infection and symptomatic chronic disease is controversial. Multiple trials with long-term follow-up have yielded mixed results, with an estimated response rate of 6-20% for chronic disease. The definition of response in itself is...
problematic, and parasitologic cure is nearly impossible to demonstrate given the limitations of the sensitivity and specificity of detection methods. Instead, serologic conversion is seen as an appropriate treatment response, although some patients who achieve this still eventually develop symptoms. Recommendations from authorities are mixed, with some advocating for treatment regardless of disease phase and others recommending against treatment because of uncertain benefit and the toxicity of the drugs involved. Proponents of the latter approach instead advocate symptomatic treatment of disease manifestations.

Treatment of congestive heart failure is generally in line with recommendations for management of dilated cardiomyopathy from other causes. β-Blockers have been validated in the management of these patients. Digitalis toxicity occurs frequently in patients with Chagas cardiomyopathy. Pacemakers may be necessary in cases of severe heart block. Although cardiac transplantation has been used successfully in chagasic patients, it is reserved for those with the most severe disease manifestations. Plasmapheresis to remove antibodies with adrenergic activity has been proposed for refractory patients, as this approach has been tried and has worked in patients with dilated cardiomyopathy from other causes. However, its application to Chagas disease is unproven.

A light, balanced diet is recommended for megaesophagus. Surgery or dilation of the lower esophageal sphincter treats megaesophagus; pneumatic dilation is the superior mode of therapy. Nitrates and nifedipine have been used to reduce lower esophageal sphincter pressure in patients with megaesophagus. Treatment of megacolon is surgical and symptomatic. Treatment of meningoencephalitis is also supportive.

In accidental infection when parasitic penetration is certain, treatment should be initiated immediately and continued for 10-15 days. Blood is usually collected and tested for seroconversion at 15, 30, and 60 days.

**PREVENTION**

Massive coordinated vector control programs under the auspices of the World Health Organization and Pan-American Health Organization and the institution of widespread blood donor screening and targeted surveillance of chronically infected mothers and infants at risk have effectively eliminated or at least drastically reduced transmission in most endemic countries. As Chagas disease remains linked to poverty, improvement of living conditions is likewise essential to successful control and eradication. Education of residents in endemic areas, use of bed nets, use of insecticides, and destruction of adobe houses that harbor reduviid bugs are effective methods to control the bug population. Synthetic pyrethroid insecticides help keep houses free of vectors for up to 2 yr and have low toxicity for humans. Paints incorporating insecticides have also been used. A therapeutic vaccine composed of bivalent recombinant *T. cruzi* antigens has been shown to be effective in preclinical proof-of-concept animal models and is currently undergoing further development.

Blood transfusions in endemic areas are a significant risk. Gentian violet, an amphophilic cationic agent that acts photodynamically, has been used to kill the parasite in blood. Photoirradiation of blood containing gentian violet and ascorbate generates free radicals and superoxide anions that are trypanosomicidal. Mepacrine and maprotiline have also been used to eradicate the parasite in blood transfusions.

Because immigrants can carry this disease to nonendemic areas, serologic testing should be performed in blood and organ donors from endemic areas. Potential seropositive donors can be identified by determining whether they have been or have spent extensive time in an endemic area. Questionnaire-based screening of potentially infected blood and organ donors from areas endemic for infection can reduce the risk for transmission. Seropositivity should be considered a contraindication to organ donation, particularly for heart transplantation.

*Bibliography is available at Expert Consult.*
Bibliography
Malaria is an acute and chronic illness characterized by paroxysms of fever, chills, sweats, fatigue, anemia, and splenomegaly. It has played a major role in human history, causing harm to more people than perhaps any other infectious disease. Malaria is of overwhelming importance in the developing world today, with an estimated 300-500 million cases and more than 1 million deaths each year. Most malarial deaths occur among infants and young children. Although malaria is not endemic in the United States, approximately 1,000 imported cases are recognized in the United States each year. Physicians practicing in nonendemic areas should consider the diagnosis of malaria in any febrile child who has returned from a malaria-endemic area within the previous year, because delay in diagnosis and treatment can result in severe illness or death.

ETIOLOGY
Malaria is caused by intracellular *Plasmodium* protozoa transmitted to humans by female *Anopheles* mosquitoes. Prior to 2004, only 4 species of *Plasmodium* were known to cause malaria in humans: *P. falciparum*, *P. malariae*, *P. ovale*, and *P. vivax*. In 2004 *P. knowlesi* (a primate malaria species) was also shown to cause human malaria, and cases of *P. knowlesi* infection have been documented in Malaysia, Indonesia, Singapore, and the Philippines. Malaria also can be transmitted through blood transfusion, use of contaminated needles, and transplacentally from a pregnant woman to her fetus. The risk for blood transmission is small and decreasing in the United States, but may occur by way of whole blood, packed red blood cells, platelets, leukocytes, and organ transplantation.

EPIDEMIOLOGY
Malaria is a major worldwide problem, occurring in more than 100 countries with a combined population of more than 1.6 billion people (Fig. 288-1). The principal areas of transmission are Africa, Asia, and South America. *P. falciparum* and *P. malariae* are found in most malarious areas. *P. falciparum* is the predominant species in Africa, Haiti, and New Guinea. *P. vivax* predominates in Bangladesh, Central America, India, Pakistan, and Sri Lanka. *P. vivax* and *P. falciparum* predominate in Southeast Asia, South America, and Oceania. *P. ovale* is the least-common species and is transmitted primarily in Africa. Transmission of malaria has been eliminated in most of North America (including the United States), Europe, and the Caribbean, as well as Australia, Chile, Israel, Japan, Korea, Lebanon, and Taiwan.

Most cases of malaria in the United States occur among previously infected visitors to the United States from endemic areas and among U.S. citizens who travel to endemic areas without appropriate chemoprophylaxis. The most common regions of acquisition of the 10,100 cases of malaria reported to the Centers for Disease Control and Prevention (CDC) among U.S. citizens between 1985 and 2001 were sub-Saharan Africa (58%), Asia (18%), and the Caribbean and Central or South America (16%). Most of the fatal cases were caused by *P. falciparum* (94% or 66 of the 70 cases), of which 47 (71%) were acquired in sub-Saharan Africa. More than 60% of imported cases of *P. vivax* come from Asia; the remaining species usually come from Africa. Rare cases of apparent locally transmitted malaria have been reported since the 1950s. These cases are likely a result of transmission from untreated and often asymptomatic infected individuals from malaria endemic countries who travel to the United States and infect local mosquitoes or to infected mosquitoes from malaria-endemic areas that are transported to the United States on airplanes.
PATHOGENESIS

Plasmodium species exist in a variety of forms and have a complex life cycle that enables them to survive in different cellular environments in the human host (sexual phase) and the mosquito (sexual phase) (Fig. 288-2). A marked amplification of Plasmodium, from approximately $10^2$ to as many as $10^{10}$ organisms, occurs during a 2-step process in humans, with the first phase in hepatic cells (exoerythrocytic phase) and the second phase in the red cells (erythrocytic phase). The exoerythrocytic phase begins with inoculation of sporozoites into the bloodstream by a female Anopheles mosquito. Within minutes, the sporozoites enter the hepatocytes of the liver, where they develop and multiply asexually as a schizont. After 1-2 wk, the hepatocytes rupture and release thousands of merozoites into the circulation. The tissue schizonts of P. falciparum, P. malariae, and apparently P. knowlesi rupture once and do not persist in the liver. There are 2 types of tissue schizonts for P. ovale and P. vivax. The primary type ruptures in 6-9 days, and the secondary type remains dormant in the liver cell for weeks, months, or as long as 5 yr before releasing merozoites and causing relapse of infection. The erythrocytic phase of Plasmodium asexual development begins when the merozoites from the liver penetrate erythrocytes. Once inside the erythrocyte, the parasite transforms into the ring form, which then enlarges to become a trophozoite. These latter 2 forms can be identified with Giemsa stain on blood smear, the primary means of confirming the diagnosis of malaria (Fig. 288-3). The trophozoite multiplies asexually to produce a number of small erythrocytic merozoites that are released into the bloodstream when the erythrocyte membrane ruptures, which is associated with fever. Over time, some of the merozoites develop into male and female gametocytes that complete the Plasmodium life cycle when they are ingested during a blood meal by the female anopheline mosquito. The male and female gametocytes fuse to form a zygote in the stomach cavity of the mosquito. After a series of further transformations, sporozoites enter the salivary gland of the mosquito and are inoculated into a new host with the next blood meal.

Four important pathologic processes have been identified in patients with malaria: fever, anemia, immunopathologic events, and tissue anoxia. Fever occurs when erythrocytes rupture and release merozoites into the circulation. Anemia is caused by hemolysis, sequestration of erythrocytes in the spleen and other organs, and bone marrow suppression. Immunopathologic events that have been documented in patients with malaria include excessive production of proinflammatory cytokines, such as tumor necrosis factor, that may be responsible for most of the pathology of the disease, including tissue anoxia; clonal activation resulting in both hypergammaglobulinemia and the formation of immune complexes; and immunosuppression. Cytoadherence of infected erythrocytes to vascular endothelium occurs in P. falciparum malaria and may lead to obstruction of blood flow and capillary damage, with resultant vascular leakage of blood, protein, and fluid and tissue anoxia. In addition, hypoglycemia and lactic acidemia are caused by anaerobic metabolism of glucose. The cumulative effects of these pathologic processes may lead to cerebral, cardiac, pulmonary, intestinal, renal, and hepatic failure.

Immunity after Plasmodium species infection is incomplete, preventing severe disease but still allowing future infection. In some cases, parasites circulate in small numbers for a long time but are prevented from rapidly multiplying and causing severe illness. Repeated episodes of infection occur because the parasite has developed a number of immune evasive strategies, such as intracellular replication, vascular cytoadherence that prevents infected erythrocytes from circulating through the spleen, rapid antigenic variation, and alteration of the host immune system resulting in partial immune suppression. The human host response to Plasmodium infection includes natural immune mechanisms that prevent infection by other Plasmodium species, such as those of birds or rodents, as well as several alterations in erythrocyte physiology that prevent or modify malarial infection. Erythrocytes containing hemoglobin S (sickle erythrocytes) resist malaria parasite growth, erythrocytes lacking Duffy blood group antigen are resistant to P. vivax, and erythrocytes containing hemoglobin F (fetal hemoglobin) and ovalocytes are resistant to P. falciparum. In hyperendemic areas, newborns rarely become ill with malaria, in part because of passive maternal antibody and high levels of fetal hemoglobin. Children 3 mo to 2-5 yr of age have little specific immunity to malaria species and therefore suffer yearly attacks of debilitating and potentially fatal disease. Immunity is subsequently acquired, and severe cases of malaria become less common. Severe disease may occur during pregnancy, particularly first pregnancies or after extended residence outside the endemic region. In general, extracellular Plasmodium organisms are targeted by antibody, whereas intracellular organisms are targeted by cellular defenses such as T lymphocytes, macrophages, polymorphonuclear leukocytes, and the spleen.
Figure 288-2 Life cycle of Plasmodium spp. (From Centers for Disease Control and Prevention [CDC]: Laboratory diagnosis of malaria: Plasmodium spp. Available at: http://www.dpd.cdc.gov/dpdx/HL/ImageLibrary/M-R/Malaria/body_Malaria_il1.h)

Figure 288-3 Giemsa-stained thick (A) and thin (B-H) smears used for the diagnosis of malaria and the speciation of Plasmodium parasites. A, Multiple signet-ring Plasmodium falciparum trophozoites, which are visualized outside erythrocytes. B, A multiply infected erythrocyte containing signet-ring P. falciparum trophozoites, including an accolade form positioned up against the inner surface of the erythrocyte membrane. C, Banana-shaped gametocyte unique to P. falciparum. D, Ameboid trophozoite characteristic of Plasmodium vivax. Both P. vivax– and Plasmodium ovale–infected erythrocytes exhibit Schüffner dots and tend to be enlarged compared with uninfected erythrocytes. E, P. vivax schizont. Mature P. falciparum parasites, by contrast, are rarely seen on blood smears because they sequester in the systemic microvasculature. F, P. vivax spherical gametocyte. G, P. ovale trophozoite. Note Schüffner dots and ovoid shapes of the infected erythrocyte. H, Characteristic band form trophozoite of Plasmodium malariae, containing intracellular pigment hemozoin. (A, B, and F from Centers for Disease Control and Prevention [CDC]: DPDx: laboratory identification of parasites of public health concern. Available at: http://www.dpd.cdc.gov/dpdx/. C, D, E, G, and H courtesy of David Wyler, Newton Centre, MA.)
CLINICAL MANIFESTATIONS

Children and adults are asymptomatic during the initial phase of infection, the incubation period of malaria infection. The usual incubation periods are 9-14 days for *P. falciparum*, 12-17 days for *P. vivax*, 16-18 days for *P. ovale*, and 18-40 days for *P. malariae*. The incubation period can be as long as 6-12 mo for *P. vivax* and can also be prolonged for patients with partial immunity or incomplete chemoprophylaxis. A prodrome lasting 2-3 days is noted in some patients before parasites are detected in the blood. Prodromal symptoms include headache, fatigue, anorexia, myalgia, slight fever, and pain in the chest, abdomen, and joints.

The classic presentation of malaria is seldom noted with other infectious diseases and consists of paroxysms of fever alternating with periods of fatigue but otherwise relative wellnes. Febrile paroxysms are characterized by high fever, sweats, and headache, as well as myalgia, back pain, abdominal pain, nausea, vomiting, diarrhea, pallor, and jaundice. Paroxysms coincide with the rupture of schizonts that occurs every 48 hr with *P. vivax* and *P. ovale*, resulting in fever spikes every other day. Rupture of schizonts occurs every 72 hr with *P. malariae*, resulting in fever spikes every third or fourth day. Periodicity is less apparent with *P. falciparum* and mixed infections and may not be apparent early on in infection, when parasite broods have not yet synchronized. Patients with primary infection, such as travelers from nonendemic regions, also may have irregular symptomatic episodes for 2-3 days before regular paroxysms begin. Children with malaria often lack typical paroxysms and have nonspecific symptoms, including fever (may be low-grade but is often greater than 40°C [104°F]), headache, drowsiness, anorexia, nausea, vomiting, and diarrhea. Distinctive physical signs may include splenomegaly (common), hepatomegaly, and pallor as a consequence of anemia. Typical laboratory findings include anemia, thrombocytopenia, and a normal or low leukocyte count. The erythrocyte sedimentation rate is often elevated.

*P. falciparum* is the most severe form of malaria and is associated with higher density parasitemia and a number of complications (Fig. 288-4). The most common serious complication is severe anemia, which also is associated with other malaria species. Serious complications that appear unique to *P. falciparum* include cerebral malaria, acute renal failure, respiratory distress from metabolic acidosis, algid malaria and bleeding diatheses (see “Complications of Plasmodium falciparum Malaria” below and Table 288-1). The diagnosis of *P. falciparum* malaria in a nonimmune individual constitutes a medical emergency. Severe complications and death can occur if appropriate therapy is not instituted promptly. In contrast to malaria caused by *P. ovale*, *P. vivax*, and *P. malariae*, which usually results in parasitemias of less than 2%, malaria caused by *P. falciparum* can be associated with parasitemia levels as high as 60%. The differences in parasitemia reflect the fact that *P. falciparum* infects both immature and mature erythrocytes, whereas *P. ovale* and *P. vivax* primarily infect immature erythrocytes and *P. malariae* infects only mature erythrocytes. Like *P. falciparum*, *P. knowlesi* has a 24 hr replication cycle and can also lead to very-high-density parasitemia.

*P. vivax* malaria has long been considered less severe than *P. falciparum* malaria, but recent reports suggest that in some areas of Indonesia it is as frequent a cause of severe disease and death as *P. falciparum*. Severe disease and death from *P. vivax* are usually a consequence of severe anemia and sometimes of splenic rupture. *P. ovale* malaria is the least-common type of malaria. It is similar to *P. vivax* malaria and commonly is found in conjunction with *P. falciparum* malaria. *P. malariae* is the mildest and most chronic of all malaria infections. Nephrotic syndrome is a rare complication of *P. malariae* infection that is not observed with any other human malaria species. Nephrotic syndrome associated with *P. malariae* infection is poorly responsive to steroids. Low-level, undetected *P. malariae* infection may be present for years and is sometimes unmasked by immunosuppression or physiologic stress such as splenectomy or corticosteroid treatment.

Recrudescence after a primary attack may occur from the survival of erythrocyte forms in the bloodstream. Long-term relapse is caused by release of merozoites from an exoerythrocytic source in the liver, which occurs with *P. vivax* and *P. ovale*, or from persistence within the

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**Table 288-1** World Health Organization Criteria for Severe Malaria, 2000

<table>
<thead>
<tr>
<th>Impaired consciousness</th>
<th>Prostration</th>
<th>Respiratory distress</th>
<th>Multiple seizures</th>
<th>Jaundice</th>
<th>Hemoglobinuria</th>
<th>Abnormal bleeding</th>
<th>Severe anemia</th>
<th>Circulatory collapse</th>
<th>Pulmonary edema</th>
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<tr>
<td>Recrudescence</td>
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erythrocyte, which occurs with *P. malariae* and rarely with *P. falciparum*. A history of typical symptoms in a person more than 4 wk after return from an endemic area is therefore more likely to be *P. vivax*, *P. ovale*, or *P. malariae* infection than *P. falciparum* infection. In the most recent survey of malaria in the United States among individuals in whom a malaria species was identified, 48.6% of cases were caused by *P. falciparum*, 22.1% by *P. vivax*, 3.5% by *P. malariae*, and 2.5% by *P. ovale*. Ninety-four percent of *P. falciparum* infections were diagnosed within 30 days of arrival in the United States, and 99% within 90 days of arrival. In contrast, 50.7% of *P. vivax* cases occurred more than 30 days after arrival in the United States.

**Congenital malaria** is acquired from the mother prenatally or perinatally and is a serious problem in tropical areas but is rarely reported in the United States. In endemic areas, congenital malaria is an important cause of abortions, miscarriages, stillbirths, premature births, intrauterine growth retardation, and neonatal deaths. Congenital malaria usually occurs in the offspring of a nonimmune mother with *P. vivax* or *P. malariae* infection, although it can be observed with any of the human malaria species. The first sign or symptom most commonly occurs between 10 and 30 days of age (range: 14 hr to several months of age). Signs and symptoms include fever, restlessness, drowsiness, pallor, jaundice, poor feeding, vomiting, diarrhea, cyanosis, and hepatosplenomegaly. Malaria is often severe during pregnancy and may have an adverse effect on the fetus or neonate, resulting in intrauterine growth retardation and low birthweight, even in the absence of transmission from mother to child.

**DIAGNOSIS**

Any child who presents with fever or unexplained systemic illness and has traveled or resided in a malaria-endemic area within the previous year should be assumed to have life-threatening malaria until proven otherwise. Malaria should be considered regardless of the use of chemoprophylaxis. Important criteria that suggest *P. falciparum* malaria include symptoms occurring less than 1 mo after return from an endemic area, more than 2% parasitemia, ring forms with double chromatin dots, and erythrocytes infected with more than 1 parasite.

The diagnosis of malaria is established by identification of organisms on Giemsa-stained smears of peripheral blood (see Fig. 288-3) or by rapid immunochromatographic assay (rapid diagnostic test). Giemsa stain is superior to Wright stain or Leishman stain. Both thick and thin blood smears should be examined. The concentration of erythrocytes on a **thick smear** is 20-40 times that on a thin smear and is used to quickly scan large numbers of erythrocytes. The **thin smear** allows for positive identification of the malaria species and determination of the percentage of infected erythrocytes and is useful in following the response to therapy. Identification of the species is best made by an experienced microscopist and checked against color plates of the various *Plasmodium* species (see Fig. 288-3). Morphologically it is impossible to distinguish *P. knowlesi* from *P. malariae*, so polymerase chain reaction detection by a reference lab or the CDC is required. Although *P. falciparum* is most likely to be identified from blood just after a febrile paroxysm, the timing of the both thick and thin smears is less important than their being obtained several times a day over a period of 3 successive days. A single negative blood smear does not exclude malaria. Most symptomatic patients with malaria will have detectable parasites on thick blood smears within 48 hr. For nonimmune persons, symptoms typically occur 1-2 days before parasites are detectable on blood smear.

The BinaxNOW Malaria test is approved by the FDA for rapid diagnosis of malaria. This immunochromatographic test for *P. falciparum* histidine-rich protein (HRP2) and aldolase is approved for testing for *P. falciparum* and *P. vivax*. Aldolase is present in all 5 of the malaria species that infect humans. Thus, a positive result for *P. vivax* could be because of *P. ovale* or *P. malariae* infection. Sensitivity and specificity for *P. falciparum* (94-99% and 94-99%, respectively) and *P. vivax* (87-93% and 99%, respectively) are good, but sensitivity for *P. ovale* and *P. malariae* is lower. Sensitivity for *P. falciparum* decreases at lower levels of parasitemia, so microscopy is still advised in areas where expert microscopy is available. The test is simple to perform and can be done in the field or laboratory in 10 min. Polymerase chain reaction is even more sensitive than microscopy but is technically more complex. It is available in some reference laboratories, but the time delay in availability of results generally precludes its use for acute diagnosis of malaria.

**DIFFERENTIAL DIAGNOSIS**

The differential diagnosis of malaria is broad and includes viral infections such as influenza and hepatitis, sepsis, pneumonia, meningitis, encephalitis, endocarditis, gastroenteritis, pyelonephritis, babesiosis, brucellosis, leptospirosis, tuberculosis, relapsing fever, typhoid fever, yellow fever, viral hemorrhagic fevers, amebic liver abscess, Hodgkin disease, and collagen vascular disease.

**TREATMENT**

Physicians caring for patients with malaria or traveling to endemic areas need to be aware of current information regarding malaria because resistance to antimalarial drugs has complicated therapy and prophylaxis. The best source for such information is the CDC Malaria webpage (http://www.cdc.gov/malaria/diagnosis_treatment/treatment.hl), which provides up-to-date guidelines for malaria treatment, and an algorithm for an approach to malaria treatment (Fig. 288-5). In cases in which treatment is unclear or complex, the CDC Malaria Hotline, which is available to physicians 24 hr a day (770-488-7788 from 8:00 AM to 4:30 PM Eastern Standard Time [EST] and 770-488-7100 from 4:30 PM to 8:00 AM EST, and on weekends and holidays; ask the operator to page the person on call for the Malaria Epidemiology Branch), is an excellent resource.

Fever without an obvious cause in any patient who has left a *P. falciparum* endemic area within 30 days and is nonimmune should be considered a medical emergency. Thick and thin blood smears should be obtained immediately, and all children with symptoms of severe disease should be hospitalized. If blood films are negative, they should be repeated every few hours. If the patient is severely ill, antimalarial therapy should be initiated immediately. Outpatient therapy generally is not given to nonimmune children but may be considered in immune or semi-immune children who have low-level parasitemia (<1%), no evidence of complications defined by the World Health Organization, no vomiting, and a lack of toxic appearance; who are able to contact the physician or emergency department at any time; and in whom follow-up within 24 hr is assured.

**Plasmodium Falciparum Malaria**

Malarious regions considered chloroquine-sensitive include Central America west of the Panama Canal, Haiti, the Dominican Republic, and most of the Middle East except Iran, Oman, Saudi Arabia, and Yemen. The CDC website (http://www.cdc.gov/MALARIA/) should be consulted for updated information on chloroquine susceptibility in an area, and current treatment options. Individuals traveling from areas with chloroquine-susceptible *P. falciparum* can be treated with chloroquine if they do not have severe malaria. Malaria acquired in *P. falciparum* areas with chloroquine resistance or where there is any doubt about chloroquine sensitivity after conferring with the CDC should be treated with drugs other than chloroquine (Table 288-2). Trials in Asia and Africa have definitively proven that artesunate treatment of severe malaria is associated with decreased mortality when compared to quinine treatment. However, artesunate is still not FDA approved in the United States for treatment of malaria, or available outside of special request indications from the CDC, so intravenous quinidine gluconate remains first-line therapy for severe malaria in the United States (Table 288-2). Monotherapy with artesunate agents is discouraged because of the development of resistance and treatment failures. Nonetheless in endemic countries, artesunate derivatives in combination with other antimalarial agents have become the treatment of choice (Tables 288-3 and 288-4). Children with severe malaria should be admitted to the intensive care unit for monitoring of complications, plasma quinidine levels, and adverse effects during quinidine administration. During administration of quinidine, blood pressure monitoring for hypotension and cardiac monitoring for widening of the QRS
Figure 288-5 Algorithm for approach to patient with malaria in the United States. (From Centers for Disease Control and Prevention [CDC]. Available at: http://www.cdc.gov/malaria/resources/pdf/algorithm.pdf)
CDC Guidelines for Treatment of Malaria in the United States (Based on Drugs Currently Available for Use in the United States—Updated July 1, 2013)

(CDC Malaria Hotline: [770] 488-7788 or [855] 856-4713 toll-free Monday-Friday 9 AM to 5 PM EST; [770] 488-7100 after hours, weekends, and holidays)

<table>
<thead>
<tr>
<th>CLINICAL DIAGNOSIS/PLASMODIUM SPECIES</th>
<th>REGION INFECTION ACQUIRED</th>
<th>RECOMMENDED DRUG AND ADULT DOSE</th>
<th>RECOMMENDED DRUG AND PEDIATRIC DOSE&lt;sup&gt;1&lt;/sup&gt;</th>
<th>PEDIATRIC DOSE SHOULD NEVER EXCEED ADULT DOSE</th>
</tr>
</thead>
</table>
| Uncomplicated malaria/ P. falciparum | Chloroquine-resistant or unknown resistance<sup>2</sup> (All malarious regions except those specified as chloroquine-sensitive listed in the box below) | A. Atovaquone-proguanil (Malarone)<sup>3</sup>  
Adult tab = 250 mg atovaquone/100 mg proguanil  
4 adult tabs PO qd × 3 days | A. Atovaquone-proguanil (Malarone)<sup>3</sup>  
Adult tab = 250 mg atovaquone/100 mg proguanil | Pediatric (ped) tab = 62.5 mg atovaquone/25 mg proguanil  
5-8 kg: 2 ped tabs PO qd × 3 days  
9-10 kg: 3 ped tabs PO qd × 3 days  
11-20 kg: 1 adult tab PO qd × 3 days  
21-30 kg: 2 adult tabs PO qd × 3 days  
31-40 kg: 3 adult tabs PO qd × 3 days  
> 40 kg: 4 adult tabs PO qd × 3 days |

B. Artemether-lumefantrine (Coartem)<sup>4</sup>  
1 tablet = 20 mg artemether and 120 mg lumefantrine  
A 3 day treatment schedule with a total of 6 oral doses is recommended for both adult and pediatric patients based on weight. The patient should receive the initial dose, followed by the second dose 8 hr later, then 1 dose PO bid for the following 2 days  
5<15 kg: 1 tablet per dose  
15<25 kg: 2 tablets per dose  
25<35 kg: 3 tablets per dose  
≥35 kg: 4 tablets per dose |
| | C. Quinine sulfate plus 1 of the following:  
doxycline, tetracycline, or clindamycin  
Quinine sulfate: 542 mg base (=650 mg salt)<sup>5</sup> PO tid × 3 or 7 days<sup>3</sup>  
Doxycline: 100 mg PO bid × 7 days  
Tetracycline: 250 mg PO qid × 7 days  
Clindamycin: 20 mg base/kg/day PO divided tid × 7 days | C. Quinine sulfate<sup>6</sup> plus 1 of the following:  
doxycline, tetracycline, or clindamycin  
Quinine sulfate: 8.3 mg base/kg (=10 mg salt/kg) PO tid × 3 or 7 days<sup>3</sup>  
Doxycline: 2.2 mg/kg PO every 12 hr × 7 days  
Tetracycline: 25 mg/kg/day PO divided qid × 7 days  
Clindamycin: 20 mg base/kg/day PO divided tid × 7 days | D. Mefloquine (Lariam and generics)<sup>7</sup>  
684 mg base (=750 mg salt) PO as initial dose, followed by 456 mg base (=500 mg salt) PO given 6-12 hr after initial dose  
Total dose = 1,250 mg salt | 13.7 mg base/kg (=15 mg salt/kg) PO as initial dose, followed by 9.1 mg base/kg (=10 mg salt/kg) PO every 12 hours after initial dose. Total dose = 25 mg salt/kg |

Uncomplicated malaria/ P. falciparum or Species not identified | Chloroquine-sensitive  
(Central America west of Panama Canal; Haiti; the Dominican Republic; and most of the Middle East) | Chloroquine phosphate (Aralen and generics)<sup>8</sup>  
600 mg base (=1,000 mg salt) PO immediately, followed by 300 mg base (=500 mg salt) PO at 6, 24, and 48 hr  
Total dose: 1,500 mg base (=2,500 mg salt) | Chloroquine phosphate (Aralen and generics)<sup>8</sup>  
10 mg base/kg PO immediately, followed by 5 mg base/kg PO at 6, 24, and 48 hr  
Total dose: 25 mg base/kg |
| | or Hydroxychloroquine (Plaquenil and generics)  
620 mg base (=800 mg salt) PO immediately, followed by 310 mg base (=400 mg salt) PO at 6, 24, and 48 hr  
Total dose: 1,550 mg base (=2,000 mg salt) | or Hydroxychloroquine (Plaquenil and generics)  
10 mg base/kg PO immediately, followed by 5 mg base/kg PO at 6, 24, and 48 hr  
Total dose: 25 mg base/kg |

<sup>1</sup>If a person develops malaria despite taking chemoprophylaxis, that particular medicine should not be used as a part of their treatment regimen. Use 1 of the other options instead.

<sup>2</sup>NOTE: There are 4 options (A, B, C, or D) available for treatment of uncomplicated malaria caused by chloroquine-resistant P. falciparum. Options A, B, and C are equally recommended. Because of a higher rate of severe neuropsychiatric reactions seen at treatment doses, we do not recommend option D (mefloquine) unless the other options cannot be used. For option C, because there is more data on the efficacy of quinine in combination with doxycycline or tetracycline, these treatment combinations are generally preferred to quinine in combination with clindamycin.

<sup>3</sup>Take with food or whole milk. If patient vomits within 30 min of taking a dose, then patient should repeat the dose.

<sup>4</sup>U.S. manufactured quinine sulfate capsule is in a 324 mg dosage; therefore 2 capsules should be sufficient for adult dosing. Pediatric dosing may be difficult because of unavailability of noncapsule forms of quinine.

<sup>5</sup>For infections acquired in Southeast Asia, quinine treatment should continue for 7 days. For infections acquired elsewhere, quinine treatment should continue for 3 days.

<sup>6</sup>Doxycycline and tetracycline are not indicated for use in children younger than 8 yr old. For children younger than 8 yr old with chloroquine-resistant P. falciparum, atovaquone-proguanil and artemether-lumefantrine are recommended treatment options; mefloquine can be considered if no other options are available. For children younger than 8 yr old with chloroquine-resistant P. vivax, mefloquine is the recommended treatment. If it is not available or is not being tolerated and if the treatment benefits outweigh the risks, atovaquone-proguanil or artemether-lumefantrine should be used instead.

<sup>7</sup>Treatment with mefloquine is not recommended in persons who have acquired infections from Southeast Asia as a consequence of drug resistance.

<sup>8</sup>When treating chloroquine-sensitive infections, chloroquine and hydroxychloroquine are recommended options. However, regimens used to treat chloroquine-resistant infections may also be used if available, more convenient, or preferred.

Continued
Chloroquine-resistant species are well documented in Papua New Guinea and Indonesia. Rare case reports of chloroquine-resistant \textit{P. vivax} are documented in Burma (Myanmar), India, and Central and South America. Persons acquiring infections in these regions should be treated with doxycycline or tetracycline as recommended for \textit{P. vivax}. If other treatment options are not available or are not being tolerated, and the benefit is judged to outweigh the risks, primaquine phosphate, at a dose of 30 mg base PO qd × 14 days, may be used if the patient is not pregnant or does not have G6PD deficiency. If the patient is pregnant or has G6PD deficiency, primaquine should not be used. If the patient is pregnant and has G6PD deficiency, primaquine phosphate at a dose of 0.5 mg base/kg PO qd × 14 days may be used. Consultation with an expert in infectious disease and/or tropical medicine is advised if this alternative regimen is considered in G6PD-deficient persons.

Primaquine must not be used during pregnancy. Pregnant women with G6PD deficiency or as an alternate to the above regimen, primaquine may be given 45 mg base PO qd; consultation with an expert in infectious disease and/or tropical medicine is advised if this alternative regimen is considered in G6PD-deficient persons.

Primaquine is used to eradicate any hypnozoites that may remain dormant in the liver, and thus prevent relapses, in \textit{P. vivax}. For pregnant women diagnosed with uncomplicated malaria caused by chloroquine-resistant \textit{P. vivax}, primaquine phosphate for radical treatment of hypnozoites should not be given during pregnancy. Pregnant patients with \textit{P. vivax} and \textit{P. ovale} infections, primaquine phosphate for radical treatment of hypnozoites should not be given during pregnancy. Pregnant patients who do not have G6PD deficiency should be treated with primaquine.

\textit{Note:} There are 3 options (A, B, or C) available for treatment of uncomplicated malaria caused by chloroquine-resistant \textit{P. vivax}. High treatment failure rates as a result of chloroquine-resistant \textit{P. vivax} are well documented in Papua New Guinea and Indonesia. Rare case reports of chloroquine-resistant \textit{P. vivax} are also documented in Burma (Myanmar), India, and Central and South America. Persons acquiring \textit{P. vivax} infections outside of Papua New Guinea or Indonesia should be started on chloroquine. If the patient does not respond, the treatment should be changed to a chloroquine-resistant \textit{P. vivax} regimen and CDC should be notified (Malaria Hotline number listed above). For treatment of chloroquine-resistant \textit{P. vivax} infections, options A, B, and C are equally recommended.

For pregnant women diagnosed with uncomplicated malaria caused by chloroquine-resistant \textit{P. falciparum} or chloroquine-resistant \textit{P. vivax} infection, treatment with doxycycline or tetracycline is generally not indicated. However, doxycycline or tetracycline may be used in combination with quinine (as recommended for non-pregnant adults) if other treatment options are not available or are not being tolerated, and the benefit is judged to outweigh the risks.

For \textit{P. vivax} and \textit{P. ovale} infections, primaquine phosphate for radical treatment of hypnozoites should not be given during pregnancy. Pregnant patients with \textit{P. vivax} and \textit{P. ovale} infections should be maintained on chloroquine prophylaxis for the duration of their pregnancy. The chemoprophylactic dose of chloroquine phosphate is 300 mg base (≤500 mg salt) orally once per week. After delivery, pregnant patients who do not have G6PD deficiency should be treated with primaquine.

### Table 288-2: CDC Guidelines for Treatment of Malaria in the United States (Based on Drugs Currently Available for Use in the United States—Updated July 1, 2013)—cont’d

<table>
<thead>
<tr>
<th>CLINICAL DIAGNOSIS/PLASMODIUM SPECIES</th>
<th>REGION INFECTION ACQUIRED</th>
<th>RECOMMENDED DRUG AND ADULT DOSE†</th>
<th>RECOMMENDED DRUG AND PEDIATRIC DOSE† PEDIATRIC DOSE SHOULD NEVER EXCEED ADULT DOSE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Uncomplicated malaria/\textit{P. malariae} or \textit{P. knowlesi}</strong></td>
<td>All regions</td>
<td>Chloroquine phosphate² treatment as above or Hydroxychloroquine: treatment as above</td>
<td>Chloroquine phosphate³ treatment as above or Hydroxychloroquine: treatment as above</td>
</tr>
<tr>
<td><strong>Uncomplicated malaria/\textit{P. vivax} or \textit{P. ovale}</strong></td>
<td>All regions Note: for suspected chloroquine-resistant \textit{P. vivax}, see row below</td>
<td>Chloroquine phosphate⁶ plus primaquine phosphate³ Quinine sulfate: treatment as above or Doxycycline or tetracycline: treatment as above</td>
<td>Chloroquine phosphate⁶ plus primaquine phosphate³ Quinine sulfate: treatment as above or Doxycycline or tetracycline: treatment as above</td>
</tr>
<tr>
<td><strong>Uncomplicated malaria/\textit{P. vivax}</strong></td>
<td>Chloroquine-resistant² \textit{(Papua New Guinea and Indonesia)}</td>
<td>A. Quinine sulfate plus either doxycycline or tetracycline plus primaquine phosphate³ Quinine sulfate: treatment as above</td>
<td>A. Quinine sulfate plus either doxycycline⁴ or tetracycline⁵ plus primaquine phosphate³ Quinine sulfate: treatment as above</td>
</tr>
<tr>
<td></td>
<td></td>
<td>B. Atovaquone-proguanil plus primaquine phosphate³ Atovaquone-proguanil: treatment as above</td>
<td>B. Atovaquone-proguanil: treatment as above</td>
</tr>
<tr>
<td></td>
<td></td>
<td>C. Mefloquine plus primaquine phosphate⁹ Mefloquine: treatment as above</td>
<td>C. Mefloquine plus primaquine phosphate⁹ Mefloquine: treatment as above</td>
</tr>
<tr>
<td><strong>Uncomplicated malaria: alternatives for pregnant women¹⁰¹¹</strong></td>
<td>Chloroquine-sensitive \textit{(See uncomplicated malaria sections above for chloroquine-sensitive species by region)}</td>
<td>Chloroquine phosphate: treatment as above or Hydroxychloroquine: treatment as above</td>
<td>Not applicable</td>
</tr>
<tr>
<td></td>
<td>Chloroquine-resistant \textit{(See sections above for regions with chloroquine-resistant \textit{P. falciparum} and \textit{P. vivax})}</td>
<td>Quinine sulfate plus clindamycin Quinine sulfate: treatment as above or Clindamycin: treatment as above</td>
<td>Not applicable</td>
</tr>
</tbody>
</table>

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²Primaquine is used to eradicate any hypnozoites that may remain dormant in the liver, and thus prevent relapses, in \textit{P. vivax} and \textit{P. ovale} infections. Because primaquine can cause hemolytic anemia in glucose-6-phosphate dehydrogenase (G6PD)-deficient persons, G6PD screening must occur prior to starting treatment with primaquine. For persons with borderline G6PD deficiency or as an alternate to the above regimen, primaquine may be given 45 mg orally 1 time per week for 8 wk; consultation with an expert in infectious disease and/or tropical medicine is advised if this alternative regimen is considered in G6PD-deficient persons. Primaquine must not be used during pregnancy.

¹¹NOTE: There are 3 options (A, B, or C) available for treatment of uncomplicated malaria caused by chloroquine-resistant \textit{P. vivax}. High treatment failure rates as a result of chloroquine-resistant \textit{P. vivax} are well documented in Papua New Guinea and Indonesia. Rare case reports of chloroquine-resistant \textit{P. vivax} are also documented in Burma (Myanmar), India, and Central and South America. Persons acquiring \textit{P. vivax} infections outside of Papua New Guinea or Indonesia should be started on chloroquine. If the patient does not respond, the treatment should be changed to a chloroquine-resistant \textit{P. vivax} regimen and CDC should be notified (Malaria Hotline number listed above). For treatment of chloroquine-resistant \textit{P. vivax} infections, options A, B, and C are equally recommended.

¹²For pregnant women diagnosed with uncomplicated malaria caused by chloroquine-resistant \textit{P. falciparum} or chloroquine-resistant \textit{P. vivax} infection, treatment with doxycycline or tetracycline is generally not indicated. However, doxycycline or tetracycline may be used in combination with quinine (as recommended for non-pregnant adults) if other treatment options are not available or are not being tolerated, and the benefit is judged to outweigh the risks.

¹³Atovaquone-proguanil and artemether-lumefantrine are generally not recommended for use in pregnant women, particularly in the 1st trimester because of a lack of sufficient safety data. For pregnant women diagnosed with uncomplicated malaria caused by chloroquine-resistant \textit{P. falciparum} or atovaquone-proguanil or artemether-lumefantrine may be used if other treatment options are not available or are not being tolerated, and if the potential benefit is judged to outweigh the potential risks.

¹⁴For \textit{P. vivax} and \textit{P. ovale} infections, primaquine phosphate for radical treatment of hypnozoites should not be given during pregnancy. Pregnant patients with \textit{P. vivax} and \textit{P. ovale} infections should be maintained on chloroquine prophylaxis for the duration of their pregnancy. The chemoprophylactic dose of chloroquine phosphate is 300 mg base (≤500 mg salt) orally once per week. After delivery, pregnant patients who do not have G6PD deficiency should be treated with primaquine.
complex or lengthening of the QTc interval should be performed continuously, and blood glucose monitoring for hypoglycemia should be performed periodically. Cardiac adverse events may require temporary discontinuation of the drug or slowing of the intravenous infusion. Parenteral therapy should be continued until the parasitemia is less than 1%, which usually occurs within 48 hr, and the patient can tolerate oral medication. Quinidine gluconate (United States) or quinine sulfate (other countries) is administered for a total of 3 days for malaria acquired in Africa or South America and for 7 days for malaria acquired in Southeast Asia. Doxycycline, tetracycline, or clindamycin is then given orally to complete the therapeutic course.

Although there are no data to support the use of sequential quinine and atovaquone-proguanil, the difficulty of maintaining compliance with oral quinine has meant many clinicians to use a complete course of atovaquone-proguanil.

Parenteral administration of artesunate or artemether can be substituted for quinine for treatment of severe malaria in children and adults (see Table 288-2). Artesunate is now available on special request from the CDC (770-488-7788) for treatment of severe malaria, but empirical therapy should not be delayed while awaiting delivery of artesunate. Children who do receive artesunate may follow up with

From the Centers for Disease Control and Prevention. Available at: http://www.cdc.gov/malaria/resources/pdf/treatmenttable.pdf
Artemether-lumefantrine oral therapy. Oral and rectal administration of these artemisinin-based antimalarial drugs is effective in treatment of malaria, but such formulations are not indicated or approved in the United States.

Patients from areas with chloroquine-resistant P. falciparum who have mild infection, parasitemia less than 1%, no evidence of complications, and no vomiting and who can take oral medication can be considered for oral therapy with either oral atovaquone-proguanil (Malarone), oral artemether-lumefantrine (Coartem), or oral quinine plus doxycycline, tetracycline, or clindamycin (see Table 288-2). However, as noted in Figure 288-5, all children with clinical malaria, even those started on oral therapy, should be admitted to evaluate for progression of disease. Coartem is approved by the FDA for the treatment of uncomplicated malaria and is an appealing choice because it is highly effective and well-tolerated. Pediatric dosing is well established, but pediatric dispersible tablets, available in some other countries, are not yet available in the United States. Coartem should not be used in children with known QT interval prolongation. Patients who acquire P. falciparum in Thailand, Myanmar, or Cambodia should receive 7 days of quinine therapy if they are prescribed quinine. Mefloquine is contraindicated for use in patients with a known hypersensitivity to mefloquine or with a history of epilepsy or severe psychiatric disorders. Mefloquine is not recommended for persons with cardiac conduction abnormalities but may be administered to persons concurrently receiving β-blockers if they have no underlying arrhythmia. Quinidine or quinine may exacerbate the adverse effects of mefloquine and should generally not be given to patients who have received mefloquine unless there are no other alternatives.

Patients with uncomplicated P. falciparum malaria acquired in areas without chloroquine resistance should be treated with oral chloroquine phosphate. If the parasite count does not drop rapidly (within 24–48 hr) and become negative after 4 days, chloroquine resistance should be assumed and the patient started on a different antimalarial regimen.

Supportive therapy is very important and may include red blood cell transfusion(s) to maintain the hematocrit at more than 20%, exchange transfusion in P. falciparum malaria with parasitemia greater than 10% and evidence of severe complications (e.g., severe malarial anemia, cerebral malaria), supplemental oxygen andventilatory support for pulmonary edema or cerebral malaria, careful intravenous rehydration for severe malaria, intravenous glucose for hypoglycemia, anticonvulsants for cerebral malaria with seizures, and dialysis for renal failure. Exchange transfusion is thought to be useful in severe malaria with high-level parasitemia, but no randomized clinical trial has ever been conducted to assess its utility, and some groups, including the Centers for Disease Control and Prevention, no longer advocate its use for severe malaria. Corticosteroids are not recommended for cerebral malaria.

### Table 288-3: Treatment of Uncomplicated Malaria

<table>
<thead>
<tr>
<th>Plasmodium species</th>
<th>REMEDIES</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All Plasmodium falciparum malaria</strong></td>
<td>Artemether-lumefantrine 1.5 mg/kg-9 mg/kg twice daily for 3 days with food or milk. Artesunate 4 mg/kg daily for 3 days and mefloquine 25 mg base per kg (8 mg/kg/daily for 3 days)*.</td>
</tr>
<tr>
<td>Sensitive P. falciparum malaria</td>
<td>Artesunate 4 mg/kg daily for 3 days and a single dose of sulfadoxine-pyrimethamine 25 mg/kg-1.25 mg/kg. Artesunate 4 mg/kg and amodiaquine* 10 mg base per kg daily for 3 days.</td>
</tr>
<tr>
<td>Chloroquine-sensitive Plasmodium vivax, Plasmodium malariae, Plasmodium ovale, Plasmodium knowlesi</td>
<td>Chloroquine 10 mg base per kg immediately, followed by 10 mg/kg at 24 hr and 5 mg/kg at 48 hr.</td>
</tr>
</tbody>
</table>

*World Health Organization prequalified fixed dose formulations are preferable to loose tablets. A taste masked dispersible pediatric tablet formulation of artemether-lumefantrine is available.

†High failure rates with artesunate-mefloquine have been reported on the Thailand-Myanmar border.

Any of the artemisinin combination treatments can be given except for artesunate-sulfadoxine-pyrimethamine where P. vivax is resistant. Patients with P. vivax or P. ovale infections should also be given a 14 day course of primaquine to eradicate hypnozoites (radical cure). However, severe glucose-6-phosphate dehydrogenase deficiency is a contraindication because a 14 day course of primaquine can cause severe hemolytic anemia in this group.


### Table 288-4: Treatment of Severe Malaria in Adults and Children

<table>
<thead>
<tr>
<th><strong>Severe Malaria</strong></th>
<th><strong>TREATMENT</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>P. falciparum</td>
<td>Artesunate 2.4 mg/kg as intravenous or intramuscular* injection, followed by 2.4 mg/kg at 12 hr and 24 hr; continue injection once daily if necessary†.</td>
</tr>
<tr>
<td>P. vivax</td>
<td>Artesunate 3.2 mg/kg by immediate intramuscular* injection, followed by 1.6 mg/kg daily.</td>
</tr>
<tr>
<td>P. ovale</td>
<td>Quinine dihydrochloride 20 mg salt per kg infused during 4 hr, followed by maintenance of 10 mg salt per kg infused during 2-8 hr every 8 hr (can also be given by intramuscular injection* when diluted to 60-100 mg/mL).</td>
</tr>
<tr>
<td>P. knowlesi</td>
<td>Artesunate is the treatment of choice. Artemether should only be used if artesunate is unavailable. Quinine dihydrochloride should be given only when artemether and artemether are unavailable.</td>
</tr>
</tbody>
</table>

*Intramuscular injections should be given to the anterior thigh.

†Young children with severe malaria have lower exposure to artesunate and its main biologically active metabolite dihydroartemisinin than do older children and adults. Revised dose regimens to ensure similar drug exposures have been suggested.

COMPLICATIONS OF PLASMODIUM FALCIPARUM MALARIA

The World Health Organization has identified 10 complications of \(P. falciparum\) malaria that define severe malaria (see Table 288-1 and Fig. 288-4). The most common complications in children are severe anemia, impaired consciousness (including cerebral malaria), respiratory distress (a result of metabolic acidosis), multiple seizures, prostration, and jaundice.

Severe malarial anemia (hemoglobin level <5 g/dL) is the most common severe complication of malaria in children and is the leading cause of anemia leading to hospital admission in African children. Anemia is associated with hemolysis, but removal of infected erythrocytes by the spleen and impairment of erythropoiesis likely play a greater role than hemolysis in the pathogenesis of severe malarial anemia. The primary treatment for severe malarial anemia is blood transfusion. With appropriate and timely treatment, severe malarial anemia usually has a relatively low mortality (~1%).

Cerebral malaria is defined as the presence of coma in a child with \(P. falciparum\) parasitemia and an absence of other reasons for coma. Children with altered mental status who are not in coma fall into the larger category of impaired consciousness. Cerebral malaria is most common in children in areas of midlevel transmission and in adolescents or adults in areas of very low transmission. It is less frequently seen in areas of very high transmission. Cerebral malaria often develops after the patient has been ill for several days but may develop precipitously. Cerebral malaria has a fatality rate of 15-20% and is associated with long-term cognitive impairment in children. Repeated seizures are frequent in children with cerebral malaria. Hypoglycemia is common, but children with true cerebral malaria fail to arouse from coma even after receiving a dextrose infusion that normalizes their glucose level. Physical findings may include high fever, seizures, muscular twitching, rhythmic movement of the head or extremities, contracted or unequal pupils, retinal hemorrhages, hemiplegia, absent or exaggerated deep tendon reflexes, and a positive Babinski sign. Lumbar puncture reveals increased pressure and cerebrospinal fluid protein with no pleocytosis and normal glucose and protein concentrations. Studies suggest that funduscopic findings of malaria retinopathy (retinal hemorrhages, peripheral whitening, macular whitening, vessel changes) are specific for cerebral malaria and may identify children in whom malaria is the reason for coma, as opposed to children with coma and incidental \(P. falciparum\) parasitemia. Treatment of cerebral malaria other than antimalarial medications is largely supportive and includes evaluation of and treatment of seizures and hypoglycemia. Although increased intracranial pressure has been documented in some children with cerebral malaria, treatment with mannitol and corticosteroids has not improved outcomes in these children.

Respiratory distress is a poor prognostic indicator in severe malaria and appears to be caused by metabolic acidosis rather than intrinsic pulmonary disease. To date, no successful interventions for treatment of metabolic acidosis in children with severe malaria have been described, but trials of dichloroacetate treatment and fluid expansion are ongoing.

Seizures are a common complication of severe malaria, particularly cerebral malaria. Benzodiazepines are first-line therapy for seizures, and intrarectal diazepam has been used successfully in children with malaria and seizures. Many seizures resolve with a single dose of diazepam. For persistent seizures, phenobarbital or phenytoin are the standard medications used. Phenytoin may be preferred for seizure treatment, particularly in hospitals or clinics where ventilatory support is not available. However, no comparative trials of the 2 drugs have been performed, and phenytoin is considerably more expensive than phenobarbital. There are currently no drugs recommended for seizure prophylaxis in children with severe malaria. Phenobarbital prophylaxis decreased seizure activity but increased mortality in 1 major study of children with severe malaria, probably because of the respiratory depression associated with phenobarbital that may have been exacerbated by benzodiazepine therapy.

Hypoglycemia is a complication of malaria that is more common in children, pregnant women, and patients receiving quinine therapy. Patients may have a decreased level of consciousness that can be confused with cerebral malaria. Any child with impaired consciousness and malaria should have a glucose level checked, and if glucometers are not available, an empirical bolus of dextrose should be given. Hypoglycemia is associated with increased mortality and neurologic sequelae.

Circulatory collapse (algid malaria) is a rare complication that manifests as hypotension, hypothermia, rapid weak pulse, shallow breathing, pallor, and vascular collapse. Death may occur within hours. Severe malaria is occasionally accompanied by bacteremia, which may have been the cause of some of the cases previously referred to as algid malaria. Any child with severe malaria and hypotension or hypoperfusion should have a blood culture obtained and be treated empirically for bacterial sepsis.

Long-term cognitive impairment occurs in 25% of children with cerebral malaria and also occurs in children with repeated episodes of uncomplicated disease. Prevention of attacks in these children improves educational attainment.

Tropical splenomegaly syndrome is a chronic complication of \(P. falciparum\) malaria in which massive splenomegaly persists after treatment of acute infection. The syndrome is characterized by marked splenomegaly, hepatomegaly, anemia, and an elevated immunoglobulin M level. Tropical splenomegaly syndrome is thought to be caused by an impaired immune response to \(P. falciparum\) antigens. Prolonged antimalarial prophylaxis (for at least several years) is required to treat this syndrome if the child remains in a malaria endemic area. Spleen size gradually regresses on antimalarial prophylaxis but often increases again if prophylaxis is stopped.

Other complications in children include jaundice, which is associated with a worse outcome, and prostration. Prostration is defined as the inability to sit, stand, or eat without support, in the absence of impaired consciousness. Prostration also has been associated with increased mortality in some studies, but the pathophysiology of this process is not well understood. Uncommon complications include hemoglobinuria, abnormal bleeding, pulmonary edema, and renal failure. These are uncommon complications in children with severe malaria and are more common in adults, particularly pulmonary edema and renal failure. Although frank renal failure is uncommon in children, uremia (when defined as an elevation in blood urea nitrogen levels) is not, particularly in older children. It remains unclear whether BUN elevation reflects a degree of renal failure or primarily dehydration.

PREVENTION

Malaria prevention consists of reducing exposure to infected mosquitoes and chemoprophylaxis. The most accurate and current information on areas in the world where malaria risk and drug resistance exist can be obtained by contacting local and state health departments or the CDC or consulting Health Information for International Travel, which is published by the U.S. Public Health Service.

Travelers to endemic areas should remain in well-screened areas from dusk to dawn, when the risk for transmission is highest. They should sleep under permethrin-treated mosquito netting and spray insecticides indoors at sundown. During the day the travelers should wear clothing that covers the arms and legs, with trousers tucked into shoes or boots. Mosquito repellent should be applied to thin clothing and exposed areas of the skin, with applications repeated every 1-2 hr. A child should not be taken outside from dusk to dawn, but if at risk for exposure, a solution with 25-35% N,N-diethyl-3-methylbenzamide (DEET) (not greater than 40%) should be applied to exposed areas except for the eyes, mouth, or hands. Hands are excluded because they are often placed in the mouth. DEET should then be washed off as soon as the child comes back inside. The American Academy of Pediatrics recommends that DEET solutions be avoided in children less than 2 mo of age. Adverse reactions to DEET include rashes, toxic encephalopathy; and seizures, but these reactions occur almost exclusively with inappropriate application of high concentrations of DEET. Picaridin is an alternative and sometimes better tolerated repellent. Even with these precautions, a child should be taken to a physician immediately if the child develops illness when traveling to a malarial area.
Chemoprophylaxis is necessary for all visitors to and residents of the tropics who have not lived there since infancy, including children of all ages (Table 288-5). Healthcare providers should consult the latest information on resistance patterns before prescribing prophylaxis for their patients. Chloroquine is given in the few remaining areas of the world free of chloroquine-resistant P. falciparum strains. In areas where chloroquine-resistant P. falciparum exists, atovaquone-proguanil, mefloquine, or doxycycline may be given as chemoprophylaxis. Atovaquone-proguanil is generally recommended for shorter trips (up to 2 wk) because it must be taken daily. Pediatric tablets are available and are generally well tolerated, although the taste is sometimes unpleasant to very young children. For longer trips, mefloquine is preferred, as it is given only once a week. Mefloquine does not have a pediatric formulation and has an unpleasant taste that usually requires that the cut tablet be “disguised” in another food, such as chocolate syrup. Mefloquine should not be given to children if they have a known hypersensitivity to mefloquine, are receiving cardiotropic drugs, have a history of convulsive or certain psychiatric disorders, or travel to an area where mefloquine resistance exists (the borders of Thailand with Myanmar and Cambodia, the western provinces of Cambodia, and the eastern states of Myanmar). Atovaquone-proguanil is started 1-2 days before travel, and mefloquine is started 2 wk before travel. It is important that these doses are given, both to allow therapeutic levels of the drugs to be achieved and to be sure that the drugs are tolerated. Doxycycline is an alternative for children older than 8 yr of age. It must be given daily and should be given with food. Side effects of doxycycline include photosensitivity and vaginal yeast infections. Primaquine is a daily prophylaxis option for children who cannot tolerate any of the other options, but it should be provided in consultation with a travel medicine specialist if needed, and all children should be checked for glucose-6-phosphate dehydrogenase deficiency prior to prescribing this medication, which is contraindicated in children with glucose-6-phosphate dehydrogenase deficiency. Provision of medication can be considered in individuals who refuse to take prophylaxis or will be in very remote areas without accessible medical care. Provision of medication for self-treatment of malaria should be done in

<table>
<thead>
<tr>
<th>AREA</th>
<th>DRUG</th>
<th>DOSAGE (ORAL)</th>
<th>ADVANTAGES</th>
<th>DISADVANTAGES</th>
<th>BEST USE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chloroquine-resistant area</td>
<td>Mefloquine*</td>
<td>&lt;10 kg: 4.6 mg base (5 mg salt)/kg/wk</td>
<td>Once weekly dosing</td>
<td>Bitter taste</td>
<td>Children going to malaria endemic area for 4 wk or more</td>
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<tr>
<td></td>
<td></td>
<td>10-19 kg: ½ tab/wk</td>
<td></td>
<td>No pediatric formulation</td>
<td>Children unlikely to take daily medication</td>
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<tr>
<td></td>
<td></td>
<td>20-30 kg: ½ tab/wk</td>
<td></td>
<td>Side effects of sleep disturbance, vivid dreams</td>
<td>Children going to area for &lt;4 wk who cannot take or cannot obtain atovaquone-proguanil</td>
</tr>
<tr>
<td></td>
<td></td>
<td>31-45 kg: ½ tab/wk</td>
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<td></td>
<td></td>
<td>&gt;45 kg: 1 tab/wk (228 mg base)</td>
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<td></td>
<td>Doxycycline³</td>
<td>2 mg/kg daily (max 100 mg)</td>
<td>Inexpensive</td>
<td>Cannot give to children &lt;8 yr</td>
<td>Children going to area for &lt;4 wk</td>
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<td>Daily dosing</td>
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<td>Must take with food or causes stomach upset</td>
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<td>Photosensitivity</td>
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<td>Daily dosing</td>
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<td>Expensive</td>
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<td></td>
<td></td>
<td>Can cause stomach upset</td>
<td></td>
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<td></td>
<td>Atovaquone/ proguanil (Malarone)</td>
<td>Pediatric tabs: 62.5 mg atovaquone/25 mg proguanil</td>
<td>Pediatric formulation</td>
<td>Generally well tolerated</td>
<td>Children going to malaria endemic area for &lt;4 wk</td>
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<tr>
<td></td>
<td></td>
<td>Adult tabs: 250 mg atovaquone/100 mg proguanil</td>
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<td>5-8 kg: pediatric tab once daily (off-label)</td>
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<td>9-10 kg: pediatric tab once daily (off-label)</td>
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<td>11-20 kg: 1 pediatric tab once daily</td>
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<td>21-30 kg: 2 pediatric tabs once daily</td>
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<td></td>
<td>31-40 kg: 3 pediatric tabs once daily</td>
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<td></td>
<td></td>
<td>&gt;40 kg: 1 adult tab once daily</td>
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</table>

Table 288-5 Chemoprophylaxis of Malaria for Children

*Chloroquine and mefloquine should be started 1-2 wk prior to departure and continued for 4 wk after last exposure.

1Mefloquine resistance exists in western Cambodia and along the Thailand–Cambodia and Thailand–Myanmar borders. Travelers to these areas should take doxycycline or atovaquone-proguanil. See text for precautions about mefloquine use.

Doxycycline should be started 1-2 days prior to departure and continued for 4 wk after last exposure. Do not use in children younger than 8 yr of age or in pregnant women.

Atovaquone/proguanil (Malarone) should be started 1-2 days prior to departure and continued for 7 days after last exposure. Should be taken with food or a milky drink. Not recommended in pregnant women, children weighing <5 kg, and women breastfeeding infants who weigh <5 kg. Contraindicated in individuals with severe renal impairment (creatinine clearance <30 mL/min).
consultation with a travel medicine specialist, and the medication provided should be different than that used for prophylaxis.

A number of other efforts are currently underway to prevent malaria in malaria endemic countries. Some have been highly successful, leading to a significant decrease in malaria incidence in many countries in Africa, Asia, and South America in the last decade. These interventions include the use of insecticide-treated bed nets (which have decreased all-cause mortality in children under 5 yr of age in several highly malaria endemic areas by ~20%), indoor residual spraying with long-lasting insecticides, and the use of artemisinin-combination therapy for first-line malaria treatment. The first malaria vaccine to have any degree of efficacy is the RTS,S vaccine, which is based on the circumsporozoite protein of \textit{P. falciparum}. In various clinical trials, this vaccine has shown an efficacy of 17-56% against uncomplicated malaria and 38-50% against severe malaria in young children in malaria endemic areas for periods as long as 48 mo after vaccination. The vaccine is in large phase III trials. Given the relatively low efficacy of this vaccine, it is unclear if it will be implemented as part of a combination strategy that includes the already successful interventions mentioned. Numerous other vaccines are also in current clinical trials, and it is hoped that future vaccines will improve upon the efficacy of the RTS,S vaccine. There is currently no vaccine with sufficient efficacy to be considered for prevention of malaria in travelers.

Interruption prevention treatment during infancy has been particularly successful in reducing the incidence of malaria in sub Saharan Africa. Sulfadoxine-pyrimethamine given to infants at the second and third doses of the diphtheria, tetanus toxoid, and pertussis and measles vaccinations is safe and relatively effective. Intermittent prevention treatment has also been given to pregnant women; 3 doses of sulfadoxine-pyrimethamine have resulted in a reduction of low birth-weight infants.

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Babesiosis is an emerging disease caused by intraerythrocytic protozoa that are transmitted by hard body (ixodid) ticks. The clinical manifestations of babesiosis range from subclinical illness to fulminant disease resulting in death.

ETIOLOGY

There are more than 100 species of Babesia that infect a wide variety of wild and domestic animals throughout the world. Only a few of these species have been reported to infect humans, including Babesia microti (and B. microti-like species), Babesia divergens (and B. divergens-like species), Babesia duncani, Babesia venatorum, and KO1.

EPIDEMIOLOGY

Babesia are transmitted to humans from vertebrate reservoir hosts by the Ixodes species of ticks. B. microti is the most common cause of babesiosis in humans. The primary reservoir for B. microti is the white-footed mouse, Peromyscus leucopus, and the primary vector is Ixodes scapularis, the black legged tick. I. scapularis ticks also transmit the causative agents of Lyme disease, human granulocytic anaplasmosis, Borrelia miyamotoi, and Powassan virus and may simultaneously transmit 2 or more microorganisms. White-tailed deer (Odocoileus virginianus) serve as the host on which adult ticks most abundantly feed but are incompetent reservoirs. Babesiosis may be transmitted through blood transfusion, and B. microti is the most frequently reported transfusion-transmitted microbial agent in the United States. Rarely, babesiosis is acquired by transplacental transmission.

Human B. microti infection is endemic (most cases occurring in June, July, and August) in the northeastern and upper midwestern United States and has been sporadically reported in China, Taiwan, and Europe (Fig. 289-1). Human babesial infections caused by the cattle parasite, B. divergens, have been described in many countries in Europe, while B. divergens-like infections have been described in Kentucky, Missouri, and Washington State. B. duncani infects humans along the northern Pacific coast. B. venatorum infects people in Austria, Germany, China, and Italy. Human babesiosis cases also have been documented in Africa, Australia, and South America.

In certain sites and in certain years of high transmission, babesiosis constitutes a significant public health burden. On Nantucket Island, case rates as high as 280 per 100,000 population have been recorded, placing the community burden of disease in a category with gonorrhea as “moderately common.” Comparable incidence rates have been described elsewhere on the southern New England coast.

PATHOGENESIS

The pathogenesis of human babesiosis is not well understood. Cytoskeleton and lysis of infected erythrocytes and excessive production of proinflammatory cytokines such as tumor necrosis factor and interleukin-1 may account for most of the clinical manifestations and complications of the disease. The spleen has an important role in clearing parasitemia as do T and B cells, macrophages, polymorphonuclear leukocytes, cytokines, antibody, and complement.

CLINICAL MANIFESTATIONS

The clinical severity of babesiosis ranges from subclinical infection to fulminating disease and death. In clinically apparent cases, symptoms of babesiosis begin after an incubation period of 1-4 wk from the beginning of tick feeding or 1 wk to 6 mo after transfusion. Typical symptoms in moderate to severe infection include intermittent fever to as high as 40.9°C (105.6°F) accompanied by any combination of fatigue, chills, sweats, myalgias, headache, and anorexia. Less commonly noted are emotional lability, hyperesthesia, headache, sore throat, abdominal pain, conjunctival injection, photophobia, weight loss, and nonproductive cough. The findings on physical examination generally are minimal, often consisting only of fever. Splenomegaly, hepatomegaly, or both are noted occasionally, but rash seldom is reported. Abnormal laboratory findings include moderately severe anemia, elevated reticulocyte count, thrombocytopenia, proteinuria, and elevated bilirubin, blood urea nitrogen, and creatinine levels. The leukocyte count is normal to slightly decreased, with increased bands. Babesiosis symptoms usually last for 1 to 2 weeks, with prolonged recovery of up to a year or more in severe cases. Complications include respiratory failure, disseminated intravascular coagulation, congestive heart failure, renal failure, liver failure, and coma. A prolonged relapsing course of illness has been described in highly immunocompromised hosts, such as those with cancer, with asplenia, and on treatment with immunosuppressive agents, even though they received multiple courses of antibabesial therapy. About a quarter of these patients died, while the remainder were cured after an average of 3 mo (range: 1-24 mo) of antibabesial therapy.

Risk factors for severe disease include anatomic or functional asplenia, concomitant malignancy or HIV infection, immunosuppressive drugs, age of more than 50 yr, acquisition of infection through blood transfusion, or infection with B. divergens or B. duncani. Concurrent babesiosis and Lyme disease occurs in 3-11% of patients experiencing Lyme disease depending upon location in southern New England and the northern Midwest. Such coinfection results in more severe acute Lyme disease illness. Moderate to severe babesiosis may occur in children, but infection generally is less severe than in adults. About half of infected children are asymptomatic or experience minimal symptoms. Neonates may develop severe illness and usually are infected from blood transfusion.
DIAGNOSIS
The diagnosis of babesiosis should be considered in any patient with an unexplained febrile illness who has resided in or traveled to an endemic area within the previous 2 mo or received a blood transfusion within the previous 6 mo. The diagnosis is confirmed by microscopic identification of parasites on blood smear or amplifiable Babesia DNA in blood and antibacterial antibody in serum. Babesia are identified on blood smear using Giemsa or Wright staining. Parasitemia may be exceedingly low, especially early in the course of illness. Thick blood smears may be examined, but the organisms may be mistaken for stain precipitate or iron inclusion bodies. The polymerase chain reaction is a sensitive and specific test for detection of Babesia DNA. Subinoculation of blood into hamsters or gerbils and in vitro cultivation are too specialized for all but the most experienced laboratories. The indirect immunofluorescence serologic assay for both immunoglobulin G and immunoglobulin M antibodies is sensitive and specific and can help confirm a diagnosis of babesiosis when parasites are scarce or undetectable. The diagnosis of active babesial infection based on seropositivity alone is unreliable.

TREATMENT
The combination of clindamycin (7-10 mg/kg given every 6-8 hr [up to a maximum of 600 mg per dose] intravenously or orally) and quinine (8 mg/kg given every 8 hr [up to a maximum of 650 mg per dose] orally) for 7-10 days was the first effective therapeutic combination for the treatment of babesiosis and remains the treatment of choice for severe disease. Adverse reactions are common, however, especially tinnitus and abdominal distress. The combination of atovaquone (20 mg/kg every 12 hr [up to a maximum of 750 mg per dose]) and azithromycin (10 mg/kg per day once per day on day 1 [up to a maximum of 500 mg per dose]) and 5 mg/kg once per day [up to a maximum of 250 mg per dose] thereafter orally) for 7-10 days is as effective as clindamycin and quinine but has fewer adverse effects. Combination atovaquone and azithromycin has been used successfully to treat babesiosis in infants and should be considered for initial use in children experiencing mild to moderate infection. Treatment failure with clindamycin and quinine and with atovaquone and azithromycin may occur in highly immunocompromised hosts. Consultation with an infectious diseases expert is recommended in these cases. Exchange blood transfusion can decrease parasitemia rapidly and remove toxic by-products of infection. It should be considered for all patients experiencing severe babesiosis.

PROGNOSIS
Moderate to severe disease is frequently observed in some highly endemic areas. The case fatality rate was estimated at 5% in a retrospective study of 136 New York cases but may be as high as 21% in immunocompromised hosts. Immunity is sometimes incomplete with low-level asymptomatic parasitemia persisting for as long as 26 mo after symptoms have resolved or with relapsing symptomatic disease in immunocompromised hosts.

PREVENTION
Prevention of babesiosis can be accomplished by avoiding areas where ticks, deer, and mice are known to thrive. Use of clothing that covers the lower part of the body and that is sprayed or impregnated with diethyltoluamide (DEET), dimethyl phthalate, or permethrin (Permone) is recommended for those who travel in the foliage of endemic areas. A search for ticks on people and pets should be carried out and the ticks removed using tweezers. Prospective blood donors with a history of babesiosis are excluded from giving blood to prevent transfusion-related cases.

Bibliography is available at Expert Consult.
Bibliography


Toxoplasma gondii, an obligate intracellular protozoan, is acquired per-orally, transplacentally, or, rarely, parenterally in laboratory accidents; by transfusion; or from a transplanted organ. In immunologically normal children, acute acquired infection may be asymptomatic, cause lymphadenopathy, or affect almost any organ. Once acquired, latent encysted organisms persist in the host throughout life. In immunocompromised persons either initial acquisition or recrudescence of latent organisms often causes signs or symptoms related to the central nervous system (CNS) and can result in systemic disease in bone marrow transplant recipients. If untreated, congenital infection often causes disease either perinatally or later in life, most frequently chorioretinitis and CNS lesions. Other manifestations, such as intrauterine growth retardation, prematurity, being small for gestational age, cognitive and motor deficits, fever, lymphadenopathy, rash, hearing loss, pneumonitis, hepatitis, thrombocytopenia, and cerebrospinal fluid (CSF) inflammatory changes such as pleocytosis, elevated CSF protein, and low CSF glucose, may also occur. Congenital toxoplasmosis in infants with HIV infection may be fulminant.

ETIOLOGY

*T. gondii* is a coccidian protozoan that multiplies only in living cells. The tachyzoites are oval or crescent-like, measuring 2-4 \( \times 4-7 \) \( \mu \)m. Tissue cysts, which are 10-100 \( \mu \)m in diameter, may contain thousands of parasites, and will remain in tissues, especially the CNS and skeletal heart muscle, for the life of the host. *Toxoplasma* can multiply in all tissues of mammals and birds.

Newly infected cats and other Felidae species excrete infectious *Toxoplasma* oocysts in their feces. *Toxoplasma* organisms are transmitted to cats by ingestion of infected meat containing encysted bradyzoites or by ingestion of oocysts excreted by other recently infected cats. The parasites then multiply through schizogonic and gametogonic cycles in the distal ileal epithelium of the cat intestine. Oocysts containing 2 sporozoites are excreted, and, under proper conditions of temperature and moisture, each sporocyst matures into 4 sporozoites. For approximately 2 wk the cat excretes 10\(^{10}-10\)\(^{12}\) oocysts/day, which may retain their viability for longer than 1 yr in a suitable environment. Oocysts sporulate 1-5 days after excretion and are then infectious. Oocysts are killed by drying or boiling but not exposure to bleach. Oocysts can be killed by freezing meat to \(-20^\circ C\) (\(-4^\circ F\)) or heating meat to 66°C (150.8°F) renders the cysts noninfectious. Outbreaks of acute acquired infection have occurred in families, at social gatherings, and in restaurants where people have consumed the same infected food. *Toxoplasma* organisms are not known to be transmitted from person to person except for transplacental infection from mother to fetus and, rarely, by organ transplantation or transfusion. Seronegative transplant recipients who receive an organ or bone marrow from seropositive donors have experienced life-threatening illness requiring therapy. Seropositive recipients may have increased serologic titers without associated disease. Laboratory accidents have resulted in infections, including fatalities.

Congenital Toxoplasmosis

Transmission to the fetus usually follows acquisition of primary infection by an immunologically normal pregnant woman during gestation. Congenital transmission from mothers infected before pregnancy is extremely rare except for immunocompromised women who are chronically infected. The incidence of congenital infection in the United States ranges from 1 in 1,000 to 1 in 8,000 live births. The incidence of infection among pregnant women depends on the general risk for infection in the specific locale and the proportion of the population that has not been infected previously.

PATHOGENESIS

*T. gondii* is acquired by children and adults from ingesting food that contains cysts or that is contaminated with oocysts from acutely infected cats. Oocysts also may be transported to food by flies and cockroaches or be carried on the fur of dogs. When the organism is ingested, bradyzoites are released from cysts or sporozoites from oocysts. The organisms enter gastrointestinal cells where they multiply, rupture cells, infect contiguous cells, enter the lymphatics, and disseminate hematogenously throughout the body. Tachyzoites proliferate, producing necrotic foci surrounded by a cellular reaction. With development of a normal immune response that is both humoral and cell mediated, tachyzoites disappear from tissues. In immunocompromised persons and also some apparently immunocompetent persons, acute infection progresses and may cause potentially lethal disease, including pneumonitis, myocarditis, or encephalitis.

Alterations of T-lymphocyte populations during acute *T. gondii* infection are common and include lymphocytosis, increased CD8 count, and decreased CD4:CD8 ratio. Depletion of CD4 cells in patients with AIDS may contribute to severe manifestations of toxoplasmosis. Characteristic lymph node changes include reactive follicular hyperplasia with irregular clusters of epithelioid histiocytes that encroach on and blur margins of germinal centers, and focal distention of sinuses with monocyctoid cells.

Cysts form as early as 7 days after infection and remain for the life of the host. During latent infection they produce little or no inflammatory response but can cause recrudescence disease in immunocompromised persons. Recrudescence chorioretinitis occurs in children with postnatal infection and in older children and adults with congenital infection. Host and parasite genetics influence outcome.

Congenital Toxoplasmosis

When a mother acquires infection during gestation, organisms may disseminate hematogenously to the placenta. Infection may be transmitted to the fetus transplacentally or during vaginal delivery. Of
Infectious Diseases

Infectious Diseases appear to have Toxoplasma antigen–specific cell-mediated anergy, which may be important in the pathogenesis of disease.

CLINICAL MANIFESTATIONS

Manifestations of primary infection with T. gondii are highly variable and are influenced primarily by host immunocompetence. There may be no signs or symptoms or severe disease. Reactivation of previously asymptomatic congenital toxoplasmosis usually manifests as ocular toxoplasmosis.

Acquired Toxoplasmosis

Immunocompetent children who acquire infection postnatally usually do not have clinically recognizable symptoms. When clinical manifestations are apparent, they may include almost any combination of fever, stiff neck, myalgia, arthralgia, maculopapular rash that spares the palms and soles, localized or generalized lymphadenopathy, hepatomegaly, hepatitis, reactive lymphocytosis, meningoencephalitis, brain abscess, encephalitis, confusion, malaise, pneumonia, polyarthritis, pericarditis, pericardial effusion, and myocarditis. Chorioretinitis is usually

untreated maternal infections acquired in the 1st trimester, approximately 17% of fetuses are infected, usually with severe disease. Of untreated maternal infection acquired in the 3rd trimester, approximately 65% of fetuses are infected, usually with disease that is more mild or inapparent at birth. These different rates of transmission and outcomes are most likely related to placental blood flow, virulence, inoculum of T. gondii, and immunologic capacity of the mother and fetus to limit parasitemia.

Examination of the placenta of infected newborns may reveal chronic inflammation and cysts. Tachyzoites can be seen with Wright or Giemsa stains but are best demonstrated with immunoperoxidase technique. Tissue cysts stain well with periodic acid–Schiff and silver stains as well as with the immunoperoxidase technique. Gross or microscopic areas of necrosis may be present in many tissues, especially the CNS, choroid and retina, heart, lungs, skeletal muscle, liver, and spleen. Areas of calcification occur in the brain.

Almost all congenitally infected individuals who are not treated manifest signs or symptoms of infection, such as chorioretinitis, by adolescence. Some severely involved infants with congenital infection appear to have Toxoplasma antigen–specific cell-mediated anergy, which may be important in the pathogenesis of disease.

Figure 290-1 Life cycle of Toxoplasma gondii and prevention of toxoplasmosis by interruption of transmission to humans.

Prevent infection or reduce manifestations in the fetus

- Prevent infection of mother.
- Identify women of risk by serologic testing.
- Treat acutely infected mother during pregnancy to reduce (by 60%) transmission.
- Identify infected fetus by ultrasound and amniocentesis.
- Treat fetus in utero to reduce severity of disease.

Prevent infection from meat, eggs and milk

- Cook meat to “well done,” smoke it, or cure it in brine.
- Do not touch mucous membranes of mouth or eyes while handling raw meat.
- Wash hands thoroughly after handling meat.
- Wash kitchen surfaces that come in contact with raw meat.
- Cook eggs. Do not drink unpasteurized milk.

Prevent infection via blood transfusion or organ transplantation

- Do not use blood products and organs from seropositive donors for seronegative recipients.

Prevent infection with oocysts excreted by cats

- Wash fruits and vegetables before consumption.
- Prevent access of flies, cockroaches, etc. to food.
- Avoid contact with materials that are potentially contaminated with cat feces, e.g. cat litter boxes, or wear gloves when handling such materials or when gardening or playing with children in a sandbox.
- Disinfect cat litter box for 5 min with nearly boiling water.

Prevent infection of mother

- Identify women of risk by serologic testing.
- Treat acutely infected mother during pregnancy to reduce (by 60%) transmission.
- Identify infected fetus by ultrasound and amniocentesis.
- Treat fetus in utero to reduce severity of disease.
unilateral and is estimated to occur in approximately 1% of cases in the United States. Approximately 10% of mothers of congenitally infected infants also have eye lesions. Acquired chorioretinal lesions cannot be distinguished from congenital infection based on their appearance. In some areas of Brazil, 80% of the population is infected and, of these, 20% have retinal involvement. Ocular symptoms may be present for a few days only or may persist for many months. The most common manifestation of acute acquired toxoplasmosis is enlargement of 1 or a few cervical lymph nodes. Cases of Toxoplasma lymphadenopathy can resemble infectious mononucleosis, lymphoma, or other lymphadenopathies (see Chapter 490). In the pectoral area in older girls and women, enlarged nodes may be confused with breast neoplasms. Mediastinal, mesenteric, and retroperitoneal lymph nodes may be involved. Involvement of intraabdominal lymph nodes may be associated with fever, mimicking appendicitis. Nodes may be tender but do not suppurate. Lymphadenopathy may wax and wane for as long as 1-2 yr. However, almost all patients with lymphadenopathy recover spontaneously without antimicrobial therapy. Significant organ involvement in immunologically normal persons is uncommon, although some individuals have suffered significant morbidity, including rare cases of encephalitis, brain abscesses, hepatitis, myocarditis, pericarditis, and polyarthritis. In persons acquiring T. gondii in Guyana and along Amazon tributaries, a severe form of multivisceral involvement with fever has occurred.

**Ocular Toxoplasmosis**

In the United States and Western Europe, T. gondii is estimated to cause 35% of cases of chorioretinitis (Fig. 290-2). In Brazil, T. gondii retinal lesions are common. Clinical manifestations include blurred vision, visual floaters, photophobia, epiphora, and, with macular involvement, loss of central vision. Ocular findings of congenital toxoplasmosis also include strabismus, microphthalmia, microcornea, cataracts, anisometropia, nystagmus, glaucoma, optic neuritis, and optic atrophy. Episodic recurrences are common, but precipitating factors have not been defined. Recurrent, active disease occurs most commonly at school-entry age and during adolescence. Anecdotally, stress or trauma seems to precipitate symptoms. Recurrences are most common closest to the time of acquisition of infection, and treatment leads to resolution of activity.

**Immunocompromised Persons**

Disseminated T. gondii infection among older children who are immunocompromised by AIDS, malignancy, cytotoxic therapy, corticosteroids, or immunosuppressive drugs given for organ transplantation involves the CNS in 50% of cases and may also involve the heart, lungs, and gastrointestinal tract. Stem cell transplant recipients present a special problem, because active infection is difficult to diagnose serologically. After transplantation, T. gondii-specific antibody levels may remain the same, increase, or decrease, and can even become undetectable. Toxoplasmosis in transplantation patients almost always results from transplantation from a seropositive donor to a seronegative recipient. Active infection is often fulminant and rapidly fatal without treatment.

Congenital T. gondii infection in infants with HIV infection is rare and can be a severe and fulminant disease with substantial CNS involvement. Alternatively, it may be more indolent in presentation, with focal neurologic deficits or systemic manifestations such as pneumonitis occurring with CD4 depletion.

**Figure 290-2** Toxoplasmic chorioretinitis. A, Retinal photographs of a child with severe vitreitis that is less intense than the classic “headlight in fog” appearance (left). Resolving vitreitis caused by underlying active lesion (middle). Resolved healed lesion without vitreitis (right). B, Retina photographs for a newborn infant with active vitreitis (left, labeled “near birth”) with clearing of vitreitis and marked, but not complete, resolution of activity of the lesion 3 wk later (right, labeled “with ongoing treatment”). C, Retinal photographs of a child showing an active lesion at presentation (left), and scarred lesion (right). D, Retinal photographs showing an active retinal lesion before treatment (left) and a completely resolved normal appearing retina within 1 mo of initiating treatment (right). E, Example of active choroidal neovascular membranes (CNVMs) in a child. Fundus photographs (top row), fluorescein angiogram (FA; middle row), and ocular coherence tomography (OCT; bottom row) of a child at presentation (first column), 7 wk after first ranibizumab (Lucentis, antibody to VEGF) injection (second column), and 11 wk after first ranibizumab injection (third column). (A to D adapted from Delair E, Latkany P, Noble AG, et al: Clinical manifestations of ocular toxoplasmosis, Ocul Immunol Inflamm 19:91–102, 2011; E adapted from Benevento JD, Jager RD, Noble AG, et al: Toxoplasmosis-associated neovascular lesions treated successfully with ranibizumab and antiparasitic therapy, Arch Ophthalmol 126:1152–1156, 2008.)
From 25-50% of persons with \textit{T. gondii} antibodies and \textit{HIV} infection without antiretroviral treatment eventually experience toxoplasmonic encephalitis, which is fatal if not treated. Highly active antiretroviral therapy and trimethoprim-sulfamethoxazole prophylaxis have diminished the incidence of toxoplasmosis in patients with HIV infection, but toxoplastic encephalitis remains a presenting manifestation in adult patients with AIDS. Typical findings include fever, headache, altered mental status, psychosis, cognitive impairment, seizures, and focal neurologic defects, including hemiparesis, aphasia, ataxia, visual field loss, cranial nerve palsies, and dysmetria or movement disorders. In adult patients with AIDS, toxoplastic retinal lesions are often large, with diffuse necrosis and contain many organisms but little inflammatory cellular infiltrate. Diagnosis of presumptive toxoplasmic encephalitis based on neuroradiologic studies in patients with AIDS necessitates a prompt therapeutic trial of medications effective against \textit{T. gondii}. Clear clinical improvement within 7-14 days and improvement of neuroradiologic findings within 3 wk makes the presumptive diagnosis almost certain.

\textbf{Congenital Toxoplasmosis}

Congenital toxoplasmosis usually occurs when a woman acquires primary infection while pregnant. Most often, maternal infection is asymptomatic or without specific symptoms or signs. As with other adults with acute toxoplasmosis, lymphadenopathy is the most common symptom.

In monozygotic twins the clinical pattern of involvement is most often similar, whereas in dizygotic twins the manifestations often differ, including cases of congenital infection in only 1 twin. The major histocompatibility complex class II gene DQ3 appears to be more frequent among HIV-infected persons seropositive for \textit{T. gondii} who develop toxoplastic encephalitis, and in children with congenital toxoplasmosis who develop hydrocephalus. These findings suggest that the presence of HLA-DQ3 is a risk factor for severity of toxoplasmosis. Other allelic variants of genes, including \textit{COL2A}, \textit{ABC4R}, \textit{P2X7R}, \textit{NALP1}, \textit{TLR9}, and \textit{ERAP}, are also associated with susceptibility.

Congenital infection may present as a mild or severe neonatal disease. It may also present with sequelae or relapse of a previously undiagnosed and untreated infection later in infancy or even later in life. There is a wide variety of manifestations of congenital infection, ranging from hydrops fetalis and perinatal death to small size for gestational age, prematurity, peripheral retinal scars, persistent jaundice, mild thrombocytopenia, CSF pleocytosis, and the characteristic triad of chorioretinitis, hydrocephalus, and cerebral calcifications. More than 50% of congenitally infected infants are considered normal in the perinatal period, but almost all such children develop ocular involvement later in life if they are not treated during infancy. Neurologic signs such as convulsions, setting-sun sign with downward gaze, and hydrocephalus with increased head circumference may be associated with substantial cerebral damage or with relatively mild inflammation obstructing the aqueduct of Sylvius. If affected infants are treated and shunted promptly, signs and symptoms may resolve and development may be normal.

The spectrum and frequency of neonatal manifestations of 210 newborns with congenital \textit{Toxoplasma} infection identified by a serologic screening program of pregnant women were described in 1984. In this study, 10% had severe congenital toxoplasmosis with CNS involvement, eye lesions, and general systemic manifestations; 34% had mild involvement with normal clinical examination results other than retinal scars or isolated intracranial calcifications; and 55% had no detectable manifestations. These numbers represent an underestimation of the incidence of severe congenital infection for several reasons: the most-severe cases, including most of those individuals who died, were not referred; therapeutic abortion sometimes was performed when acute acquired infection of the mother was diagnosed early during pregnancy; in utero spiramycin therapy prevented or diminished the severity of infection; only 13 of the 210 congenitally infected newborns had brain CT, and only 77% of these 210 infants had a CSF examination. Routine newborn examinations often yield normal findings for congenitally infected infants, but more careful evaluations may reveal significant abnormalities. In a 2012 analysis of the National Collaborative Chicago-Based Congenital Toxoplasmosis Study (NCCCTS) (1981-2009) data, it was found that 72% of children at or near birth had chorioretinal scars, 70% had CNS calcifications, 12% had microcephalus, 37% had hydrocephalus, 41% had thrombocytopenia, 39% had hepatomegaly, 32% had splenomegaly, and 41% were born prematurely (Fig. 290-3). In 1 study of 28 infants identified by a universal state-mandated serologic screening program for \textit{T. gondii}–specific immunoglobulin (Ig) M, 26 had normal findings on routine newborn examination but 14 had significant abnormalities detected with more careful evaluation. The abnormalities included retinal scars (7 infants), active chorioretinitis (3 infants), and CNS abnormalities (8 infants). In Fiocruz, Belo Horizonte, Brazil, infection is common, occurring in 1 in 600 live births. Half of these infected infants have active chorioretinitis at birth. When the infection is acquired in utero and the fetus is treated by treatment of the pregnant woman with pyrimethamine, sulfadiazine, and leucovorin, signs and symptoms in the infant may be prevented. The newborn infant may appear normal with no CSF abnormalities and no brain or eye disease. In utero treatment initiated rapidly results in a reduction of ocular and neurologic sequelae.

There is also a wide spectrum of symptoms of untreated congenital toxoplasmosis that presents later in the 1st yr of life (Table 290-1). More than 80% of these children have IQ scores of <70, and many have convulsions and severely impaired vision.

\textbf{SYSTEMIC SIGNS}

From 25% to >50% of infants with clinically apparent disease at birth are born prematurely. Parasite clonal types other than type II are more often associated with prematurity and more-severe disease. Intrauterine growth retardation, low Apgar scores, and temperature instability are common. Other manifestations may include lymphadenopathy, hepatosplenomegaly, myocarditis, pneumonitis, nephrotic syndrome, vomiting, diarrhea, and feeding problems. Bands of metaphyseal lucency and irregularity of the line of provisional calcification at the epiphyseal plate may occur without peristiole reaction in the ribs, femurs, and vertebrae. Congenital toxoplasmosis may be confused with erythroblastosis fetalis resulting from isosensitization, although...
Endocrine Abnormalities

Endocrine abnormalities may occur secondary to hypothalamic or pituitary involvement or end-organ involvement but are not common. Occasionally reported endocrinopathies include myxedema, persistent hypernatremia with vasopressin-sensitive diabetes insipidus, sexual precocity, and partial anterior hypopituitarism.

Central Nervous System

Neurologic manifestations of congenital toxoplasmosis vary from massive acute encephalopathy to subtle neurologic syndromes. Toxoplasmosis should be considered as a potential cause of any undiagnosed neurologic disease in children younger than 1 yr of age, especially if retinal lesions are present.

Hydrocephalus may be the sole clinical neurologic manifestation of congenital toxoplasmosis and almost always requires shunt placement. Hydrocephalus may present prenatally and progress during the perinatal period, or, much less commonly, may present later in life. Patterns of seizures are protean and have included focal motor seizures, petit and grand mal seizures, muscular twitching, opisthotonus, and hypsarrhythmia. Spinal or bulbar involvement may be manifested by paralytic scoliosis, difficulty swallowing, and respiratory distress. Microcephaly usually reflects severe brain damage, but some children with microcephaly caused by congenital toxoplasmosis who have been treated have normal or superior cognitive function. Untreated congenital toxoplasmosis that is symptomatic in the 1st yr of life can cause substantial diminution in cognitive function and developmental delay. Intellectual impairment also occurs in some children with subclinical infection without or despite treatment with pyrimethamine and sulfonamides. Seizures and focal motor defects may become apparent after the newborn period, even when infection is subclinical at birth.

CSF abnormalities occur in at least 50% of infants with congenital toxoplasmosis. A CSF protein level of >1 g/dl is characteristic of severe CNS toxoplasmosis and is usually accompanied by hydrocephalus. Local production of T. gondii-specific IgG and IgM antibodies may be demonstrated. CT of the brain is useful to detect calcifications, determine ventricular size, and demonstrate porencephalic cystic structures (Fig. 290-4). Calcifications occur throughout the brain, but there is a propensity for development of calcifications in the caudate nucleus and basal ganglia, choroid plexus, and subependyma. MRI and contrast-enhanced CT brain scans are useful for detecting active inflammatory lesions. MRIs that take only a brief time (<45 sec) for imaging or ultrasonography may be useful for following ventricular size. Treatment in utero and in the 1st yr of life results in improved neurologic outcomes.

Eyes

Almost all untreated congenitally infected infants develop chorioretinal lesions by adulthood, and may have severe visual impairment. T. gondii causes a focal necrotizing retinitis in congenitally infected individuals (see Fig. 290-2). Retinal detachment may occur. Any part of the retina may be involved, either unilaterally or bilaterally, including the maculae. The optic nerve may be involved, and toxoplasmic lesions that involve projections of the visual pathways in the brain or the visual cortex also may lead to visual impairment. In association with severe retinal lesions and vitreitis, secondary anterior uveitis may develop and occasionally lead to erythema of the external eye. Other ocular findings include cells and protein in the anterior chamber, large keratic precipitates, posterior synechiae, nodules on the iris, and neovascular formation on the surface of the iris, sometimes with increased intraocular pressure and glaucoma. Rarely, the extraocular musculature may also be involved directly. Other manifestations include strabismus, nystagmus, visual impairment, and microphthalmia. Enucleation has been required for a blind, phthisical, painful eye. The differential diagnosis of ocular toxoplasmosis includes congenital coloboma and inflammatory lesions caused by cytomegalovirus, Treponema pallidum, Mycobacterium tuberculosis, or vasculitis. Ocular toxoplasmosis may be a recurrent and progressive disease that requires multiple courses of therapy.

<table>
<thead>
<tr>
<th>Table 290-1</th>
<th>Signs and Symptoms Occurring Before Diagnosis or During the Course of Untreated Acute Congenital Toxoplasmosis in 152 Infants (A) and in 101 of These Same Children After They Had Been Followed 4 Yr or More (B)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SIGNS AND SYMPTOMS</strong></td>
<td><strong>Frequency of Occurrence in Patients with</strong></td>
</tr>
<tr>
<td>A. INFANTS</td>
<td>108 PATIENTS (%)</td>
</tr>
<tr>
<td>Chorioretinitis</td>
<td>102 (94)</td>
</tr>
<tr>
<td>Abnormal cerebrospinal fluid</td>
<td>59 (55)</td>
</tr>
<tr>
<td>Anemia</td>
<td>55 (51)</td>
</tr>
<tr>
<td>Convulsions</td>
<td>54 (50)</td>
</tr>
<tr>
<td>Intracranial calcification</td>
<td>54 (50)</td>
</tr>
<tr>
<td>Jaundice</td>
<td>31 (29)</td>
</tr>
<tr>
<td>Hydrocephalus</td>
<td>30 (28)</td>
</tr>
<tr>
<td>Fever</td>
<td>27 (25)</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>23 (21)</td>
</tr>
<tr>
<td>Lymphadenopathy</td>
<td>18 (17)</td>
</tr>
<tr>
<td>Hepatomegaly</td>
<td>18 (17)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>17 (16)</td>
</tr>
<tr>
<td>Microcephalus</td>
<td>14 (13)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>7 (6)</td>
</tr>
<tr>
<td>Cataracts</td>
<td>5 (5)</td>
</tr>
<tr>
<td>Eosinophilia</td>
<td>6 (4)</td>
</tr>
<tr>
<td>Abnormal bleeding</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Hypothermia</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Glaucoma</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Optic atrophy</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Microphthalmia</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Rash</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>0 (0)</td>
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<tr>
<td>B. CHILDREN ≥4 YR</td>
<td>70 PATIENTS (%)</td>
</tr>
<tr>
<td>Mental retardation</td>
<td>62 (89)</td>
</tr>
<tr>
<td>Convulsions</td>
<td>58 (83)</td>
</tr>
<tr>
<td>Spasticity and palsies</td>
<td>53 (76)</td>
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<tr>
<td>Severely impaired vision</td>
<td>48 (69)</td>
</tr>
<tr>
<td>Hydrocephalus or microcephalus</td>
<td>31 (44)</td>
</tr>
<tr>
<td>Deafness</td>
<td>12 (17)</td>
</tr>
<tr>
<td>Normal</td>
<td>6 (9)</td>
</tr>
</tbody>
</table>

* Patients with otherwise undiagnosed central nervous system disease in the 1st yr of life.
† Patients with otherwise undiagnosed nonneurologic diseases during the 1st 2 mo of life.


Study performed in 1947. The most severely involved institutionalized patients were not included in the later study of 101 children.
DNA in CSF and amniotic fluid, and has been reported to be useful with infant peripheral blood and characteristic lymph node histologic features establish the diagnosis of congenital toxoplasmosis, and antimicrobial therapy was initiated. This scan shows significant residual atrophy and calcifications. This child had substantial motor dysfunction, development delays, and visual impairment. D, CT scan obtained during the 1st mo of life of a microcephalic child. Note the numerous calcifications. This child’s IQ scores using the Stanford-Binet Intelligence Scale for children when she was 3 yr of age and the Wechsler Preschool and Primary Scale Intelligence when she was 5 yr of age were 100 and 102, respectively. She received antimicrobial therapy during her 1st yr of life. E, CT scan with hydrocephalus owing to aqueductal obstruction, before shunt. F, Scan from the same patient as the scan in E, after shunt. This child’s IQ scores using the Stanford-Binet Intelligence Scale for children were approximately 100 when she was 3 and 6 yr of age. (A to F adapted from McAuley J, Boyer K, Patel D, et al: Early and longitudinal evaluations of treated infants and children and untreated historical patients with congenital toxoplasmosis: the Chicago Collaborative Treatment Trial, Clin Infect Dis 18:38–72, 1994.)

Limited data suggest that occurrence of lesions in the early years of life may be prevented by instituting antimicrobial treatment with pyrimethamine and sulfonamides during the 1st yr of life and that treatment of the infected fetus in utero followed by treatment in the 1st yr of life with pyrimethamine, sulfadiazine, and leucovorin reduces the incidence and the severity of the retinal disease.

**Ears**

Sensorineural hearing loss, both mild and severe, may occur. It is not known whether this is a static or progressive disorder. Treatment in the 1st yr of life is associated with decreased frequency of hearing loss.

**DIAGNOSIS**

Diagnosis of acute *Toxoplasma* infection can be established by a number of methods (Table 290-2). For example, isolation of *T. gondii* from blood or body fluids; identification of tachyzoites in sections or preparations of tissues and body fluids, amniotic fluid, or placenta; identification of cysts in the placenta or tissues of a fetus or newborn; and characteristic lymph node histologic features establish the diagnosis. Serologic tests are very useful for diagnosis. Polymerase chain reaction (PCR) is useful to identify *T. gondii* DNA in CSF and amniotic fluid, and has been reported to be useful with infant peripheral blood and urine to definitively establish the diagnosis.

**Isolation**

Organisms are isolated by inoculation of body fluids, leukocytes, or tissue specimens into mice or tissue cultures. Body fluids should be processed and inoculated immediately, but *T. gondii* has been isolated from tissues and blood that have been stored overnight or even for 4–5 days at 4°C (39.2°F). Freezing or treatment of specimens with formalin kills *T. gondii*. From 6–10 days after inoculation into mice, or earlier if mice die, peritoneal fluids should be examined for tachyzoites. If inoculated mice survive for 6 wk and seroconvert, definitive diagnosis is made by visualization of *Toxoplasma* cysts in mouse brain. If cysts are not seen, subinoculations of mouse tissue into other mice are performed.

Microscopic examination of tissue culture inoculated with *T. gondii* shows necrotic, heavily infected cells with numerous extracellular tachyzoites. Isolation of *T. gondii* from blood or body fluids reflects acute infection. Except in the fetus or neonate, it is usually not possible to distinguish acute from past infection by isolation of *T. gondii* from tissues such as skeletal muscle, lung, brain, or eye obtained by biopsy or at autopsy.

Diagnosis of acute infection can be established by visualization of tachyzoites in biopsy tissue sections, bone marrow aspirate, or body fluids such as CSF or amniotic fluid. Immunofluorescent antibody and immunoperoxidase staining techniques may be necessary, because it is often difficult to distinguish the tachyzoite using ordinary stains. Tissue cysts are diagnostic of infection but do not differentiate between acute and chronic infection, although the presence of many cysts suggests recent acute infection. Cysts in the placenta or tissues of the newborn infant establish the diagnosis of congenital infection. Characteristic histologic features strongly suggest the diagnosis of toxoplasmic lymphadenitis.

**Serologic Testing**

Serologic tests are useful in establishing the diagnosis of congenital or acutely acquired *Toxoplasma* infection. Each laboratory that reports serologic test results must have established values for their tests that diagnose infection in specific clinical settings, provide interpretation of their results, and ensure appropriate quality control before therapy is based on serologic test results. Serologic test results used as the basis for therapy should be confirmed in a reference laboratory.

The Sabin-Feldman dye test is sensitive and specific. It measures primarily IgG antibodies. Results should be expressed in international units (IU/mL), based on international standard reference sera available from the World Health Organization.

The IgG indirect fluorescent-antibody (IgG-IFA) test measures the same antibodies as the dye test, and the titers tend to be parallel. These antibodies usually appear 1–2 wk after infection, reach high titers (≥1:1,000) after 6–8 wk, and then decline over months to years. Low titers (1:4 to 1:64) usually persist for life. Antibody titer does not correlate with severity of illness.

An agglutination test (Bio-Mérieux, Lyon, France) that is available commercially in Europe uses formalin-preserved whole parasites to detect IgG antibodies. This test is accurate, simple to perform, and inexpensive.

The IgM-IFA test is useful for the diagnosis of acute acquired infection with *T. gondii* in the older child because IgM antibodies appear earlier, often by 5 days after infection, and diminish more quickly than IgG antibodies. In most instances, IgM antibodies rise rapidly (1:50 to <1:1,000) and then fall to low titers (1:10 or 1:20) or disappear after weeks or months. However, some patients continue to have positive IgM results with low titers for several years. The IgM-IFA test detects *Toxoplasma*-specific IgM in only approximately 25% of congenitally infected infants at birth. IgM antibodies may not be present in sera of...
immunocompromised patients with acute toxoplasmosis or in patients with reactivation of ocular toxoplasmosis. The IgM-IFA test may yield false-positive results as a result of rheumatoid factor.

The double-sandwich IgM enzyme-linked immunosorbent assay (IgM-ELISA) is also useful for detection of Toxoplasma IgM antibodies. In the older child, serum IgM-ELISA Toxoplasma antibodies of >2 (a value of 1 reference laboratory; each laboratory must establish its own value for positive results) indicates that Toxoplasma infection most likely has been acquired recently. The IgM-ELISA identifies approximately 50-75% of infants with congenital infection. IgM-ELISA avoids both the false-positive results from rheumatoid factor and the false-negative results from high levels of passively transferred maternal...
IgG antibody in fetal serum, as may occur in the IgM-IFA test. Results obtained with commercial kits must be interpreted with caution, because false-positive reactions are not infrequent. Care must also be taken to determine whether kits have been standardized for diagnosis of infection in specific clinical settings, such as in the newborn infant. The IgA-ELISA also is a sensitive test for detection of maternal and congenital infection, and results may be positive when those of the IgM-ELISA are not.

The immunosorbent agglutination assay (ISAGA) combines trapping of a patient's IgM to a solid surface and use of formalin-fixed organisms or antigen-coated latex particles. It is read as an agglutination test. There are no false-positive results from rheumatoid factor or antinuclear antibodies. The IgM-ISAGA is more sensitive than the IgM-ELISA and may detect specific IgM antibodies before and for longer periods than the IgM-ELISA.

At present, the IgM-ISAGA and the IgA-ELISA are the most useful tests for diagnosis of congenital infection in the newborn. The IgG-ELISA and IgE-ISAGA are also sometimes useful in establishing the diagnosis of congenital toxoplasmosis or acute acquired T. gondii infection. The presence of IgM antibodies in the older child or adult can never be used alone to diagnose acute acquired infection.

The differential agglutination test (HS/AC) compares antibody titers obtained with formalin-fixed tachyzoites (HS antigen) with titers obtained using acetone- or methanol-fixed tachyzoites (AC antigen) to differentiate recent and remote infections in adults and older children. This method may be particularly useful in differentiating remote infection in pregnant women, because levels of IgM and IgA antibodies detectable by ELISA or ISAGA may remain elevated for months to years in adults and older children.

The avidity test can be helpful to establish time of acquisition of infection. A high-avidity test result indicates that infection began more than 12-16 wk earlier, which is especially useful in determining time of acquisition of infection in the 1st or final 16 wk of gestation. A low-avidity test result may be present for many months and is not diagnostic of recent acquisition of infection.

A relatively higher level of Toxoplasma antibody in the aqueous humor or in CSF demonstrates local production of antibody during active ocular or CNS toxoplasmosis. This comparison is performed, and a coefficient \( C \) is calculated as follows:

\[
C = \frac{\text{Antibody titer in body fluid}}{\text{Antibody titer in serum}} \times \frac{\text{Concentration of IgG in serum}}{\text{Concentration of IgG in body fluid}}
\]

Significant coefficients \( C \) are >8 for ocular infection, >4 for CNS for congenital infection, and >1 for CNS infection in patients with AIDS. If the serum dye test titer is >300 IU/mL, it is not possible to demonstrate significant local antibody production using this formula with either the dye test or the IgM-IFA test titer. IgM antibody may be detectable in CSF.

Comparative Western immunoblot tests of sera from a mother and infant may detect congenital infection. Infection is suspected when the mother's serum and her infant's serum contain antibodies that react with different Toxoplasma antigens.

The enzyme-linked immunofiltration assay using micropore membranes permits simultaneous study of antibody specificity by immunoprecipitation and characterization of antibody isotypes by immunoprecipitation with enzyme-labeled antibodies. This method is capable of detecting 85% of cases of congenital infection in the 1st few days of life.

PCR is used to amplify the DNA of T. gondii, which can then be detected by using a DNA probe. Detection of repetitive T. gondii genes, the B1 or 529 bp, 300 copy gene, in amniotic fluid is the PCR target of choice for establishing the diagnosis of congenital Toxoplasma infection in the fetus. Sensitivity and specificity of this test in amniotic fluid obtained to diagnose infections acquired between 12 and 21 wk of gestation are approximately 95%. Before and after that time, PCR with the 529 bp, 300 copy repeat gene as the template is 92% sensitive and 100% specific for detection of congenital infection. PCR of vitreous or aqueous fluids also has been used to diagnose ocular toxoplasmosis. PCR of peripheral white blood cells, CSF, and urine has been reported to detect congenital infection.

Lymphocyte blastogenesis to Toxoplasma antigens has been used to diagnose congenital toxoplasmosis when the diagnosis is uncertain and other test results are negative. However, a negative result does not exclude the diagnosis because peripheral blood lymphocytes of infected newborns may not respond to T. gondii antigens.

Acquired Toxoplasmosis

Recent infection is diagnosed by seroconversion from a negative to a positive IgG antibody titer (in the absence of transfusion); a 2 tube increase in Toxoplasma-specific IgG titer when serial sera are obtained 3 wk apart and tested in parallel; or the detection of Toxoplasma-specific IgM antibody in conjunction with other tests, but never alone.

Ocular Toxoplasmosis

IgG antibody titers of 1:4 to 1:64 are usual in older children with active Toxoplasma chorioretinitis. Even the presence of antibodies measurable only when serum is tested undiluted is helpful in establishing the diagnosis. The diagnosis is likely with characteristic retinal lesions and positive serologic tests. PCR of aqueous or vitreous fluid has been used to diagnose ocular toxoplasmosis but is infrequently performed because of the risks associated with obtaining intraocular fluid.

Immunocompromised Persons

IgG antibody titers may be low, and Toxoplasma-specific IgM is often absent in immunocompromised stem cell transplant recipients, but not in kidney or heart transplant recipients with toxoplasmosis. Demonstration of Toxoplasma DNA in serum, blood, and CSF may identify disseminated Toxoplasma infection in immunocompromised persons. Resolution of CNS lesions during a therapeutic trial of pyrimethamine and sulfadiazine has been useful to diagnose toxoplasmic encephalitis in patients with AIDS. Brain biopsy has been used to establish the diagnosis if there is no response to a therapeutic trial and to exclude other likely diagnoses such as CNS lymphoma.

Congenital Toxoplasmosis

Fetal ultrasound examination, performed every 2 wk during gestation, beginning at the time acute acquired infection is diagnosed in a pregnant woman, and PCR analysis of amniotic fluid are used for prenatal diagnosis. T. gondii may also be isolated from the placenta at delivery.

Serologic tests are also useful in establishing a diagnosis of congenital toxoplasmosis. Either persistent or rising titers in the dye test or IFA test, or a positive IgM-ELISA or IgM-ISAGA result is diagnostic of congenital toxoplasmosis. The half-life of IgM is approximately 2 days, so if there is a placental leak, the level of IgM antibodies in the infant's serum decreases significantly, usually within 1 wk. Passively transferred maternal IgG antibodies may require many months to a year to disappear from the infant's serum, depending on the magnitude of the original titer. The half-life of passively transferred maternal IgG is approximately 30 days, so the titer diminishes by half each 30 days. Synthesis of Toxoplasma antibody is usually demonstrable by the 3rd mo of life if the infant is untreated, although the rate of IgG synthesis varies considerably in infants younger than 1 year of age. If the infant is treated, synthesis may be delayed as long as the 9th mo of life and, infrequently, may not occur at all. When an infant begins to synthesize IgG antibody, infection may be documented serologically even without demonstration of IgM antibodies by an increase in the ratio of specific serum IgG antibody titer to the total IgG, whereas the ratio will decrease if the specific IgG antibody has been passively transferred from the mother.

Newborns suspected of having congenital toxoplasmosis should be evaluated by general, ophthalmologic, and neurologic examinations; head CT scan; attempt to isolate T. gondii from the placenta and infant's leukocytes from peripheral blood buffy coat; measurement of serum Toxoplasma-specific IgG, IgM, IgA, and IgE antibodies, and the levels
of total serum IgM and IgG; lumbar puncture including analysis of CSF for cells, glucose, protein, Toxoplasma-specific IgG and IgM antibodies, and level of total IgG; and testing of CSF for T. gondii by PCR and inoculation into mice. Presence of Toxoplasma-specific IgM in CSF that is not contaminated with blood or confirmation of local antibody production of Toxoplasma-specific IgG antibody in CSF establishes the diagnosis of congenital Toxoplasma infection.

Many manifestations of congenital toxoplasmosis are similar to findings that occur in other perinatal infections, especially congenital cytomegalovirus infection. Thus, neither cerebral calcification nor chorioretinitis is pathognomonic. The clinical picture in the newborn infant may also be compatible with sepsis, aseptic meningitis, syphilis, or hemolytic disease. Some children younger than 5 yr of age with chorioretinitis have postnatally acquired T. gondii infection.

**TREATMENT**

Pyrimethamine and sulfadiazine act synergistically against Toxoplasma, and combination therapy is indicated for many of the forms of toxoplasmosis. Use of pyrimethamine is contraindicated during the 1st trimester of pregnancy. Spiramycin should be used to attempt to prevent vertical transmission of infection to the fetus of acutely infected pregnant women. Pyrimethamine inhibits the enzyme dihydrofolate reductase, and thus the synthesis of folic acid, and therefore produces a dose-related, reversible, and usually gradual depression of the bone marrow. Neutropenia is most common but rarely treatment has been reported to result in thrombocytopenia and anemia. Reversible neutropenia is the most common adverse effect in treated infants. All patients treated with pyrimethamine should have platelet and leucocyte counts twice weekly. Seizures may occur with overdosage of pyrimethamine. Folinic acid, as calcium leucovorin, should always be administered concomitantly and for 1 wk after treatment with pyrimethamine is discontinued to prevent bone marrow suppression. Potential toxic effects of sulfonamides (e.g., crystalluria, hematuria, and rash) should be monitored. Hypersensitivity reactions occur, especially in patients with AIDS.

**Acquired Toxoplasmosis**

Patients with acquired toxoplasmosis and lymphadenopathy usually do not need specific treatment unless they have severe and persistent symptoms or evidence of damage to vital organs (see Table 290-2). If such signs and symptoms occur, treatment with pyrimethamine, sulfadiazine, and leucovorin should be initiated. Patients who appear to be immunocompetent but have severe and persistent symptoms or damage to vital organs (e.g., chorioretinitis, myocardiitis) need specific therapy until these specific symptoms resolve, followed by therapy for an additional 2 wk. Therapy often is administered for at least 4-6 wk. The optimal duration of therapy is unknown. A loading dose of pyrimethamine for older children is 2 mg/kg/day divided bid (maximum: 50 mg/bid), given for the 1st 2 days of treatment. The maintenance dose begins on the 3rd day and is 1 mg/kg/day (maximum: 50 mg/day). Sulfadiazine is administered at a dosage of 100 mg/kg/day divided bid (maximum: 4 g/day). Leucovorin is administered orally at a dosage of 5-20 mg 3 times a week (or even daily depending on the leukocyte count).

**Ocular Toxoplasmosis**

Patients with active ocular toxoplasmosis are treated with pyrimethamine, sulfadiazine, and leucovorin (see Table 290-2). They are treated while disease is active and then for approximately 1 wk after the lesion has developed a quiescent appearance (i.e., sharp borders, pigmentation at margins of the lesion, and resolution of associated inflammatory cells in the vitreous), which usually occurs in 2-4 wk when treatment is initiated promptly. Within 7-10 days the borders of the retinal lesions sharpen, and visual acuity usually returns to that noted before development of the acute lesion. Systemic corticosteroids have been administered concomitantly with antimicrobial treatment when lesions involve the macula, optic nerve head, or papillomacular bundle. Corticosteroids are never given alone and are begun after loading doses of pyrimethamine and sulfadiazine have been administered (2 days). With recurrences, new lesions often appear contiguous to old ones. Very rarely, vitrectomy and removal of the lens are needed to restore visual acuity. Suppressive treatment has prevented frequent recurrences of vision-threatening lesions.

Active choroidal neovascular membranes as a result of toxoplasmic chorioretinitis have been treated successfully in children with intravitreal injection of antibody to vascular endothelial growth factor in addition to oral anti-Toxoplasma medicines.

**Immunocompromised Persons**

Serologic evidence of acute infection in an immunocompromised patient, regardless of whether signs and symptoms of infection are present or tachyzoites are demonstrated in tissue, are indications for therapy similar to that described for immunocompetent persons with symptoms of organ injury (see Table 290-2). It is important to establish the diagnosis as rapidly as possible and institute treatment early. In immunocompromised patients other than those with AIDS, therapy should be continued for at least 4-6 wk beyond complete resolution of all signs and symptoms of active disease and resolution of cause for immune suppression. Careful follow-up observation of these patients is imperative because relapse may occur, requiring prompt reinstitution of therapy. Relapse used to be frequent in patients with AIDS without antiretroviral treatment, and suppressive therapy with pyrimethamine and sulfonamides, or trimethoprim-sulfamethoxazole, was continued for life. Now it is possible to discontinue maintenance therapy when the CD4 count remains at >200 cells/µL for 4 mo and all lesions have resolved. Therapy usually induces a beneficial response clinically, but it does not eradicate cysts. Treatment of T. gondii–seropositive patients with AIDS should be continued as long as CD4 counts remain at <200 cells/µL. Prophylactic treatment with trimethoprim-sulfamethoxazole for Pneumocystis carinii pneumonia significantly reduces the incidence of toxoplasmosis in patients with AIDS.

**Congenital Toxoplasmosis**

All fetuses and newborns infected with T. gondii should be treated whether or not they have clinical manifestations of the infection because treatment may be effective in interrupting acute disease that damages vital organs (see Table 290-2 and Fig. 290-5). The fetus is treated by treating the pregnant woman with pyrimethamine and sulfadiazine (with leucovorin). Infants should be treated for 1 yr with pyrimethamine (2 mg/kg/day divided bid for 2 days, then beginning on the 3rd day, 1 mg/kg/day for 2 or 6 mo, and then 1 mg/kg given on Monday, Wednesday, and Friday, PO), sulfadiazine (100 mg/kg/day divided bid PO), and leucovorin (5-10 mg given on Monday, Wednesday, and Friday, or more often depending on neutrophil count, PO). The relative efficacy in reducing sequelae of infection and the safety of treatment with 2 vs 6 mo of the higher dosage of pyrimethamine are being compared in the U.S. National Collaborative Study. Updated information about this study and these regimens is available from Dr. Rima McLeod (773-834-4131). Pyrimethamine and sulfadiazine are available only in tablet form and can be prepared as suspensions. Prednisone (1 mg/kg/day divided bid PO) has been used in addition when active chorioretinitis involves the macula or otherwise threatens vision or the CSF protein is >1,000 mg/dL at birth, but the efficacy is not established. Prednisone is continued only for as long as the active inflammatory process in the posterior pole of the eye is vision threatening or CSF protein is >1,000 mg/dL and then tapered rapidly if the duration of treatment has been brief.

**Pregnant Women with Toxoplasma gondii Infection**

The immunologically normal pregnant woman who acquired T. gondii more than 6 mo before conception does not need treatment to prevent congenital infection of her fetus. Although data are not available to allow for a definitive time interval, if infection occurs during or shortly before the pregnancy, it is reasonable to evaluate the fetus by use of PCR with amniotic fluid and ultrasonography and treat to prevent congenital infection in the fetus (see Table 290-2).

Treatment of a pregnant woman who acquires infection at any time during pregnancy reduces the chance of congenital infection in her
infant. Spiramycin (1 g every 8 hr PO without food) is recommended for prevention of fetal infection if the mother develops acute toxoplasmosis during pregnancy. Spiramycin is available in the United States upon an “emergency use” request by a physician through the FDA Division of Anti-Infective Drugs (301-796-1400) after the diagnosis of acute infection is confirmed in a reference laboratory (Palo Alto Medical Facility Toxoplasma Serology Lab 650-853-4828). With this approval, the physician can then contact the spiramycin manufacturer, Sanofi Pasteur (1-800-822-2463), to obtain spiramycin for the patient. Adverse reactions are infrequent and include paresthesia, rash, nausea, vomiting, and diarrhea. Following a loading dose of pyrimethamine (50 mg divided bid) for 2 days, beginning on the 3rd day, pyrimethamine is administered at a dose of 50 mg once daily. Beginning on the 1st day of treatment with pyrimethamine, sulfadiazine (1.5-2.0 g bid PO), and leucovorin (10 mg once daily PO) are recommended for treatment of the pregnant woman whose fetus has confirmed or probable fetal infection except in the 1st trimester. In the 1st trimester, when there is definite infection, sulfadiazine alone is recommended because pyrimethamine is potentially teratogenic at that time. Spiramycin treatment is used for infection acquired early in gestation when it is uncertain whether there is fetal infection. Treatment of the mother of an infected fetus with pyrimethamine and sulfadiazine reduces infection in the placenta and the severity of disease in the newborn. Delay in maternal treatment during gestation results in greater brain and eye disease in the infant. Diagnostic amniocentesis should be performed at >17-18 wk of gestation in pregnancies where there is high suspicion of fetal infection. Overall sensitivity of PCR for amniotic fluid is at 85% between 17 and 21 wk of gestation. The sensitivity of PCR using amniotic fluid is tested for presence of the 529 bp, 300 copy number. After 24 wk gestation, incidence of transmission is relatively high and pregnant women who are infected acutely after that time are treated with pyrimethamine and sulfadiazine to treat the fetus.

The approach in France to congenital toxoplasmosis includes systematic serologic screening of all women of childbearing age and again intrapartum each month during gestation beginning at ≤11 wk gestational age, at birth, and 1 mo after birth. Mothers with acute infection early in gestation and without evidence of involvement of the fetus are treated with spiramycin, which decreases the transmission. Ultrasoundography and amniocentesis for PCR at approximately 18 wk of gestation are used for fetal diagnosis and have 97% sensitivity and 100% specificity. Confidence intervals for sensitivity are largest early and late in gestation. Fetal infection is treated with pyrimethamine and sulfadiazine. Termination of pregnancy is very rare at present. Prompt initiation of treatment with pyrimethamine and sulfadiazine during pregnancy usually has an excellent outcome, with normal development of children. Only 19% have subtle findings of congenital infection, including intracranial calcifications (13%) and chorioretinal scars (6%), although 39% have chorioretinal scars detected at follow-up observation during later childhood. Several studies have demonstrated improved outcomes with shorter times between diagnosis and initiation of treatment.

Chromically infected pregnant women who are immunocompromised have transmitted T. gondii to their fetuses. Such women should be treated with spiramycin throughout gestation. The optimal management for prevention of congenital toxoplasmosis in the fetus of a pregnant woman with HIV infection with a CD4 count <200 cells/mL and inactive T. gondii infection is unknown. If the pregnancy is not terminated, some investigators suggest that the mother should be treated with spiramycin during the 1st 14 wk of gestation and thereafter with pyrimethamine and sulfadiazine until term. There are no universally accepted guidelines at present. In a study of adult patients with AIDS and toxoplasmic encephalitis, pyrimethamine (75 mg once daily PO) combined with high dosages of intravenously administered clindamycin (1,200 mg every 6 hr IV) appeared equal in efficacy to sulfadiazine and pyrimethamine in the treatment of the toxoplasmic encephalitis. Other experimental agents include the macrolides clarithromycin and azithromycin.

**PROGNOSIS**

Early institution of specific treatment for congenitally infected infants usually cures the active manifestations of toxoplasmosis, including active chorioretinitis, meningitis, encephalitis, hepatitis, splenomegaly, and thrombocytopenia. Rarely, hydrocephalus resulting from aqueductal obstruction may develop or become worse during therapy. Treatment appears to reduce the incidence of some sequelae such as diminished cognitive and abnormal motor function. Without therapy and in some treated patients as well, chorioretinitis often recurs. Children with extensive involvement at birth may function normally later in life or have mild to severe impairment of vision, hearing, cognitive

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**Table: Oral Suspension Formulations**

<table>
<thead>
<tr>
<th>Medication:</th>
<th>Sulfadiazine</th>
<th>Pyrimethamine</th>
<th>Folinic acid (calcium leucovorin)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concentration:</td>
<td>100mg/mL</td>
<td>2mg/mL</td>
<td>5mg tablets</td>
</tr>
<tr>
<td>Dispense:</td>
<td>50ml</td>
<td>25ml</td>
<td>30 tablets</td>
</tr>
<tr>
<td>Dosage:</td>
<td>Half of infant's current weight in kg equals number of mL given in AM and PM</td>
<td>Half of infant's current weight in kg equals number of mL given once daily</td>
<td>10mg (two 5mg tablets) daily on Monday, Wednesday, and Friday</td>
</tr>
<tr>
<td>* Suspend in 2% sugar solution. Suspension at usual concentration must be made each week. Store refrigerated.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
* e.g., infant weighs 5 kg, give 2.5 mL at 3AM and 7 PM. |
† e.g., infant weighs 8 kg, give 2.5 mL daily.
‡ e.g., infant weighs 12 kg, give 3.75 mL daily.
§ For pyrimethamine, first loading dose is 1 mg/kg given BID for 2 days. Beginning third day, dose is 1 mg/kg per day.

function, and other neurologic functions. Delays in diagnosis and therapy, perinatal hypoglycemia, hypoxia, hypotension, repeated shunt infections, and severe visual impairment are associated with a poorer prognosis. The prognosis is not necessarily poor for infected babies. It should be understood, however, that treatment with pyrimethamine and sulfadiazine does not eradicate encysted parasites.

Studies in Lyon and Paris, France, demonstrated that outcome of treated fetal toxoplasmosis, even when infection is acquired early in gestation, is usually favorable if no hydrocephalus is detected on ultrasound, and treatment with pyrimethamine and sulfadiazine is initiated promptly. The SYROCOT (Systematic Review on Congenital Toxoplasmosis) study in Europe indicated that neurologic outcome is improved with shorter times between diagnosis and initiation of treatment of fetal toxoplasmosis. Work in Lyon, France, has indicated a low incidence of recurrent eye disease in children with congenital toxoplasmosis who had been treated in utero and in their 1st yr of life. The National Collaborative Chicago-Based Congenital Toxoplasmosis Study (NCCCTS) (1981-2004) in the United States found that neurologic, developmental, audiologic, and ophthalmologic outcomes are considerably better for most, but not all, children who were treated in their 1st yr of life with pyrimethamine and sulfadiazine (with leucovorin) when compared to children who had not been treated or were treated for only 1 mo in earlier decades described in the literature. The mean age of the children in this study was 10.8 yr at the time of this analysis, when most of the children had not yet entered their teenage years. Recurrent disease, if it occurs, appears most commonly during adolescence.

**PREVENTION**

Counseling pregnant women about the methods of preventing transmission of *T. gondii* (see Fig. 290-1) during pregnancy can reduce acquisition of infection during gestation. Women who do not have specific antibody to *T. gondii* before pregnancy should only eat well-cooked meat during pregnancy and avoid contact with oocysts excreted by cats. Cats that are kept indoors, maintained on prepared food, and not fed fresh, uncooked meat should not contact encysted *T. gondii* or shed oocysts. Serologic screening, ultrasound monitoring, and treatment of pregnant women during gestation can also reduce the incidence and manifestations of congenital toxoplasmosis. No protective vaccine is available.

*Bibliography is available at Expert Consult.*
ETIOLOGY

Ascariasis is caused by the nematode, or roundworm, *Ascaris lumbricoides*. Adult worms of *A. lumbricoides* inhabit the lumen of the small intestine and have a life span of 10-24 mo. The reproductive potential of *Ascaris* is prodigious; a gravid female worm produces 200,000 eggs per day. The fertile ova are oval in shape with a thick mammillated covering measuring 45-70 µm in length and 35-50 µm in breadth (Fig. 291-1). After passage in the feces, the eggs embryonate and become infective in 5-10 days under favorable environmental conditions. Adult worms can live for 12-18 mo (Fig. 291-2).

EPIDEMIOLOGY

Ascariasis occurs globally and is the most prevalent human helminthiasis in the world. It is most common in tropical areas of the world where environmental conditions are optimal for maturation of ova in the soil. Approximately 1 billion persons are estimated to be infected. Although the number of cases in the United States is not known precisely, the highest prevalence is thought to be in high poverty areas of the South and Appalachia. Pig farming in Maine is also associated with *Ascaris* species. Key factors linked with a higher prevalence of infection include poor socioeconomic conditions, use of human feces as fertilizer, and geophagia. Even though infection can occur at any age, the highest rate is in preschool or early school-age children. Transmission is primarily hand to mouth, but may also involve ingestion of contaminated raw fruits and vegetables. Transmission is enhanced by the high output of eggs by fecund female worms and resistance of ova to the outside environment. *Ascaris* eggs can remain viable at 5-10°C (41-50°F) for as long as 2 yr.

PATHOGENESIS

Ascaris ova hatch in the small intestine after ingestion by the human host. Larvae are released, penetrate the intestinal wall, and migrate to
the lungs by way of the venous circulation. The parasites then cause **pulmonary ascariasis** as they enter into the alveoli and migrate through the bronchi and trachea. They are subsequently swallowed and return to the intestines, where they mature into adult worms. Female *Ascaris* begin depositing eggs in 8-10 wk.

**CLINICAL MANIFESTATIONS**
The clinical presentation depends on the intensity of infection and the organs involved. Most individuals have low to moderate worm burdens and have no symptoms or signs. The most common clinical problems are from **pulmonary disease** and **obstruction of the intestinal or biliary tract**. Larvae migrating through these tissues may cause allergic symptoms, fever, urticaria, and granulomatous disease. The pulmonary manifestations resemble Loeffler syndrome and include transient respiratory symptoms such as cough and dyspnea, pulmonary infiltrates, and blood eosinophilia. Larvae may be observed in the sputum. Vague abdominal complaints have been attributed to the presence of adult worms in the small intestine, although the precise contribution of the parasite to these symptoms is difficult to ascertain. A more serious complication occurs when a large mass of worms leads to acute bowel obstruction. Children with heavy infections may present with vomiting, abdominal distention, and cramps. In some cases, worms may be passed in the vomitus or stools. *Ascaris* worms occasionally migrate into the biliary and pancreatic ducts, where they cause cholecystitis or pancreatitis. Worm migration through the intestinal wall can lead to peritonitis. Dead worms can serve as a nidus for stone formation. Studies show that chronic infection with *A. lumbricoides* (often coincident with other helminth infections) impairs growth, physical fitness, and cognitive development.

**DIAGNOSIS**
Microscopic examination of fecal smears can be used for diagnosis because of the high number of eggs excreted by adult female worms (see Fig. 291-1). A high index of suspicion in the appropriate clinical context is needed to diagnose pulmonary ascariasis or obstruction of the gastrointestinal tract. Ultrasound examination of the abdomen is capable of visualizing intraluminal adult worms.

**TREATMENT**
Although several chemotherapeutic agents are effective against ascariasis, none has documented utility during the pulmonary phase of infection. Treatment options for gastrointestinal ascariasis include albendazole (400 mg PO once, for all ages), mebendazole (100 mg PO bid for 3 days or 500 mg once for all ages), or ivermectin (150-200 µg/kg PO once). Piperazine citrate (75 mg/kg/day for 2 days; maximum: 3.5 g/day), which causes neuromuscular paralysis of the parasite and rapid expulsion of the worms, is the treatment of choice for intestinal or biliary obstruction and is administered as syrup through a nasogastric tube. Surgery may be required for cases with severe obstruction. Nitazoxanide (100 mg PO bid for 3 days for children 1-3 yr of age, 200 mg bid for 3 days for children 4-11 yr, and 500 mg bid for 3 days for adolescents and adults) produces cure rates comparable to single-dose albendazole. Drug resistance has not been reported, but repeated treatment for ascariasis may be necessary because reinfection is common.

**PREVENTION**
Although ascariasis is the most prevalent worm infection in the world, little attention has been given to its control. Anthelmintic chemotherapy programs can be implemented in 1 of 3 ways: (1) offering universal treatment to all individuals in an area of high endemicity; (2) offering treatment targeted to groups with high frequency of infection, such as children attending primary school; or (3) offering individual treatment based on intensity of current or past infection. Improving education about and practices of sanitary conditions and sewage facilities, discontinuing the practice of using human feces as fertilizer, and education are the most effective long-term preventive measures.

*Bibliography is available at Expert Consult.*
Bibliography
Hookworms (Necator americanus and Ancylostoma Spp.)

Peter J. Hotez

ETIOLOGY
Two major genera of hookworms, which are nematodes or roundworms, infect humans. Necator americanus, the only representative of its genus, is a major anthropophilic hookworm and is the most common cause of human hookworm infection. Hookworms of the genus Ancylostoma include the anthropophilic hookworm Ancylostoma duodenale that also causes classic hookworm infection and the less common zoonotic species Ancylostoma ceylanicum, Ancylostoma caninum, and Ancylostoma braziliense. Human zoonotic infection with the dog hookworm A. caninum is associated with an eosinophilic enteritis syndrome. The larval stage of A. braziliense, whose definitive hosts include dogs and cats, is the principal cause of cutaneous larva migrans.

The infective larval stages of the anthropophilic hookworms live in a developmentally arrested state in warm, moist soil. Larvae infect humans either by penetrating through the skin (N. americanus and A. duodenale) or when they are ingested (A. duodenale). Larvae entering the human host by skin penetration undergo extraintestinal migration through the venous circulation and lungs before they are swallowed, whereas orally ingested larvae may undergo extraintestinal migration or remain in the gastrointestinal tract. Larvae returning to the small intestine undergo 2 molts to become adult, sexually mature, male and female worms ranging in length from 5-13 mm. The buccal capsule of the adult hookworm is armed with cutting plates (N. americanus) or teeth (A. duodenale) to facilitate attachment to the mucosa and submucosa of the small intestine. Hookworms can remain in the intestine for 1-5 yr, where they mate and produce eggs. Although up to 2 mo is required for the larval stages of hookworms to undergo extraintestinal migration and develop into mature adults, A. duodenale larvae may remain developmentally arrested for many months before resuming development in the intestine. Mature A. duodenale female worms produce about 30,000 eggs per day; daily egg production by N. americanus is <10,000/day (Fig. 292-1). The eggs are thin shelled and ovoid, measuring approximately 40-60 µm. Eggs that are deposited on soil with adequate moisture and shade develop into first-stage larvae and hatch. Over the ensuing several days and under appropriate conditions, the larvae molt twice to the infective stage. Infective larvae are developmentally arrested and nonfeeding. They migrate vertically in the soil until they either infect a new host or exhaust their lipid metabolic reserves and die.

EPIDEMIOLOGY
Hookworm infection is one of the most prevalent infectious diseases of humans, affecting an estimated 600-700 million individuals worldwide. New information from the Global Burden of Disease 2010 Study indicates that hookworm infection leads all neglected tropical diseases in years lost through disability. In the case of hookworm infection, all of the years lost through disability are attributed to anemia from intestinal blood loss.

Because of the requirement for adequate soil moisture, shade, and warmth, hookworm infection is usually confined to rural areas, especially where human feces are used for fertilizer or where sanitation is inadequate. Hookworm is an infection associated with economic underdevelopment and poverty throughout the tropics and subtropics. Sub-Saharan Africa, East Asia, and tropical regions of the Americas.
have the highest prevalence of hookworm infection. High rates of infection are often associated with cultivation of certain agricultural products such as tea in India; sweet potato, corn, cotton, and mulberry trees in China; coffee in Central and South America; and rubber in Africa. It is not uncommon to find dual *N. americanus* and *A. duodenale* infections. *N. americanus* predominates in Central and South America as well as in southern China and southeast Asia, whereas *A. duodenale* predominates in North Africa, in northern India, in China north of the Yangtze River, and among aboriginal people in Australia. The ability of *A. duodenale* to withstand somewhat harsher environmental and climatic conditions may reflect its ability to undergo arrested development in human tissues. *A. ceylanicum* infection occurs in India and Southeast Asia.

Eosinophilic enteritis caused by *A. caninum* was first described in Queensland, Australia, with 2 reported cases in the United States. Because of its global distribution in dogs, it was initially anticipated that human *A. caninum* infections would be identified in many locales, but this has not been found.

**PATHOGENESIS**

The major morbidity of human hookworm infection is a direct result of intestinal blood loss. Adult hookworms adhere tenaciously to the mucosa and submucosa of the proximal small intestine by using their cutting plates or teeth and a muscular esophagus that creates negative pressure in their buccal capsules. At the attachment site, host inflammation is downregulated by the release of antiinflammatory polypeptides by the hookworm. Rupture of capillaries in the lamina propria is associated with chronic hookworm disease. The eggs of *A. duodenale* infection cause loss of an estimated 0.2 mL of blood/day; blood loss is less for *N. americanus*. Individuals with light infections suffer from very little blood loss and, consequently, may have hookworm infection but not hookworm disease. There is a direct correlation between the number of adult hookworms in the gut and the volume of fecal blood loss. Hookworm disease results only when infants experience sufficient blood loss to develop iron deficiency and anemia. Hypoalbuminemia and consequent edema and anasarca from the loss of intravascular oncotic pressure can also occur. These features depend heavily on the dietary reserves of the host.

**CLINICAL MANIFESTATIONS**

Chromically infected children with moderate and heavy hookworm infections suffer from intestinal blood loss that results in iron deficiency and can lead to anemia as well as protein malnutrition. Prolonged iron deficiency associated with hookworms in childhood can lead to physical growth retardation and cognitive and intellectual deficits.

Anthropophilic hookworm larvae elicit dermatitis sometimes referred to as ground itch when they penetrate human skin. The vesication and edema of ground itch are exacerbated by repeated infection. Infection with a zoonotic hookworm, especially *A. braziliense*, can result in lateral migration of the larvae to cause the characteristic cutaneous tracts of cutaneous larva migrans (see Chapter 292.1). Cough subsequently occurs in *A. duodenale* and *N. americanus* hookworm infection when larvae migrate through the lungs to cause laryngotracheobronchitis, usually about 1 wk after exposure. Pharyngitis also can occur. The onset of eosinophilia coincides with the entry of hookworm larvae into the gastrointestinal tract. Upper abdominal pain can occur during this period, but it eventually subsides.

Chronic intestinal hookworm infection is not typically associated with specific gastrointestinal complaints, although pain, anorexia, and diarrhea have been attributed to the presence of hookworms. The major clinical manifestations are related to intestinal blood loss. Heavily infected children exhibit all of the signs and symptoms of iron deficiency anemia and protein malnutrition. In some cases, children with chronic hookworm disease acquire a yellow-green pallor known as chlorosis.

An infantile form of ancylostomiasis resulting from heavy *A. duodenale* infection has been described. Affected infants experience diarrhea, melena, failure to thrive, and profound anemia. Infantile ancylostomiasis has significant mortality.

Eosinophilic enteritis caused by *A. caninum* is associated with colicky abdominal pain that begins in the epigastrium and radiates outward and is usually exacerbated by food. Extreme cases may mimic acute appendicitis.

**DIAGNOSIS**

Children with hookworm release eggs that can be detected by direct fecal examination (Fig. 292-2). Quantitative methods are available to determine whether a child has a heavy worm burden that can cause hookworm disease. The eggs of *N. americanus* and *A. duodenale* are morphologically indistinguishable. Species identification typically requires egg hatching and differentiation of third-stage infective larvae; newer methods using polymerase chain reaction methods have been developed but are not generally used in clinical practice.

In contrast, eggs are generally not present in the feces of patients with eosinophilic enteritis caused by *A. caninum*. Eosinophilic enteritis is often diagnosed by demonstrating ileal and colonic ulcerations by colonoscopy in the presence of significant blood eosinophilia. An adult canine hookworm may occasionally be recovered during colonoscopic biopsy. Patients with this syndrome develop immunoglobulin G and immunoglobulin E serologic responses.

**TREATMENT**

The goal of deworming is removal of the adult hookworms with an anthelmintic drug. The benzimidazole anthelmintics, mebendazole and albendazole, are effective at eliminating hookworms from the
Cutaneous larva migrans (creeping eruption) is caused by the larvae of several nematodes, primarily hookworms, which are not usually parasitic for humans. *A. braziliense*, a hookworm of dogs and cats, is the most common cause, but other animal hookworms may also produce the disease.

**ETIOLOGY**

Cutaneous larva migrans is usually caused by *A. braziliense*, which is endemic to the southeastern United States and Puerto Rico. Travelers account for a significant percentage of the cases.

**CLINICAL MANIFESTATIONS**

After penetrating the skin, larvae localize at the epidermal-dermal junction and migrate in this plane, moving at a rate of 1-2 cm/day. The response to the parasite is characterized by raised, erythematous, serpiginous tracks, which occasionally form bullae (Fig. 292-3). These lesions may be single or numerous and are usually localized to an extremity, although any area of the body may be affected. As the organism migrates, new areas of involvement may appear every few days. Intense localized pruritus, without any systemic symptoms, may be associated with the lesions. Bacterial superinfection can occur.

**PREVENTION**

In 2001, the World Health Assembly urged its member states to implement programs of periodic deworming so as to control the morbidity of hookworm and other soil-transmitted helminth infections. Although anthelmintic drugs are effective at eliminating hookworms from the intestine, the high rates of drug failure from single-dose mebendazole and posttreatment reinfection among children suggest that mass drug administration alone is not effective for controlling hookworm in highly endemic areas. Moreover, data suggest that the efficacy of mebendazole decreases with frequent, periodic use, leading to concerns about the possible emergence of anthelmintic drug resistance. To reduce the reliance exclusively on anthelmintic drugs, a recombinant human hookworm vaccine has been developed and is undergoing clinical testing. Economic development and associated improvements in sanitation, health education, and avoidance of human feces as fertilizer remain critical for reducing hookworm transmission and endemicity.

**TREATMENT**

If left untreated, the larvae die, and the syndrome resolves within a few weeks to several months. Treatment with ivermectin (200 µg/kg daily PO for 1-2 days; considered the drug of choice by some investigators), mebendazole (400 mg daily PO for 3 days, for all ages), or topical thiabendazole hastens resolution, if symptoms warrant treatment. Nausea and vomiting frequently preclude repeated administration of oral thiabendazole. The safety of ivermectin in young children (weighing <15 kg) and pregnant women remains to be established. Ivermectin should be taken on an empty stomach with water, whereas albendazole should be taken with a fatty meal.

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ETIOLOGY
Trichuriasis is caused by the *whipworm*, *Trichuris trichiura*, a nematode, or roundworm, that inhabits the cecum and ascending colon. The principal hosts of *T. trichiura* are humans who acquire infection by ingesting embryonated, barrel-shaped eggs (Fig. 293-1). The larvae escape from the shell in the upper small intestine and penetrate the intestinal villi. The worms slowly move toward the cecum, where the...
developmental and cognitive deficits. There is no significant eosinophilia, even though a portion of the worm is embedded in the mucosa of the large bowel.

**DIAGNOSIS**

Because egg output is so high, fecal smears frequently reveal the characteristic barrel-shaped ova of *T. trichiura*.

**TREATMENT**

Albendazole (400 mg PO for 3 days for all ages) is the drug of choice and is safe and effective, in part because it is poorly absorbed from the gastrointestinal tract. It reduces egg output by 90-99% and has cure rates of 70-90%, although reinfection and resumption of egg production by live worms that presumably survive after treatment may occur. Alternatives include mebendazole (100 mg PO bid for 3 days) and ivermectin (200 µg/kg PO for 3 days). Single-day treatment with albendazole, nitazoxanide, or albendazole plus nitazoxanide lead to cure rates that are low and short-lived. Combination treatment with oxantel pamoate (20 mg/kg) plus 400 mg albendazole on consecutive days may have the highest cure rate.

**PREVENTION**

Disease can be prevented by personal hygiene, improved sanitary conditions, and eliminating the use of human feces as fertilizer.

*Figure 293-1* *Trichuris trichiura*. Soil-transmitted helminth eggs. (From Bethony J, Brooker S, Albonico M, et al: Soil-transmitted helminth infections: ascariasis, trichuriasis, and hookworm, Lancet 367:1521–1532, 2006.)

*Figure 293-2* *Trichuris trichiura*. Adult male and female soil-transmitted helminths. (From Bethony J, Brooker S, Albonico M, et al: Soil-transmitted helminth infections: ascariasis, trichuriasis, and hookworm, Lancet 367:1521–1532, 2006.)

anterior three quarters whiplike portion remains within the superficial mucosa and the short posterior end is free in the lumen (*Fig. 293-2*). In 1-3 mo, the adult female worm begins producing 5,000-20,000 eggs per day. After excretion in the feces, embryonic development occurs in 2-4 wk with optimal temperature and soil conditions. The adult worm life span is approximately 2 yr.

**EPIDEMIOLOGY**

Trichuriasis occurs throughout the world and is especially common in poor rural communities with inadequate sanitary facilities and soil contaminated with human or animal feces. Trichuriasis is one of the most prevalent human helminthiases, with an estimated 1 billion infected individuals worldwide. In many parts of the world, where protein-energy malnutrition and anemia are common, the prevalence of *T. trichiura* infection can be as high as 95%. Although trichuriasis occurs in the rural southeastern United States, its prevalence has not been reported. The highest rate of infection occurs among children 5-15 yr of age. Infection develops after ingesting embryonated ova by direct contamination of hands, food (raw fruits and vegetables fertilized with human feces), or drink. Transmission can also occur indirectly through flies or other insects.

**CLINICAL MANIFESTATIONS**

Most persons harbor low worm burdens and do not have symptoms. Some individuals may have a history of right-lower-quadrant or vague periumbilical pain. Adult *Trichuris* suck approximately 0.005 mL of blood per worm per day. Children, who are most likely to be heavily infected, frequently suffer from disease. Clinical manifestations include chronic dysentery, rectal prolapse, anemia, poor growth, as well as
Bibliography

ETIOLOGY
The cause of enterobiasis, or pinworm infection, is *Enterobius vermicularis*, which is a small (1 cm in length), white, threadlike nematode, or roundworm, that typically inhabits the cecum, appendix, and adjacent areas of the ileum and ascending colon. Gravid females migrate at night to the perianal and perineal regions, where they deposit up to 15,000 eggs. Ova are convex on 1 side and flattened on the other and have diameters of approximately $30 \times 60 \mu m$. Eggs embryonate within 6 hr and remain viable for 20 days. Human infection occurs by the fecal-oral route typically by ingestion of embryonated eggs that are carried on fingernails, clothing, bedding, or house dust. After ingestion, the larvae mature to form adult worms in 36-53 days.

EPIDEMIOLOGY
Enterobiasis infection occurs in individuals of all ages and socioeconomic levels. It is prevalent in regions with temperate climates and is the most common helminth infection in the United States. It infects 30% of children worldwide, and humans are the only known host. Infection occurs primarily in institutional or family settings that include children. The prevalence of pinworm infection is highest in children 5-14 yr of age. It is common in areas where children live, play, and sleep close together, thus facilitating egg transmission. Because the life span of the adult worm is short, chronic parasitism is likely due to repeated cycles of reinfection. Autoinoculation can occur in individuals who habitually put their fingers in their mouth.
PATHOGENESIS

Enterobius infection may cause symptoms by mechanical stimulation and irritation, allergic reactions, and migration of the worms to anatomic sites where they become pathogenic. Enterobius infection has been associated with concomitant Dientamoeba fragilis infection, which causes diarrhea.

CLINICAL MANIFESTATIONS

Pinworm infection is innocuous and rarely causes serious medical problems. The most common complaints include itching and restless sleep secondary to nocturnal perianal or perineal pruritus. The precise cause and incidence of pruritus are unknown but may be related to the intensity of infection, psychologic profile of the infected individual and his or her family, or allergic reactions to the parasite. Eosinophilia is not observed in most cases, because tissue invasion does not occur. Aberrant migration to ectopic sites occasionally may lead to appendicitis, chronic salpingitis, pelvic inflammatory disease, peritonitis, hepatitis, and ulcerative lesions in the large or small bowel.

DIAGNOSIS

A history of nocturnal perianal pruritus in children strongly suggests enterobiasis. Definitive diagnosis is established by identification of parasite eggs or worms. Microscopic examination of adhesive cellophane tape pressed against the perianal region early in the morning frequently demonstrates eggs (Fig. 294-1). Repeated examinations increase the chance of detecting ova; a single examination detects 50% of infections, 3 examinations 90%, and 5 examinations 99%. Worms seen in the perianal region should be removed and preserved in 75% ethyl alcohol until microscopic examination can be performed. Digital rectal examination may also be used to obtain samples for a wet mount. Routine stool samples rarely demonstrate Enterobius ova.

TREATMENT

Anthelmintic drugs should be administered to infected individuals and their family members. Albendazole (400 mg PO with a repeat dose 2 wk later for all age groups) is the treatment of choice and results in cure rates exceeding 90%. Alternatives include mebendazole (100 mg PO with a repeat dose 2 wk later) and pyrantel pamoate (11 mg/kg base PO 3 times for 1 day up to a maximum of 1 g; repeat at 2 wk). Morning bathing removes a large portion of eggs. Frequent changing of underclothes, bed clothes, and bed sheets decreases environmental egg contamination and may decrease the risk for autoinfection.

PREVENTION

Household contacts can be treated at the same time as the infected individual. Repeated treatments every 3–4 mo may be required in circumstances with repeated exposure, such as with institutionalized children. Good hand hygiene is the most effective method of prevention.

Bibliography is available at Expert Consult.
Bibliography
Chapter 295

**Strongyloidiasis**

*(Strongyloides stercoralis)*

Arlene E. Dent and James W. Kazura

**ETIOLOGY**

Strongyloidiasis is caused by the nematode, or roundworm, *Strongyloides stercoralis*. Only adult female worms inhabit the small intestine. The nematode reproduces in the human host by parthenogenesis and releases eggs containing mature larvae into the intestinal lumen. Rhabditiform larvae immediately emerge from the ova and are passed in feces, where they can be visualized by stool examination. Rhabditiform larvae either differentiate into free-living adult male and female worms or metamorphose into the infectious filariform larvae. Sexual reproduction occurs only in the free-living stage. Humans are usually infected through skin contact with soil contaminated with infectious larvae. Larvae penetrate the skin, enter the venous circulation and then pass to the lungs, break into alveolar spaces, and migrate up the bronchial tree. They are then swallowed and pass through the stomach, and adult female worms develop in the small intestine. Egg deposition begins approximately 28 days after initial infection.

The hyperinfection syndrome occurs when large numbers of larvae transform into infective organisms during their passage in feces and then reinfect (autoinfect) the host by way of the lower gastrointestinal tract or perianal region. This cycle may be accelerated in immunocompromised persons, particularly those with depressed T-cell function.

**EPIDEMIOLOGY**

*S. stercoralis* infection is prevalent in tropical and subtropical regions of the world and is endemic in several areas of Europe, the southern United States, and Puerto Rico. Transmission requires appropriate environmental conditions, particularly warm, moist soil. Poor sanitation and crowded living conditions are conducive to high levels of transmission. Dogs and cats can act as reservoirs. The highest prevalence of infection in the United States (4% of the general population) is in impoverished rural areas of Kentucky and Tennessee. Infection may be especially common among residents of mental institutions, veterans who were prisoners of war in areas of high endemicity, and refugees and immigrants. Because of internal autoinfection, individuals may remain infected for decades. Infection may be transmitted by organ transplantation. Individuals with hematologic malignancies, autoimmune diseases, malnutrition, and drug-induced immunosuppression (especially corticosteroids) are at high risk for the hyperinfection syndrome. Patients with AIDS may experience a rapid course of disseminated strongyloidiasis with a fatal outcome.

**PATHOGENESIS**

The initial host immune response to infection is production of immunoglobulin E and eosinophilia in blood and tissues, which presumably prevents dissemination and hyperinfection in the immunocompetent host. Adult female worms in otherwise healthy and asymptomatic individuals may persist in the gastrointestinal tract for years. If infected persons become immunocompromised, the reduction in cellular and humoral immunity may lead to an abrupt and dramatic increase in parasite load with systemic dissemination.

**CLINICAL MANIFESTATIONS**

Approximately 30% of infected individuals are asymptomatic. The remaining patients have symptoms that correlate with the 3 stages of infection: invasion of the skin, migration of larvae through the lungs, and parasitism of the small intestine by adult worms. *Larva currens* is
the manifestation of an allergic reaction to filariform larvae that migrate through the skin, where they leave pruritic, tortuous, urticarial tracks. The lesions may recur and are typically found over the lower abdominal wall, buttocks, or thighs, resulting from larval migration from defecated stool. Pulmonary disease secondary to larval migration through the lung rarely occurs and may resemble Loeffler syndrome (cough, wheezing, shortness of breath, transient pulmonary infiltrates accompanied by eosinophilia). Gastrointestinal strongyloidiasis is characterized by indigestion, crampy abdominal pain, vomiting, diarrhea, steatorrhea, protein-losing enteropathy, protein-caloric malnutrition, and weight loss. Edema of the duodenum with irregular mucosal folds, ulcerations, and strictures can be seen radiographically. Infection may be chronic in nature and is associated with eosinophilia.

Strongyloidiasis is potentially lethal because of the ability of the parasite to replicate within the host and cause overwhelming hyperinfection in immunocompromised persons. The hyperinfection syndrome is characterized by an exaggeration of the clinical features that develop in symptomatic immunocompetent individuals. The onset is usually sudden, with generalized abdominal pain, distention, and fever. Multiple organs can be affected as massive numbers of larvae disseminate throughout the body and introduce bowel flora. The latter may result in bacteremia and septicemia. Cutaneous manifestations may include petechiae and purpura. Cough, wheezing, and hemoptysis are indicative of pulmonary involvement. Whereas eosinophilia is a prominent feature of strongyloidiasis in immunocompetent persons, this sign may be absent in immunocompromised persons. Because of the low incidence of strongyloidiasis in industrialized countries, it is often misdiagnosed, resulting in a significant delay in treatment.

**DIAGNOSIS**

Intestinal strongyloidiasis is diagnosed by examining feces or duodenal fluid for the characteristic larvae (Fig. 295-1). Several stool samples should be examined either by direct smear, the Koga agar plate method, or the Baermann test. Alternatively, duodenal fluid can be sampled by the enteric string test (Entero-Test) or aspiration via endoscopy. In children with the hyperinfection syndrome, larvae may be found in sputum, gastric aspirates, and, rarely, in small intestinal biopsy specimens. An enzyme-linked immunosorbent assay for immunoglobulin G antibody to *Strongyloides* may be more sensitive than parasitologic methods for diagnosing intestinal infection in the immunocompetent host. The utility of the assay in diagnosing infection in immunocompromised subjects with the hyperinfection syndrome has not been determined. Eosinophilia is common.

**TREATMENT**

Treatment is directed at eradication of infection. Ivermectin (200 µg/kg/day once daily PO for 2 days) is the drug of choice for uncomplicated strongyloidiasis. Alternatively, albendazole (400 mg PO twice daily for 7 days) may be used. Patients with the hyperinfection syndrome should be treated with ivermectin for 7-10 days and may require repeated courses. Reducing the dose of immunosuppressive therapy and treatment of concomitant bacterial infections are essential in the management of the hyperinfection syndrome. Close follow-up with repeated stool examination is necessary to ensure complete elimination of the parasite. *Strongyloides* antibodies decrease within 6 mo after successful treatment.

**PREVENTION**

Sanitary practices designed to prevent soil and person-to-person transmission are the most effective control measures. Wearing shoes is a main preventive strategy. Reduction in transmission in institutional settings can be achieved by decreasing fecal contamination of the environment such as by the use of clean bedding. Because infection is uncommon in most settings, case detection and treatment are advisable. Individuals who will be given prolonged high-dose corticosteroids, immunosuppressive drugs before organ transplantation, or cancer chemotherapy should have a screening examination for *S. stercoralis*. If infected, they should be treated before immunosuppression is initiated.

*Bibliography is available at Expert Consult.*
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ETIOLOGY

The filarial worms *Brugia malayi* (Malayan filariasis), *Brugia timori*, and *Wuchereria bancrofti* (bancroftian filariasis) are threadlike nematodes that cause similar infections. Infective larvae are introduced into humans during blood feeding by the mosquito vector. Over a period of 4-6 mo, the larval forms develop into sexually mature adult worms. Once an adequate number of male and female worms accumulate in the afferent lymphatic vessels, adult female worms release large numbers of microfilariae that circulate in the bloodstream. The life cycle of the parasite is completed when mosquitoes ingest microfilariae...
in a blood meal, which molt to form infective larvae over a period of 10-14 days. Adult worms have a 5-7 yr life span.

EPIDEMIOLOGY
More than 120 million people living in tropical Africa, Asia, and Latin America are infected; approximately 10-20% of these individuals have clinically significant morbidity attributable to filariasis. *W. bancrofti* is transmitted in Africa, Asia, and Latin America and accounts for 90% of lymphatic filariasis. *B. malayi* is restricted to the South Pacific and Southeast Asia, and *B. timori* is restricted to several islands of Indonesia. Travelers from nonendemic areas of the world who spend brief periods of time in endemic areas are rarely infected. Global elimination has been targeted for 2020.

CLINICAL MANIFESTATIONS
The clinical manifestations of *B. malayi*, *B. timori*, and *W. bancrofti* infection are similar; manifestations of acute infection include transient, recurrent lymphadenitis and lymphangitis. The early signs and symptoms include episodic fever, lymphangitis of an extremity, lymphadenitis (especially the inguinal and axillary areas), headaches, and myalgias that last a few days to several weeks. These symptoms are caused by an acute inflammatory response triggered by death of adult worms. Initial damage to lymphatic vessels may remain subclinical for years. The syndrome is most frequently observed in persons 10-20 yr of age. Manifestations of chronic lymphatic filariasis occur mostly in adults 30 yr of age or older and result from anatomic and functional obstruction to lymph flow. This obstruction results in lymphedema of the legs, arms, breasts, and/or genitalia. Male genital involvement, such as hydrocele, is very common in *W. bancrofti* infection, but uncommon in *B. timori* species infection. Chronic lymphedema predisposes affected extremities to bacterial superinfections, sclerosis, and verrucous skin changes, resulting in elephantiasis, which may involve 1 or more limbs, the breasts, or genitalia. It is uncommon for children to have overt signs of chronic filariasis.

Tropical Pulmonary Eosinophilia
The presence of microfilariae in the body has no apparent pathologic consequences except in persons with tropical pulmonary eosinophilia, a syndrome of filarial etiology in which microfilariae are found in the lungs and lymph nodes but not the bloodstream. It occurs only in individuals who have lived for years in endemic areas. Men 20-30 yr of age are most likely to be affected, although the syndrome occasionally occurs in children. The presentation includes paroxysmal nocturnal cough with dyspnea, fever, weight loss, and fatigue. Rales and rhonchi are found on auscultation of the chest. The x-ray findings may occasionally be normal, but increased bronchovascular markings, discrete opacities in the middle and basal regions of the lung, or diffuse miliary lesions are usually present (Fig. 296-1). Recurrent episodes may result in interstitial fibrosis and chronic respiratory insufficiency in untreated individuals. Hepatosplenomegaly and generalized lymphadenopathy are often seen in children. The diagnosis is suggested by residence in a filarial endemic area, eosinophilia (>2,000/µL), compatible clinical symptoms, increased serum immunoglobulin E (>1,000 IU/mL), and high titters of antimicrofilarial antibodies in the absence of microfilaria. Although microfilariae may be found in sections of lung or lymph node, biopsy of these tissues is unwarranted in most situations. The clinical response to diethylcarbamazine (2 mg/kg/dose tid PO for 12-21 days) is the final criterion for diagnosis; the majority of patients improve with this therapy. If symptoms recur, a second course of the anthelminthic should be administered. Patients with chronic symptoms are less likely to show improvement than those who have been ill for a short time.

DIAGNOSIS
Demonstration of microfilariae in the blood is the primary means for confirming the diagnosis of lymphatic filariasis. Because microfilariae is nocturnal in most cases, blood samples should be obtained between 10 PM and 2 AM. Anticoagulated blood is passed through a Nuclepore filter that is stained and examined microscopically for microfilariae. Adult worms or microfilariae can be identified in tissue specimens obtained at biopsy. Infection with *W. bancrofti* in the absence of bloodborne microfilariae may be diagnosed by detection of parasite antigen in the serum. Adult worms in lymphatic vessels can be visualized by ultrasonography.

TREATMENT
The use of antifilarial drugs in the management of acute lymphadenitis and lymphangitis is controversial. No controlled studies demonstrate that administration of drugs such as diethylcarbamazine modifies the course of acute lymphangitis. Diethylcarbamazine may be given to asymptomatic microfilaremic persons to lower the intensity of parasitemia. The drug also kills a proportion of the adult worms. Because treatment-associated complications such as pruritus, fever, generalized body pain, hypotension, and even death may occur, especially with high microfilarial levels, the dose of diethylcarbamazine should be increased gradually (children: 1 mg/kg PO as a single dose on day 1, 1 mg/kg tid PO on day 2, 1-2 mg/kg tid PO on day 3, and 6 mg/kg/day divided tid PO on days 4-14; adults: 50 mg PO on day 1, 50 mg tid PO on day 2, 100 mg tid PO on day 3, and 6 mg/kg/day divided tid PO on days 4-14). For patients with no microfilaria in the blood, the full dose (6 mg/kg/day divided tid PO) can be given beginning on day 1. Repeat doses may be necessary to further reduce the microfilariaemia and kill lymph-dwelling adult parasites. *W. bancrofti* is more sensitive than *B. malayi* to diethylcarbamazine.

Global programs to control and ultimately eradicate lymphatic filariasis from endemic populations currently recommend a single annual dose of diethylcarbamazine (6 mg/kg PO once) in combination with albendazole (400 mg PO once) for 5 yr (mass drug administration). In coendemic areas of filariasis and onchocerciasis, mass drug applications with single-dose ivermectin (150 µg/kg PO once) and albendazole are used because of severe adverse reactions with diethylcarbamazine in onchocerciasis-infected individuals. Five years of annual mass treatment is thought to be necessary to stop transmission. Adjunct medicines (e.g., doxycycline) that target endosymbiont bacteria (*Wolbachia*) in filarial parasites may accelerate eradication.

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ONCHOCERCIASIS (ONCHOCERCA VOLVULUS)

Infection with Onchocerca volvulus leads to onchocerciasis or river blindness. Onchocerciasis occurs primarily in West Africa but also in Central and East Africa and is the world’s second leading infectious cause of blindness. There have been scattered foci in Central and South America, but the infection is now thought to be eliminated in the Americas with the exception of isolated populations living in the border area of Venezuela and Brazil. O. volvulus larvae are transmitted to humans by the bite of Simulium black flies that breed in fast-flowing streams. The larvae penetrate the skin and migrate through the connective tissue and eventually develop into adult worms that can be found tangled in fibrous tissue. Adult worms can live in the human body for up to 14 yr. Female worms produce large numbers of microfilariae that migrate through the skin, connective tissue, and eye. Most infected individuals are asymptomatic. In heavily infected subjects, clinical manifestations are a result of localized host inflammatory reactions to dead or dying microfilariae and subcutaneous adult worms surrounded by a palpable fibrous capsule. Cutaneous and ocular reactions to microfilaria produce pruritic dermatitis, punctate keratitis, corneal pannus formation, and chorioretinitis. Adult worms in subcutaneous nodules are not painful and tend to occur over bony prominences of the hip. The diagnosis can be established by obtaining snips of skin covering the scapulae, iliac crests, buttocks, or calves. The snips are immersed in saline for several hours and examined microscopically for microfilariae that have emerged into the fluid. The diagnosis can also be established by demonstrating microfilariae in the cornea or anterior chamber on slit-lamp examination or finding adult worms on a nodule biopsy specimen. Ophthalmology consultation should be obtained before treatment of eye lesions. A single dose of ivermectin (150 µg/kg PO) is the drug of choice and clears O. volvulus microfilariae from the skin for several months but has no effect on the adult worm. Treatment with ivermectin should be repeated every 6-12 mo until the patient is asymptomatic or has no evidence of eye infection. Adverse effects of ivermectin therapy include fever, urticaria, and pruritus, which are more frequent in individuals not born in endemic areas who acquired the infection following periods of intense exposure, such as Peace Corps volunteers. Patients with concurrent high-density microfilaremia from loiasis may develop encephalopathy with ivermectin therapy. Treatment with ivermectin should be withheld until Loa loa microfilariaemia can be reduced by cyatherepheresis or the use of doxycycline, which kills endosymbiotic bacteria (Wolbachia) of O. volvulus. Personal protection includes avoiding areas where biting flies are numerous, wearing protective clothing, and using insect repellent. Programs of mass treatment with ivermectin have been implemented in Africa in an effort to reduce the prevalence of onchocerciasis. Although an etiologic link has not been established, epidemiologic studies have reported an association between onchocerciasis and a nodding syndrome of children living in focal areas of Uganda, Tanzania and South Sudan. The syndrome is characterized by the head dropping forward, convulsions, and periods of staring. A meta-analysis suggests an association between O. volvulus infection and epilepsy.

LOIASIS (LOA LOA)

Loiasis is caused by infection with the tissue nematode Loa loa. The parasite is transmitted to humans via diurnally biting flies (Chrysops) that live in the rain forests of West and Central Africa. Migration of adult worms through skin, subcutaneous tissue, and subconjunctival area can lead to transient episodes of pruritus, erythema, and localized edema known as Calabar swellings, which are nonerythematous areas of subcutaneous edema 10-20 cm in diameter typically found around joints such as the wrist or the knee (Fig. 297-1). They resolve over several days to wk and may recur at the same or different sites. Lifelong residents of L. loa endemic regions may have microfilaremia and eosinophilia but are often asymptomatic. In contrast, travelers to endemic regions may have a hyperreactive response to L. loa infection characterized by frequent recurrences of swelling, high level eosinophilia, debilitation, and serious complications such as glomerulonephritis and encephalitis. Diagnosis is usually established on clinical grounds, often assisted by the infected individual reporting a worm being seen crossing the conjunctivae. Microfilariae may be detected in blood smears collected between 10 AM and 2 PM. Adult worms should be surgically excised when possible. Diethylcarbamazine is the agent of choice for eradication of microfilaremia, but the drug does not kill adult worms. Because treatment-associated complications such as pruritus, fever, generalized body pain, hypertension, and even death may occur, especially with high microfilarial levels, the dose of diethylcarbamazine should be increased gradually in such cases (children: 1 mg/kg PO on day 1, 1 mg/kg tid on day 2, 1-2 mg/kg tid on day 3, 6 mg/kg in 3 doses on days 4-21; adults: 50 mg PO on day 1, 50 mg tid on day 2, 100 mg tid on day 3, 6 mg/kg in 3 doses on days 4-21). Full doses can be instituted on day 1 in persons without microfilaremia (9 mg/kg/day PO divided tid for 12 days). A single dose of ivermectin (150 µg/kg) decreases microfilarial densities in the blood in persons with high density microfilaremia. A 3 wk course of albendazole can also be used to slowly reduce L. loa microfilarial levels as a result of embryotoxic effects on the adult worms. Antihistamines or corticosteroids may be used to limit allergic reactions secondary to killing of microfilariae. Personal protective measures include avoiding areas where biting flies are present, wearing protective clothing, and using insect repellents. Diethylcarbamazine (300 mg PO once weekly) prevents infection in travelers who spend prolonged periods of time in endemic areas. L. loa do not harbor Wolbachia endosymbionts, and therefore doxycycline has no effect on infection.

INFECTION WITH ANIMAL FILARIAE

The most commonly recognized zoonotic filarial infections are caused by members of the genus Dirofilaria. The worms are introduced into humans by the bites of mosquitoes containing third-stage larvae. The most common filarial zoonosis in the United States is Dirofilaria immitis, a parasite of raccoons. In Europe, Africa, and Southeast Asia, infections are most commonly caused by the dog parasite Dirofilaria repens. The dog heartworm, Dirofilaria immitis, is the second most commonly

Figure 297-1 Calabar swelling of the right hand. (From Guerrant RL, Walker DH, Weller PF, et al: Tropical infectious diseases, Philadelphia, 2006, Churchill Livingstone, p. 1165.)
encountered filarial zoonosis worldwide. Other genera, including Dipetalonema-like worms, Onchocerca, and Brugia, are rare causes of zoonotic filarial infections.

Animal filariae do not undergo normal development in the human host. The clinical manifestations and pathologic findings correspond to the anatomic site of infection and can be categorized into 4 major groups: subcutaneous, lung, eye, and lymphatic. Pathologic examination of affected tissue reveals a localized foreign-body reaction around a dead or dying parasite. The lesion consists of granulomas with eosinophils, neutrophils, and tissue necrosis. D. tenius does not leave the subcutaneous tissues, whereas Brugia beaveri eventually localizes to superficial lymph nodes. Infections may be present for up to several months. D. immitis larvae migrate for several months in subcutaneous tissues and most frequently result in a well-circumscribed coinlike lesion in a single lobe of the lung. The chest x-ray typically reveals a solitary pulmonary nodule 1-3 cm in diameter. Definitive diagnosis and cure depend on surgical excision and identification of the nema-
tode within the surrounding granulomatous response. D. tenius and B. beaveri infections present as painful 1-5 cm rubbery nodules in the skin of the trunk, of the extremities, and around the orbit. Patients often report having been engaged in activities predisposing to exposure to infected mosquitoes, such as working or hunting in swampy areas. Diagnosis and management is by surgical excision.

**ANGIOSTRONGYLUS CANTONENSIS**

Angiostrongylus cantonensis, the rat lungworm, is the most common cause of eosinophilic meningitis worldwide. Rats are the definitive host. Human infection follows ingestion of third-stage larvae in raw or undercooked intermediate hosts such as snails and slugs, or transport hosts such as freshwater prawns, frogs, and fish. Most cases are sporadic, but clusters have been reported, including clusters related to consumption of lettuce contaminated with intermediate or transport hosts. Even though most infections have been described in Southeast Asia, the South Pacific, and Taiwan, shipboard travel of infected rats has spread the parasite to Madagascar, Africa, the Caribbean, and, most recently, Australia and North America. Larvae penetrate the vasculature of the intestinal tract and migrate to the meninges, where they usually die but induce eosinophilic aseptic meningitis. Patients present 2-35 days after ingestion of larvae with severe headache, neck pain or nuchal rigidity, hyperesthesias and paresthesias (often migrating), fatigue, fever, rash, pruritus, nausea, and vomiting. Neurologic involve-
mant varies from asymptomatic to paresthesias, severe pain, weakness, and focal neurologic findings such as cranial nerve palsies. Symptoms can last for several weeks to months, especially headache. Coma and death from hydrocephalus occur rarely in heavy infections. Peripheral blood eosinophilia is not always present on initial examination but can reach about 5 wk after exposure, often when symptoms are improving. Cerebrospinal fluid analysis reveals pleocytosis with >10% eosinophils in more than half of patients, with mildly elevated protein, a normal glucose level, and an elevated opening pressure. Head CT or MRI is usually unremarkable. The diagnosis is established clinically with support-
ting travel and diet history. A sensitive and specific enzyme-linked immunosorbent assay is available on a limited basis from the Centers for Disease Control and Prevention for testing either cerebrospinal fluid or serum. Treatment is primarily supportive because the majority of infections are mild and most patients recover within 2 mo without neurologic sequelae. Analgesics should be given for headache. Careful, repeated lumbar punctures should be performed to relieve hydro-
chephalus. Anthelmintic drugs have not been shown to influence the outcome and may exacerbate neurologic symptoms. The use of corti-
coesteroids may shorten the duration of persistent and severe head-
aches. There is a higher incidence of permanent neurologic sequela and mortality among children than among adults. Infection can be avoided by not eating raw or undercooked crabs, prawns, or snails.

**ANGIOSTRONGYLUS COSTARICENSES**

Angiostrongylus costaricensis is a nematode that infects several species of rodents and causes abdominal angiostrongyliasis, which has been described predominantly in Latin America and the Caribbean. The mode of transmission to humans, who are accidental hosts, is unknown. It is speculated that infectious larvae from a molluscan intermediate host, such as the slug Vaginulus plebeius, contaminate water or vegetation that is inadvertently consumed (chopped up in salads or on veg-
etation contaminated with the slug’s mucus secretions). Although this slug is not indigenous to the continental United States, it has been found on imported flowers and produce. The incubation period for abdominal angiostrongyliasis is unknown, but limited data suggest that it ranges from 2 wk to several months after ingestion of larvae. Third-stage larvae migrate from the gastrointestinal tract to the mesenteric arteries, where they mature into adults. These eggs degenerate and elicit an eosinophilic granulomatous reaction. The clinical findings of abdominal angiostrongyliasis mimic appendicitis, although the former are typically more indolent. Children can have fever, right lower quadrant pain, a tumor-like mass, abdominal rigidity, and a painful rectal examination. Most patients have leukocytosis with eosinophilia. Radiologic examination may show bowel wall edema, spasticity, or filling defects in the ileocecal region and the ascending colon. Examina-
tion of stool for ova and parasites is not useful for A. costaricensis but is useful for evaluating the presence of other intestinal parasites. An enzyme-linked immunosorbent assay is available for diagnosis on a limited basis from the Centers for Disease Control and Prevention, but the test has a low specificity and is known to cross react with Toxocara, Strongyloides, and Paragonimus. Many patients undergo laparotomy for suspected appendicitis and are found to have a mass in the terminal ileum to the ascending colon. No specific treatment is known for abdominal angiostrongyliasis. Even though the use of anthelmintic therapy has not been studied systematically, thiabendazole or diethylcarbamazine has been suggested. The prognosis is gener-
ally good. Most cases are self-limited, although surgery may be required in some patients. Cornerstones of prevention include avoidance of slugs and not ingesting raw food and water that may be contaminated with imperceptible slugs or slime from slugs. Rat control is also import-
tant in preventing the spread of infection.

**DRACUNCULIASIS (DRACUNCULUS MEDINENSISS)**

Dracunculiasis is caused by the guinea worm, Dracunculus medinensis. The World Health Organization has targeted dracunculiasis for eradi-
cation. As of 2012, the transmission of the infection was confined to Chad, Ethiopia, Mali, and South Sudan. Humans become infected by drinking contaminated stagnant water that contains immature forms of the parasite in the gut of tiny crustaceans (copepods or water fleas). Larvae are released in the stomach, penetrate the mucosa, mature, and mate. Approximately 1 yr later, the adult female worm (1-2 mm in diameter and up to 1 m long) migrates and partially emerges through the human host skin, usually of the legs. Thousands of immature larvae are released when the affected body part is immersed in the water. The cycle is completed when larval forms are ingested by the crustaceans. Infected humans have no symptoms until the worm reaches the subcutaneous tissue, causing a stinging papule that may be accompanied by urticaria, nausea, vomiting, diarrhea, and dyspnea. The lesion vesicu-
lates, ruptures, and forms a painful ulcer in which a portion of the worm is visible. Diagnosis is established clinically. Larvae can be iden-
tified by microscopic examination of the discharge fluid. Metronida-
azole (25 mg/kg/day PO divided into 3 doses for 10 days; maximum dose: 750 mg) decreases local inflammation. Although the drug does not kill the worm, it facilitates its removal. The worm must be physi-
cally removed by rolling the slowly emerging 1 m long parasite onto a

**GNATHOSTOMA SPINIGERUM**

Gnathostoma spinigerum is a dog and cat nematode endemic to South-
east Asia, Japan, China, Bangladesh, and India, but has been identified
in Mexico and parts of South America. Infection is acquired by ingesting intermediate hosts containing larvae of the parasite such as raw or undercooked freshwater fish, chickens, pigs, snails, or frogs. Penetration of the skin by larval forms and prenatal transmission has also been described. Nonspecific signs and symptoms such as generalized malaise, fever, urticaria, anorexia, nausea, vomiting, diarrhea, and epigastric pain develop 24-48 hr after ingestion of *G. spinigerum*. Ingested larvae penetrate the gastric wall and migrate through soft tissue for up to 10 yr. Moderate to severe eosinophilia can develop. Cutaneous gnathostomiasis manifests as intermittent episodes of localized, migratory nonpitting edema associated with pain, pruritus, or erythema. Central nervous system involvement in gnathostomiasis is suggested by focal neurologic findings, initially neuralgia followed within a few days by paralysis or changes in mental status. Multiple cranial nerves may be involved, and the cerebrospinal fluid may be xanthochromic but typically shows an eosinophilic pleocytosis. Diagnosis of gnathostomiasis is based on clinical presentation and epidemiologic background. Brain and spinal cord lesions may be seen on CT or MRI. Serologic testing varies in sensitivity and specificity and is available through the Centers for Disease Control and Prevention. There is no well-documented effective chemotherapy, although albendazole (400 mg PO bid for 21 days) as first-line therapy or ivermectin (200 µg/kg for 2 days) as an alternative is recommended without or with surgical removal. Multiple courses may be needed. Corticosteroids have been used to relieve focal neurologic deficits. Surgical resection of the *Gnathostoma* is the major mode of therapy and the treatment of choice. Blind surgical resection of subcutaneous areas of diffuse swelling is not recommended because the worm can rarely be located. Prevention through the avoidance of ingestion of poorly cooked or raw fish, poultry, or pork should be emphasized for individuals living in or visiting endemic areas.

*Bibliography is available at Expert Consult.*
Bibliography

**Onchocerciasis (Onchocerca Volvulus)**


**Loaiasis (Loa Loa)**


**Infection with Animal Filariae**


**Angiostrongylus Cantonensis**


**Angiostrongylus Costaricensis**


**Dracunculiasis (Dracunculus Medinensis)**


**Gnathostoma Spinigerum**


**Pathogenesis**

*T. canis* larvae secrete large amounts of immunogenic glycosylated proteins. These antigens induce immune responses that lead to eosinophilia and polyclonal and antigen-specific immunoglobulin E production. The characteristic histopathologic lesions are granulomas containing eosinophils, multinucleated giant cells (histiocytes), and collagen. Granulomas are typically found in the liver but may also occur in the lungs, central nervous system, and ocular tissues. Clinical manifestations reflect the intensity and chronicity of infection, anatomic localization of larvae, and host granulomatous responses.

**Clinical Manifestations**

There are 3 major clinical syndromes associated with human toxocariasis: VLM, ocular larva migrans (OLM), and covert toxocariasis (Table 298-1). The classic presentation of VLM includes eosinophilia, fever, and hepatomegaly, and occurs most commonly in toddlers with a history of pica and exposure to puppies. The findings include fever, cough, wheezing, bronchopneumonia, anemia, hepatomegaly, leukocytosis, eosinophilia, and positive *Toxocara* serology. Cutaneous manifestations such as pruritus, eczema, and urticaria can be present. OLM tends to occur in older children without signs or symptoms of VLM. Presenting symptoms include unilateral visual loss, eye pain, white pupil, or strabismus that develops over a period of weeks. Granulomas occur on the posterior pole of the retina and may be mistaken for retinoblastoma. Serologic testing for *Toxocara* has allowed the identification of individuals with less obvious or covert symptoms of infection. These children may have nonspecific complaints that do not constitute a recognizable syndrome. Common findings include hepatomegaly, abdominal pain, cough, sleep disturbance, failure to thrive, and headache with elevated *Toxocara* antibody titers. Eosinophilia may be present in only 50-75% of cases. The prevalence of positive *Toxocara* serology in the general population supports the notion that most children with *T. canis* infection are asymptomatic and will not develop overt clinical sequelae over time. A correlation between positive *Toxocara* serology and allergic asthma has also been described.

**Etiology**

Most cases of human toxocariasis are caused by the dog roundworm, *Toxocara canis*. Adult female *T. canis* worms live in the intestinal tracts of young puppies and their lactating mothers. Large numbers of eggs are passed in the feces of dogs and embryonate under optimal soil conditions. *Toxocara* eggs can survive relatively harsh environmental conditions and are resistant to freezing and extremes of moisture and pH. Humans ingest embryonated eggs contaminating soil, hands, or fomites. The larvae hatch and penetrate the intestinal wall and travel via the circulation to the liver, lung, and other tissues. Humans do not excrete *T. canis* eggs because the larvae are unable to complete their maturation to adult worms in the intestine. The cat roundworm, *Toxocara catti*, is responsible for far fewer cases of visceral larva migrans (VLM) than *T. canis*. Ingestion of infective larvae of the raccoon ascarid *Baylisascaris procyonis* rarely leads to VLM but can cause neural larva migrans resulting in fatal eosinophilic meningitis. Ingestion of larvae from the opossum ascarid *Lagochilascaris minor* leads to VLM rarely.

**Epidemiology**

Human *T. canis* infections have been reported in nearly all parts of the world, primarily in temperate and tropical areas where dogs are popular household pets. Young children are at highest risk because of their unsanitary play habits and tendency to place fingers in the mouth. Other behavioral risk factors include pica, contact with puppy litters, and institutionalization. In North America, the highest prevalences of infection are in the southeastern United States and Puerto Rico, particularly among socially disadvantaged African-American and Hispanic children. In the United States, serosurveys show that 4.6-7.3% of children are infected. Assuming an unrestrained and untreated dog population, toxocariasis is prevalent in settings where other geohelminth infections, such as ascarisiasis, trichuriasis, and hookworm infections, are common.

**Diagnosis**

A presumptive diagnosis can be established in a young child with eosinophilia (>20%), leukocytosis, hepatomegaly, fevers, wheezing, and a history of geophagia and exposure to puppies or unrestrained dogs. Supportive laboratory findings include hypergammaglobulinemia and elevated isohemagglutinin titers to A and B blood group antigens. Most patients with VLM have an absolute eosinophil count of >500/µL. Eosinophilia is less common in subjects with OLM. Biopsy confirms the diagnosis. When biopsies cannot be obtained, an enzyme-linked immunosorbent assay using excretory-secretory proteins harvested from *T. canis* larvae maintained in vitro is the standard serologic test used to confirm toxocariasis. A titer of 1:32 is associated with a sensitivity of approximately 78% and a specificity of approximately 92%. The sensitivity for OLM is significantly less. The diagnosis of OLM can be established in patients with typical clinical findings of a retinal or peripheral pole granuloma or endophthalmitis with elevated antibody titers. Vitreous and aqueous humor fluid anti-*Toxocara* titers are usually greater than serum titers. The diagnosis of covert toxocariasis should be considered in individuals with chronic weakness, abdominal pain, or allergic signs with eosinophilia and increased immunoglobulin E. In temperate regions of the world, nonparasitic causes of eosinophilia should be considered in the differential diagnosis include allergies,
drug hypersensitivity, lymphoma, vasculitis, and the idiopathic hypereosinophilic syndrome (see Chapter 129).

**TREATMENT**

Most cases do not require treatment because signs and symptoms are mild and subside over a period of weeks to months. Several anthelminthic drugs have been used for symptomatic cases, often with adjunctive corticosteroids to limit inflammatory responses that presumably result from release of *Toxocara* antigens by dying parasites. Albendazole (400 mg PO bid for 5 days for all ages) has demonstrated efficacy in both children and adults. Mebendazole (100-200 mg PO bid for 5 days for all ages) is also useful. Anthelmintic treatment of central nervous system and ocular disease should be extended (3-4 wk). Even though there are no clinical trials regarding therapy of OLM, a course of oral corticosteroids such as prednisone (1 mg/kg/day PO for 2-4 wk) has been recommended to suppress local inflammation while treatment with anthelmintic agents is initiated.

**PREVENTION**

Transmission can be minimized by public health measures that prevent dog feces from contaminating the environment. These include keeping dogs on leashes and excluding pets from playgrounds and sandboxes that toddlers use. Children should be discouraged from putting dirty fingers in their mouth and eating dirt. Vinyl covering of sandboxes reduces the viability of *T. canis* eggs. Widespread veterinary use of broad-spectrum anthelmintics effective against *Toxocara* may lead to a decline in parasite transmission to humans.

*Bibliography is available at Expert Consult.*

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**Table 298-1 Clinical Syndromes of Human Toxocariasis**

<table>
<thead>
<tr>
<th>SYNDROME</th>
<th>CLINICAL FINDINGS</th>
<th>AVERAGE AGE</th>
<th>INFECTIOUS DOSE</th>
<th>INCUBATION PERIOD</th>
<th>LABORATORY FINDINGS</th>
<th>ELISA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visceral larva migrans</td>
<td>Fevers, hepatomegaly, asthma</td>
<td>5 yr</td>
<td>Moderate to high</td>
<td>Weeks to months</td>
<td>Eosinophilia, leukocytosis, elevated IgE</td>
<td>High (≥1:16)</td>
</tr>
<tr>
<td>Ocular larva migrans</td>
<td>Visual disturbances, retinal granulomas, endophthalmitis, peripheral granulomas</td>
<td>12 yr</td>
<td>Low</td>
<td>Months to years</td>
<td>Usually none</td>
<td>Low</td>
</tr>
<tr>
<td>Covert toxocariasis</td>
<td>Abdominal pain, gastrointestinal symptoms, weakness, hepatomegaly, pruritus, rash</td>
<td>School-age to adult</td>
<td>Low to moderate</td>
<td>Weeks to years</td>
<td>±Eosinophilia, ±elevated IgE</td>
<td>Low to moderate</td>
</tr>
</tbody>
</table>

ELISA, enzyme-linked immunosorbent assay; IgE, immunoglobulin E; ±, with or without.

Bibliography


Infectious Diseases

Chapter 299

Trichinellosis (Trichinella spiralis)
Arlene E. Dent and James W. Kazura

ETIOLOGY
Human trichinellosis (also called trichinosis) is caused by consumption of meat containing encysted larvae of Trichinella spiralis, a tissue-dwelling nematode with a worldwide distribution. After ingestion of raw or inadequately cooked meat from pigs (or other commercial meat sources such as horses) containing viable Trichinella larvae, the organisms are released from the cyst by acid-pepsin digestion of the cyst walls in the stomach and then pass into the small intestine. The larvae invade the small intestine columnar epithelium at the villi base and develop into adult worms. The adult female worm produces about 500 larvae over 2 wk and is then expelled in the feces. The larvae enter the bloodstream and seed striated muscle by burrowing into individual muscle fibers. Over a period of 3 wk, they coil as they increase about 10 times in length and become capable of infecting a new host if ingested. The larvae eventually become encysted and can remain viable for years. Sylvatic Trichinella spp. (T. brivoti, T. nativa, T. pseudospiralis, and T. murrelli) present in traditional native foods such as walrus meat and game meat may also cause disease similar to that caused by T. spiralis.

EPIDEMIOLOGY
Despite public health efforts to control trichinellosis by eliminating the practice of feeding garbage to domestic swine, epidemics and isolated cases of Trichinella spp. infection continue to be a health problem in many areas of the world. It is most common in Asia, Latin America, and Central Europe. Swine fed with garbage may become infected when given uncooked trichinous scraps, usually pig meat, or when the carcasses of infected wild animals such as rats are eaten. Prevalence rates of T. spiralis in domestic swine range from 0.001% in the United States to ≥25% in China. The resurgence of this disease can be attributed to translocations of animal populations, human travel, and export of food as well as ingestion of sylvatic Trichinella (T. brivoti, T. nativa, T. pseudospiralis, and T. murrelli) through game meat. In the United States from 1997 to 2001, wild game meat (especially bear meat) was the most common source of infection. Most outbreaks occur from the consumption of T. spiralis–infected pork (or horse meat in areas of the world where horse is eaten) obtained from a single source.

PATHOGENESIS
During the 1st 2-3 wk after infection, pathologic reactions to infection are limited to the gastrointestinal tract and include a mild, partial villous atrophy with an inflammatory infiltrate of neutrophils, eosinophils, lymphocytes, and macrophages in the mucosa and submucosa. Larvae are released by female worms and disseminate over the next several weeks. Skeletal muscle fibers show the most striking changes with edema and basophilic degeneration. The muscle fiber may contain the typical coiled worm, the cyst wall derived from the host cell, and the surrounding lymphocytic and eosinophilic infiltrate.

CLINICAL MANIFESTATIONS
The development of symptoms depends on the number of viable larvae ingested. Most infections are asymptomatic or mild, and children often show milder symptoms than adults who consumed the same amount of infected meat. Watery diarrhea is the most common symptom corresponding to maturation of the adult worms in the gastrointestinal tract, which occurs during the 1st 1-2 wk after ingestion. Patients may also complain of abdominal discomfort and vomiting. Fulminant
enteritis may develop in individuals with extremely high worm burdens. The classic symptoms of facial and periorbital edema, fever, weakness, malaise, and myalgia peak approximately 2-3 wk after the infected meat is ingested as the larvae migrate and then encyst in the muscle. Headache, cough, dyspnea, dysphagia, subconjunctival and splinter hemorrhages, and a macular or petechial rash may occur. Patients with high-intensity infection may die from myocarditis, encephalitis, or pneumonia. In symptomatic patients, eosinophilia is common and may be dramatic.

**DIAGNOSIS**
The Centers for Disease Control and Prevention diagnostic criteria for trichinellosis require positive serology or muscle biopsy for Trichinella with 1 or more compatible clinical symptoms (eosinophilia, fever, myalgia, facial or periorbital edema). To declare a discrete outbreak, at least 1 person must have positive serology or muscle biopsy. Antibodies to Trichinella are detectable approximately 3 wk after infection. Severe muscle involvement results in elevated serum creatine phosphokinase and lactic dehydrogenase levels. Muscle biopsy is not usually necessary, but if needed, a sample should be obtained from a tender swollen muscle. A history of eating undercooked meat supports the diagnosis. The cysts may calcify and be visible by radiograph.

**TREATMENT**
Recommended treatment of trichinellosis diagnosed at the gastrointestinal phase is albendazole (400 mg PO bid for 8-10 days for all ages) to eradicate the adult worms if a patient has ingested contaminated meat within the previous 1 wk. An alternative regimen is mebendazole (200-400 mg PO tid for 3 days followed by 400-500 mg tid for 10 days). There is no consensus for treatment of muscle-stage trichinellosis. Corticosteroids may be used, although evidence for efficacy is anecdotal.

**PREVENTION**
Trichinella larvae can be killed by cooking meat (≥55°C [131°F]) until there is no trace of pink fluid or flesh, or by storage in a freezer (−15°C [5°F]) for ≥3 wk. Freezing to kill larvae should only be applied to pork meat, as larvae in horse, wild boar, or game meat can remain viable even after 4 wk of freezing. Smoking, salting, and drying meat are unreliable methods of killing Trichinella. Strict adherence to public health measures, including garbage feeding regulations, stringent rodent control, prevention of exposure of pigs and other livestock to animal carcasses; constructing barriers between livestock, wild animals, and domestic pets; and proper handling of wild animal carcasses by hunters, can reduce infection with Trichinella. Current meat inspection for trichinellosis is by direct digestion and visualization of encysted larvae in meat samples. Serologic testing does not have a role in meat inspection.

*Bibliography is available at Expert Consult.*
Bibliography
Chapter 300
Schistosomiasis (Schistosoma)
Charles H. King and Amaya L. Bustinduy

The term schistosomiasis (bilharzia) encompasses the acute and chronic inflammatory disorders caused by human infection with Schistosoma spp. parasites. Disease is related to both the systemic and focal effects of schistosome infection and its consequent host immune responses triggered by parasite eggs deposited in the tissues. For the affected individuals, this frequently manifests as disabling chronic morbidity.

ETIOLOGY
Schistosoma organisms are the trematodes, or flukes, that parasitize the bloodstream. Five schistosome species infect humans: Schistosoma haematobium, S. mansoni, S. japonicum, S. intercalatum, and S. mekongi. Humans are infected through contact with water contaminated with cercariae, the free-living infective stage of the parasite. These motile, forked-tail organisms emerge from infected snails and are capable of penetrating intact human skin. As they reach maturity, adult worms migrate to specific anatomic sites characteristic of each schistosome species: S. haematobium adults are found in the perivesical and periureteral venous plexus, S. mansoni in the inferior mesenteric veins, and S. japonicum in the superior mesenteric veins. S. intercalatum and S. mekongi are usually found in the mesenteric vessels. Adult schistosome worms (1-2 cm long) are clearly adapted for an intravascular existence. The female accompanies the male in a groove formed by the lateral edges of its body. On fertilization, female worms begin oviposition in the small venous tributaries. The eggs of the 3 main schistosome species have characteristic morphologic features: S. haematobium has a terminal spine, S. mansoni has a lateral spine, and S. japonicum has a smaller size with a short, curved spine (Fig. 300-1). Parasite eggs provoke a significant granulomatous inflammatory response, which allows them to ulcerate through host tissues to reach the lumen of the urinary tract or intestines. They are carried to the outside environment in urine or feces (depending on the species), where they will hatch if deposited in freshwater. Motile miracidia emerge, infect specific freshwater snail intermediate hosts, and divide asexually. After 4-12 wk, the infective cercariae are released by the snails into the contaminated water.

EPIDEMIOLOGY
Schistosomiasis infects more than 207 million people worldwide, primarily children and young adults. Prevalence is increasing in many areas as population density increases and new irrigation projects provide broader habitats for vector snails. Humans are the main definitive hosts for the 5 clinically important species of schistosomes, although S. japonicum is also a zoonosis, infecting animals such as dogs, rats, pigs, and cattle. S. haematobium is prevalent in Africa and the Middle East; S. mansoni is prevalent in Africa, the Middle East, the Caribbean, and South America; and S. japonicum is prevalent in China, the Philippines, and Indonesia, with some sporadic foci in parts of Southeast Asia. The other 2 species are less prevalent. S. intercalatum
Granulomatous injury. Eggs may be trapped at sites of deposition in which retention of eggs in the host tissues is associated with chronic major pathology of infection occurs later, with chronic schistosomiasis, complex disease associated with early infection and oviposition. The both the early and late manifestations of schistosomiasis are immuno-

maximal risk for suffering from its acute and chronic sequelae. Both the early and late manifestations of schistosomiasis are immuno-

prevalent and most severe in children and young adults, who are at more active water contact as school age children pursue recreational activities such as swimming and wading.

Transmission depends on disposal of excreta, the presence of specific intermediate snail hosts, and the patterns of water contact and social habits of the population (Fig. 300-2). The distribution of infection in endemic areas shows that prevalence increases with age, to a peak at 10-20 yr of age. Exposure to infected water starts early in life for children living in endemic areas. Passive water contact by infants (accompanying mothers in their daily household activities) evolves to more active water contact as school age children pursue recreational activities such as swimming and wading.

Measuring intensity of infection (by quantitative egg count in urine or feces) demonstrates that the heaviest worm loads are found in school-age and adolescent children. Therefore, schistosomiasis is most prevalent and most severe in children and young adults, who are at maximal risk for suffering from its acute and chronic sequelae.

**PATHOGENESIS**

Both the early and late manifestations of schistosomiasis are immunologically mediated. Acute schistosomiasis, known as snail fever or Katayama syndrome, is a febrile illness that represents an immune complex disease associated with early infection and oviposition. The major pathology of infection occurs later, with chronic schistosomiasis, in which retention of eggs in the host tissues is associated with chronic granulomatous injury. Eggs may be trapped at sites of deposition (urinary bladder, ureters, intestine) or be carried by the bloodstream to other organs, most commonly the liver and less often the lungs and central nervous system. The host response to these eggs involves local as well as systemic manifestations. The cell-mediated immune response leads to granulomas composed of lymphocytes, macrophages, and eosinophils that surround the trapped eggs and add significantly to the degree of tissue destruction. Granuloma formation in the bladder wall and at the ureterovesical junction results in the major disease manifestations of schistosomiasis haematobia: hematuria, dysuria, and obstructive uropathy. Intestinal as well as hepatic granulomas underlie the pathologic sequelae of the other schistosome infections: ulcerations and fibrosis of intestinal wall, hepatosplenomegaly, and portal hypertension due to presinusoidal obstruction of blood flow. In terms of systemic disease, antischistosome inflammation increases circulating levels of proinflammatory cytokines such as tumor necrosis factor-α and interleukin-6, associated with elevated levels of C-reactive protein. These responses are associated with hepcidin-mediated inhibition of iron uptake and use, leading to anemia of chronic inflammation. Schistosomiasis-related undernutrition may be the result of similar pathways of chronic inflammation. Acquired partial protective immunity against schistosomiasis has been demonstrated in some animal species and may occur in humans.

**CLINICAL MANIFESTATIONS**

Most chronically infected individuals experience mild symptoms and may not seek medical attention; the more severe symptoms of schistosomiasis occur mainly in those who are heavily infected or who have been infected over longer periods of time. In addition to organ-specific morbidities, infected patients frequently demonstrate anemia, chronic pain, diarhoea, exercise intolerance, and chronic undernutrition manifesting as growth stunting. Cercarial penetration of human skin may result in a papular pruritic rash known as schistosomal dermatitis or swimmer’s itch. It is more pronounced in previously exposed individuals and is characterized by edema and intense cellular infiltrates in the dermis and epidermis. Acute schistosomiasis, Katayama syndrome, may occur, particularly in heavily infected individuals 4-8 wk after exposure; this is a serum sickness–like syndrome manifested by the acute onset of fever, cough, chills, sweating, abdominal pain, lymphadenopathy, hepatosplenomegaly, and eosinophilia. Acute schistosomiasis most commonly presents in first-time visitors to endemic areas who experience primary infection at an older age.

Symptomatic children with chronic schistosomiasis haematobia usually complain of frequency, dysuria, and hematuria. Urine examination shows erythrocytes, parasite eggs, and occasional eosinophilia. In endemic areas, moderate to severe pathologic lesions have been demonstrated in the urinary tract of >20% of infected children. The extent of disease correlates with the intensity of infection, but significant morbidity can occur even in lightly infected children. The advanced stages of schistosomiasis haematobia are associated with chronic renal failure, secondary infections, and cancer of the bladder.

An important complication of *S. haematobium* infection is female genital schistosomiasis. Eggs migrate from the vesical plexus to lodge in the female genital tract where they induce a granulomatous inflammatory response that can manifest as contact bleeding, pain, and eventual infertility. Symptoms start as early as 10 yr of age with an apparent 3–4-fold greater risk of HIV transmission. Pathognomonic lesions can be visualized in the cervix by photocolposcopy.

Children with chronic schistosomiasis *mansoni, japonica, intercalatum,* or *mekongi* may have intestinal symptoms; colicky abdominal pain and bloody diarrhea are the most common. However, the intestinal phase may remain subclinical, and the late syndrome of hepatosplenic, portal hypertension, ascites, and hematemesis may then be the first clinical presentation. Liver disease is caused by granuloma formation and subsequent fibrosis; no appreciable liver cell injury occurs, and hepatic function may be preserved for a long time. Schistosome eggs may escape into the lungs, causing pulmonary hypertension and cor pulmonale. *S. japonicum* worms may migrate to the brain vasculature and produce localized lesions that cause seizures. Transverse myelitis, spinal compression, and other central nervous system involvement (meningoencephalitis) are rare but well known.

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**Figure 300-2** Lifecycles of *Schistosoma mansoni*, *Schistosoma haematobium*, and *Schistosoma japonicum*. A, Paired adult worms (larger male enfolding slender female). B, Eggs (*left* to *right*, *S. haematobium*, *S. mansoni*, *S. japonicum*). C, Ciliated miracidium. D, Intermediate host snails (*left* to *right*, *Oncomelania*, *Biomphalaria*, *Bulinus*). E, Cercariae. (From Colley DG, Bustinduy AL, Secor WE, King CH: Human schistosomiasis. Lancet 383:2253–2264, 2014, Fig. 1.)
complications in children or young adults with either acute or chronic
S. haematobium or S. mansoni infection.

Although end-organ scarring is pathognomonic, affected children may also have persistent long-term systemic effects of infection, including poor growth, anemia, decreased aerobic capacity, and cognitive impairment.

**DIAGNOSIS**
Schistosome eggs are found in the excreta of infected individuals; quantitative methods should be used to provide an indication of the burden of infection. For diagnosis of schistosomiasis haematobia, a volume of 10 mL of urine should be collected around midday, which is the time of maximal egg excretion, and filtered for microscopic examination. Stool examination by the Kato-Katz thick smear procedure and detection of parasite antigen in patient serum or urine are the methods of choice for diagnosis and quantification of other schistosome infections.

**TREATMENT**
Treatment of children with schistosomiasis should be based on an appreciation of the intensity of infection and the extent of disease. The recommended treatment for schistosomiasis is praziquantel (40 mg/kg/day divided bid PO for 1 day for schistosomiasis haematobia, mansoni, and intercalatum; 60 mg/kg/day divided tid PO for 1 day for schistosomiasis japonica and mekongi). For S. mansoni, oxamniquine has been effective in some areas where praziquantel has been less effective.

**PREVENTION**
Transmission in endemic areas may be decreased by reducing the parasite load in the human population. The availability of oral, single-dose, effective chemotherapeutic agents may help achieve this goal. When added to national control drug-based programs, other measures such as improved sanitation, focal application of molluscicidals, and animal vaccination may prove useful in breaking the cycle of transmission. Ultimately, control of schistosomiasis is closely linked to economic and social development.

*Bibliography is available at Expert Consult.*
Bibliography
Several different trematodes, or flukes, can parasitize humans and cause disease. Flukes are endemic worldwide but are more prevalent in the less-developed parts of the world. They include *Schistosoma*, or the blood flukes (see Chapter 300), as well as fluke species that cause infection in the human biliary tree, lung tissue, and intestinal tract. These latter trematodes are characterized by complex life cycles (Fig. 301-1). Sexual reproduction of adult worms in the definitive host produces eggs that are passed in the stool. Larvae, called *miracidia*, develop in freshwater. These, in turn, infect certain species of mollusks (aquatic snails or clams), in which asexual multiplication by parasite larvae produces *cercariae*. Cercariae then seek a second intermediate host, such as an insect, crustacean, or fish, or attach to vegetation to produce infectious *metacercariae*. Humans acquire liver, lung, and intestinal fluke infections by eating uncooked, lightly cooked, pickled, or smoked foods containing these infectious parasite cysts. The “alternation of generations” requires that flukes parasitize more than 1 host (often 3) to complete their life cycle. Because parasitic flukes are dependent on these nonhuman species for transmission, the distribution of human fluke infection closely matches the ecologic range of the flukes’ intermediate hosts.

**LIVER FLUKES**  
**Fascioliasis (Fasciola Hepatica)**  
*Fasciola hepatica*, the sheep liver fluke, infects cattle, other ungulates, and occasionally humans. This infection affects approximately 17 million people worldwide and has been reported in many different disease endemic regions. The infection is acquired by eating uncooked or undercooked aquatic vegetation or water that is contaminated with *Fasciola* eggs. The life cycle of *F. hepatica* is depicted in Figure 301-1.
parts of the world, particularly South America, Europe, Africa, China, Australia, and Cuba. Although *F. hepatica* is enzootic in North America, reported cases are extremely rare. Humans are infected by ingestion of metacercariae attached to vegetation, especially wild watercress, lettuce, and alfalfa. In the duodenum, the parasites excyst and penetrate the intestinal wall, liver capsule, and parenchyma. They wander for a few weeks before entering the bile ducts, where they mature. Adult *F. hepatica* (1-2.5 cm) commence oviposition approximately 12 wk after infection; the eggs are large (75-140 µm) and operculated. They pass to the intestines with bile and exit the body in the feces (see Fig. 301-1). On reaching freshwater, the eggs mature and hatch into miracidia, which infect specific snail intermediate hosts to multiply into many cercariae. These then emerge from infected snails and encyst on aquatic grasses and plants.

Clinical manifestations usually occur either during the liver migratory phase of the parasites or after their arrival at their final habitat in upper bile ducts. Fever, right upper quadrant pain, and hepatosplenomegaly characterize the first phase of illness. Peripheral blood eosinophilia is usually marked. As the worms enter bile ducts, most of the acute symptoms subside. On rare occasions, patients may suffer from obstructive jaundice or biliary cirrhosis, with signs of cholestasis, ascending cholangitis, cholelithiasis, and jaundice with elevation in liver enzymes, direct bilirubin, and γ-glutamyl transpeptidase. *F. hepatica* infection is diagnosed by identifying the characteristic eggs in fecal smears or duodenal aspirates. Diagnosis can be suggested by positive serology and imaging that reveals acute hypodense liver lesions that change over time. Presentation can be dramatic in children, with features including generalized edema, hepatic cirrhosis with esophageal varices, and, in severe cases, death from generalized organ failure.

The recommended treatment of fascioliasis is triclabendazole (10 mg/kg once or twice PO) or bithionol (30-50 mg/kg once daily PO on alternate days for a total of 10-15 doses). In the United States, bithionol is available from the Centers for Disease Control and Prevention (telephone: 404-639-3670).

**Clonorchiasis (Clonorchis Sinensis)**

Infection of bile passages with *Clonorchis sinensis*, the Chinese or oriental liver fluke, is endemic in China, other parts of East Asia, and Japan, affecting more than 35 million people. Humans acquire infection by ingestion of raw or inadequately cooked freshwater fish carrying the encysted metacercariae of the parasite under their scales or skin. Metacercariae excyst in the duodenum and pass through the ampulla of Vater to the common bile duct and bile capillaries, where they mature into hermaphroditic adult worms (3-15 cm). *C. sinensis* worms deposit small operculated eggs (14-30 µm), which are discharged by way of the bile duct to the intestine and feces (see Fig. 301-1). The eggs mature and hatch outside the body, releasing motile miracidia into local freshwater streams, rivers, or ponds. If these are taken up by the appropriate snails, they develop into cercariae, which are in turn released from the snail to encyst under the skin or scales of freshwater fish.

Most individuals with *C. sinensis* infection, particularly those with few organisms, are minimally symptomatic. In heavily infected individuals, who tend to be older (>30 yr of age), localized obstruction of a bile duct results from repeated local trauma and inflammation. In these cases, cholangitis and cholangiohepatitis may lead to liver enlargement and jaundice. In Hong Kong, Korea, and other parts of Asia, cholangiocarcinoma is associated with chronic *C. sinensis* infection.

Clonorchiasis is diagnosed by examination of feces or duodenal aspirates for the parasite eggs. The recommended treatment of clonorchiasis is praziquantel (75 mg/kg/day divided tid PO for 2 days). An alternative, used in adults, is albendazole (10 mg/kg once daily PO for 7 days).

**Opisthorchiasis (Opisthorchis Spp.)**

Infections with species of *Opisthorchis* are clinically similar to those caused by *C. sinensis*. *Opisthorchis felineus* and *Opisthorchis viverrini* are liver flukes of cats and dogs that infect humans through ingestion of metacercariae in freshwater fish. Infection with *O. felineus* is endemic in Eastern Europe and Southeast Asia, and *O. viverrini* is found mainly in Thailand, affecting an estimated 10 million people. Most individuals are minimally symptomatic; liver enlargement, relapsing cholangitis, and jaundice may occur in heavily infected individuals. Diagnosis is based on recovering eggs from stools or duodenal aspirates. The recommended treatment of opisthorchiasis is praziquantel (75 mg/kg/day divided tid PO for 2 days).

**LUNG FLUKES**

**Paragonimiasis (Paragonimus Spp.)**

Human infection by the lung fluke *Paragonimus westermani*, and less frequently other species of *Paragonimus*, occurs throughout the Far East, in localized areas of West Africa, and in several parts of Central and South America, affecting approximately 20 million people. The highest incidence of paragonimiasis occurs in older children and adolescents 11-15 yr of age. Although *P. westermani* is found in many carnivores, human cases are relatively rare and seem to be associated with specific dietary habits, such as eating raw freshwater crayfish or crabs. These crustaceans contain the infective metacercariae in their tissues. After ingestion, the metacercariae encyst in the duodenum, penetrate the intestinal wall, and migrate to their final habitat in the lungs. Adult worms (5-10 mm) encapsulate within the lung parenchyma and deposit brown operculated eggs (60-100 µm), which pass into the bronchioles and are expectorated by coughing (see Fig. 301-1). Ova can be detected in the sputum of infected individuals or in their feces. If eggs reach freshwater, they hatch and undergo asexual multiplication in specific snails. The cercariae encyst in the muscles and viscera of crayfish and freshwater crabs.

Most individuals infected with *P. westermani* harbor low or moderate worm loads and are minimally symptomatic. The clinical manifestations include cough, production of rust-colored sputum, and hemoptysis (mimicking tuberculosis), which is the principal manifestation and occurs in 98% of symptomatic children. There are no characteristic physical findings, but laboratory examination usually demonstrates marked eosinophilia. Chest x-rays often reveal small patchy infiltrates or radiolucencies in the middle lung fields; however, radiographs may appear normal in one-fifth of infected individuals. In rare circumstances, lung abscess, pleural or pericardial effusion, or bronchiectasis may develop. Extrapulmonary localization of *P. westermani* in the brain, peritoneum, intestines, or pericardium may rarely occur. Cerebral paragonimiasis occurs primarily in heavily infected individuals living in highly endemic areas of the Far East. The clinical presentation resembles Jacksonian epilepsy or the symptoms of cerebral tumors.

Definitive diagnosis of paragonimiasis is established by identification of eggs in fecal or sputum smears. The recommended treatment of paragonimiasis is praziquantel (75 mg/kg/day divided tid PO for 2 days). Triclabendazole can also be used (5 mg/kg PO daily for 3 days).

**INTESTINAL FLUKES**

Several wild and domestic animal intestinal flukes, including *Fasciolopsis buski*, *Nanophyetus salmincola*, and *Heterophyes heterophyes*, may accidentally infect humans who eat uncooked or undercooked fish or water plants. For example, *F. buski* is endemic in the Far East, where humans who ingest metacercariae encysted on aquatic plants become infected. These develop into large flukes (1-5 cm) that inhabit the duodenum and jejunum. Mature worms produce operculated eggs that pass with feces; the organism completes its life cycle through specific snail intermediate hosts. Individuals with *F. buski* infection are usually asymptomatic; heavily infected subjects complain of abdominal pain and diarrhea and show signs of malabsorption. Diagnosis of fasciolopsiasis and other intestinal fluke infections is established by fecal examination and identification of the eggs (see Fig. 301-1). As for other fluke infections, praziquantel (75 mg/kg/day divided tid PO for 2 days) is the drug of choice.

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Bibliography
Tapeworms are adult forms of cestodes, multicellular helminth parasites, that live in human intestines and cause non–life-threatening illness. Invasive larval forms of cestodes are associated with cysts that lead to severe human disease such as neurocysticercosis (Taenia solium, discussed in Chapter 303) and echinococcosis (mostly Echinococcus granulosus and Echinococcus multilocularis, discussed in Chapter 304). The worms are flat and multisegmented, varying in length from 8 mm to 10 meters. Table 302-1 summarizes the key features of tapeworms that affect children.

### ETIOLOGY

The beef tapeworm (Taenia saginata), the pork tapeworm (T. solium), and the Asian tapeworm (Taenia asiatica) are long worms (4-10 m) named for their intermediate hosts (T. saginata, T. solium) or geographic distribution (T. asiatica; larval host is the pig). The adult worms are found only in the human intestine. Like the adult stage of all tapeworms, their body is a series of hundreds or thousands of flattened segments (proglottids) with an anterior attachment organ (scolex) that anchors the parasite to the bowel wall. New segments arise from the distal aspect of the scolex with progressively more mature segments attached distally. The gravid terminal segments contain 50,000-100,000 eggs, and the eggs or even detached intact proglottids pass out of the child via the anus (with or separate from defecation). These tapeworms differ most significantly in that the intermediate stage of the pork tapeworm (cysticercus) can also infect humans and cause significant morbidity (see Chapter 303), whereas the larval stage of T. saginata does not cause human disease. T. asiatica is similar to and often confused with the beef tapeworm.

### EPIDEMIOLOGY

The pork and beef tapeworms are distributed worldwide, with the highest risk for infection in Central America, Africa, India, Southeast Asia, and China where the relevant intermediate host is raised domestically. The prevalence in adults may not reflect the prevalence in young children, because cultural practices may dictate how well meat is cooked and how much is served to children.

### PATHOGENESIS

When children ingest raw or undercooked meat containing larval cysts, gastric acid and bile facilitate release of immature scolecites that attach to the lumen of the small intestine. The parasite grows, adding new segments at the base of the scolex. The terminal segments mature and after 2-3 mo produce eggs that are released in stool. The surface of proglottids serves as an absorptive organ to "steal" nutritional elements from the child’s small bowel for use by the parasite. There is sometimes a transient eosinophilia prior to the parasite maturing enough to release eggs.

### CLINICAL MANIFESTATIONS

Nonspecific abdominal symptoms have been reported with beef and pork tapeworm infections, but the most bothersome symptom is the psychologic distress caused by seeing proglottids in the stool or undergarments. The released segments of the worms are motile (especially those of T. saginata) and sometimes lead to anal pruritus. The adult beef and pork tapeworms are only rarely associated with other symptoms.

### DIAGNOSIS

Identification of the infecting tapeworm species facilitates understanding of risk for invasive disease. Carriers of adult pork tapeworms are at increased risk for transmitting eggs with the pathogenic intermediate stage (cysticercus) to themselves or others, whereas children infected with the beef tapeworm or T. asiatica are a risk only to livestock. Because proglottids are generally passed intact, visual examination for gravid proglottids in the stool is a sensitive test; these segments may be used to identify species. Eggs, by contrast, are often absent from stool and cannot distinguish between T. saginata and T. solium (Fig. 302-1). If the parasite is completely expelled, the scolex of each species is diagnostic. The scolex of T. saginata has only a set of 4 anteriorly oriented suckers, whereas T. solium is armed with a double row of hooks in addition to suckers. The proglottids of T. saginata have more than 20 branches from a central uterine structure, and those of T. solium have 10 or fewer. Expelled proglottid segments are usually about 0.5 × 1-2 × 0.1 cm in size. Molecular methods can distinguish T. saginata from T. asiatica. Antigen detection tests are increasingly available.

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<td>Asia, Africa, Latin America</td>
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Part XVII  Infectious Diseases

Differential Diagnosis

Anal pruritus may mimic symptoms of pinworm (Enterobius vermicularis) infection. Diphyllobothrium latum and Ascaris lumbricoides (a long round worm) may be mistaken for T. saginata or T. solium in stools.

TREATMENT

Infections with all adult tapeworms respond to praziquantel (25 mg/kg PO once). When available, an alternative treatment for taeniasis is niclosamide (50 mg/kg PO once for children, 2 g PO once for adults). Nitazoxanide is sometimes effective as well. The parasite is usually expelled on the day of administration. Treatment with electrolyte-polynethylene glycol bowel preparations can increase the yield of passage of scolices.

PREVENTION

Prolonged freezing or thorough cooking of beef and pork kills the larval cystic forms of the parasite. Appropriate human sanitation can interrupt transmission by preventing infection in livestock.

Diphyllobothriasis (Diphyllobothrium Species)

Etiology

The fish tapeworms of the genus Diphyllobothrium are the longest human tapeworms, reaching more than 10 meters in length, and have an anatomic organization similar to that of other adult cestodes. An elongated scolex equipped with slits (bothria) along each side but no suckers or hooks is followed by thousands of segments looped in the small bowel. Gravid terminal proglottids detach periodically but tend to disintegrate before expulsion, thus releasing eggs rather than intact worm segments in the feces. In contrast to taeniids, the life cycle of Diphyllobothrium species requires 2 intermediate hosts. Small fresh water crustaceans (copepods) take up the larvae that hatch from parasite eggs. The parasite passes up the food chain as small fish eat the copepods and are in turn eaten by larger fish. In this way, the juvenile parasite becomes concentrated in pike, walleye, perch, burbot, and perhaps salmon associated with aquaculture of this species. Consumption of raw or undercooked fish leads to human infection with adult fish tapeworms.

Epidemiology

The fish tapeworm is most prevalent in the temperate climates of Europe, North America, and Asia but may be found along the Pacific coast of South America and in Africa. In North America, the prevalence is highest in Alaska, Canada, and northern areas of continental United States. The tapeworm is found in fish from those areas that are then taken to market. Persons who prepare raw fish for home or commercial use or who sample fish before cooking are particularly at risk for infection.

Pathogenesis

The adult worm of D. latum (found in northern Europe) has high affinity receptors and efficiently scavenges vitamin B12 for its own use in the constant production of large numbers of segments and as many as 1 million eggs per day. As a result, diphyllobothriasis causes megaloblastic anemia in 2-9% of infections. Interestingly, other Diphyllobothrium species do not out-compete the host for vitamin B12. Children with other causes of vitamin B12 or folate deficiency, such as chronic infectious diarrhea, celiac disease, or congenital malabsorption, are more likely to develop symptomatic infection.

Clinical Manifestations

Infection is largely asymptomatic. Segments may be noted in stool. Those who develop vitamin B12 or folate deficiency present with megaloblastic anemia with leukopenia, thrombocytopenia, glossitis, and/or signs of spinal cord posterior column dysfunction (loss of vibratory sense, proprioception, and coordination).

Diagnosis

Parasitologic examination of the stool is useful because eggs are abundant in the feces and have morphology distinct from that of all other tapeworms. The eggs are ovoid and have an operculum, which is a cap structure at 1 end that opens to release the embryo (Fig. 302-2). The worm itself has a distinct scolex and proglottid morphology; however, these are not likely to be passed spontaneously.

Differential Diagnosis

A segment or a whole section of the worm might be confused with Taenia or Ascaris after it is passed. Pernicious anemia, bone marrow toxins, and dietary restriction may contribute to or mimic the nutritional deficiencies associated with diphyllobothriasis.

Treatment

As with all adult tapeworms, D. latum infections respond to praziquantel (5-10 mg/kg PO once). Niclosamide (50 mg/kg in a single oral dose) is also effective.

Prevention

The intermediate stage is easily killed by brief cooking or prolonged freezing of fish prior to ingestion. Because humans are the major reservoir for adult worms, health education is one of the most important tools for preventing transmission, together with improved human sanitation.
**HYMENOLEPIASIS (HYMENOLEPIS)**
Infection with *Hymenolepis nana*, the dwarf tapeworm, is very common in developing countries. It is a major cause of eosinophilia, and although it rarely causes overt disease, the presence of *H. nana* eggs in stool may serve as a marker for exposure to poor hygienic conditions and the risk of additional fecal-oral contamination. The intermediate stage of *Hymenolepis diminuta* develop in various hosts (e.g., rodents, ticks, and fleas), but the entire life cycle of *H. nana* is completed in humans. Therefore, hyperinfection with thousands of small adult worms in a single child may occur. A similar infection may occur less commonly with the species *H. diminuta*. Eggs but not segments may be found in the stool. *H. nana* infection responds to praziquantel (25 mg/kg PO once). Nitazoxanide is effective in about three-fourths of children (100 mg by mouth twice daily for 3 days for children 1-3 yr of age, 200 mg by mouth twice daily for 3 days for children 4-11 yr of age, and 500 mg by mouth twice daily for 3 days for older children).

**DIPYLIDIASIS (DIPYLIDUM CANINUM)**
*Dipylidium caninum* is a common tapeworm of domestic dogs and cat. Human infection is relatively rare. Direct transmission between pets and humans does not occur; human infection requires ingestion of the parasite's intermediate host, the dog or cat flea. Infants and small children are particularly susceptible because of their level of hygiene, generally more intimate contact with pets, and activities in areas where fleas can be encountered. Thus, children are most at risk of inadvertent ingestion of fleas infected with the larvae. The most common symptoms is passage of proglottids in stool. The proglottids are similar in size and shape to white rice grains. Anal pruritus, vague abdominal pain, and diarrhea have at times been associated with dipylidiasis, which is thus sometimes confused with pinworm (*E. vermicularis*). Dipylidiasis responds to treatment with praziquantel (5-10 mg/kg PO once) and niclosamide (50 mg/kg orally as a single dose). Deworming of pets and flea control are the best preventive measures.

*Bibliography is available at Expert Consult.*


Cysticercosis, but individuals harboring an adult worm may infect them through the ingestion of undercooked pork. Ingestion of pork is not necessary to develop cysticercosis. The pork tapeworm is widely distributed wherever pigs are raised and have contact with human fecal material. Intense transmission occurs undercooked pork. Ingestion of pork is not necessary to develop cysticercosis. The pork tapeworm is widely distributed wherever pigs are raised and have contact with human fecal material. Intense transmission occurs

EPIDEMIOLOGY

The pork tapeworm is widely distributed wherever pigs are raised and have contact with human fecal material. Intense transmission occurs in Central and South America, southern and Southeast Asia, and much of sub-Saharan Africa. In these areas, approximately 30% of cases of seizures may be a result of cysticercosis. Most cases of cysticercosis in the United States are imported; however local transmission has been rarely documented.

PATHOGENESIS

Living, intact cystic stages usually suppress the host immune and inflammatory responses. Intact cysts can be associated with disease when they obstruct the flow of cerebrospinal fluid. Most cysts remain asymptomatic for a few years. Symptoms typically develop as the cysts begin to degenerate, associated with a host inflammatory response. The natural history of cysts is to eventually resolve by complete resorption or calcification, but this process may take years. Cysticerci can also present as subcutaneous nodules, ocular infection, or spinal lesions with myelopathy or radiculopathy.

CLINICAL MANIFESTATIONS

Seizures are the presenting finding in the vast majority of children with neurocysticercosis. Less-common manifestations include hydrocephalus, diffuse cerebral edema, or focal neurologic findings. It is important to classify neurocysticercosis as parenchymal, intraventricular, subarachnoid, spinal, or ocular on the basis of anatomic location, clinical presentation, and radiologic appearance since the prognosis and management vary with location.

Parenchymal neurocysticercosis typically presents with seizures. The seizures are usually focal, but often generalize. Children may present with a single seizure or recurrent epilepsy. Mild neurocognitive defects have been documented from cysticerci alone, but are more commonly associated with poorly controlled seizures. A fulminant encephalitis-like presentation may rarely occur, after a massive initial infection associated with cerebral edema. Intraventricular neurocysticercosis (up to 20% of cases) is associated with obstructive hydrocephalus and acute, subacute, or intermittent signs of increased intracranial pressure, usually without localizing signs. Subarachnoid neurocysticercosis is rare in children. It can be associated with basilar arachnoiditis that can present with signs of meningeal irritation, communicating hydrocephalus, cerebral infarction, or spinal disease with radiculitis or transverse myelitis. Cysticerci in the tissues may present with focal findings from mass effect. Ocular neurocysticercosis causes decreased visual acuity because of cysticerci in the retina or vitreous, retinal detachment, or iridocyclitis.

DIAGNOSIS

Neurocysticercosis should be suspected in a child with onset of seizures or hydrocephalus and who also has a history of residence in an endemic area or a care provider from an endemic area. The most useful diagnostic study for parenchymal disease is MRI of the head. MRI provides the most information about cyst location, viability, and associated inflammation. The protoscolex is sometimes visible within the cyst, which provides a pathognomonic sign for cysticercosis (Fig. 303-1A). The MRI also better detects basilar arachnoiditis (Fig. 303-1B), intraventricular cysts (Fig. 303-1C), and cysts in the spinal cord. CT is best for identifying calcifications. A solitary parenchymal cyst, with or without contrast enhancement, and central nervous system calcifications are the most common findings in children (Fig. 303-2). Plain films may reveal calcifications in muscle or brain consistent with cysticercosis. In children from endemic regions, the presentation with a single enhancing lesion that is round and >2 cm in diameter, absence of symptoms or signs of other diseases (e.g., no fever or lymph nodes), no local findings, and no evidence of increased intracranial pressure is highly specific for neurocysticercosis.

Serologic diagnosis using the enzyme-linked immunotransfer blot is available commercially in the United States and through the Centers for Disease Control and Prevention. Serum antibody testing is highly specific, but is frequently negative in children with single lesions or just calcifications. Antigen-detection assays and polymerase chain reaction assays show promise as diagnostic procedures but are currently not commercially available.
**Figure 303-1** A, MRI (T1 weighted) demonstrating 2 parenchymal cysts with protoscoleces. B, MRI (T1 weighted) of cysticercal basilar arachnoiditis. C, MRI (T1 weighted) showing a cyst below the fourth ventricle (arrow). D, MRI (T2 weighted) showing a cysticercus (C) above the optic nerve (ON).

**Figure 303-2** CT image of a solitary lesion of neurocysticercosis with (A) and without (B) contrast, showing contrast enhancement. (Courtesy of Dr. Wendy G. Mitchell and Dr. Marvin D. Nelson, Children’s Hospital, Los Angeles.)
DIFFERENTIAL DIAGNOSIS
Neurocysticercosis is often confused clinically with other seizure disorders. Clinical suspicion is based on travel history, a history of contact with an individual who might carry an adult tapeworm, or suggestive imaging studies. The imaging appearance can be confused with brain abscess, granulomas (including tuberculosis, fungal infections, Langherhans histiocytoysis, and toxoplasmosis), and tumors.

TREATMENT
The initial management of cysticercosis should focus on symptomatic therapy for seizures and/or hydrocephalus. Seizures can usually be controlled using standard antiepileptic drugs. If the lesions resolve, antiepileptic drugs can often be tapered off. Frequent seizures or the development of calcified lesions are risk factors for recurrent seizures and indications for prolonged or lifelong antiepileptic therapy.

The natural history of parenchymal lesions is to resolve spontaneously with or without antiparasitic drugs, but this process is often prolonged (months to years). Solitary parenchymal cysts resolve slightly more rapidly with antiparasitic therapy. Antiparasitic drugs also decrease the frequency of recurrent seizures. Other forms of the disease are less common in children. In adults with cystic lesions, randomized, controlled trials suggested an overall 2-fold decrease in recurrence of generalized seizures with albendazole treatment. The benefit to children was significantly less, perhaps because most of these infections were with only 1-2 cysts. Corticosteroids likely also decrease seizure frequency.

Albendazole is the most commonly used antiparasitic (15 mg/kg/day PO divided bid). It can be taken with a fatty meal to improve absorption. The most common duration of therapy is 7 days for parenchymal lesions. However, longer duration (months), higher doses (up to 30 mg/kg/day), or combination therapy with praziquantel is often required for multiple lesions or subarachnoid disease. Praziquantel (50-100 mg/kg/day PO divided tid for 28 days) can be used with albendazole or as an alternative to it. First-pass metabolism is common with corticosteroids or antiepileptic drugs. Cimetidine can be used in conjunction with praziquantel to blunt the first-pass metabolism. A worsening of symptoms can follow the use of either drug based on the host’s inflammatory response to the dying parasite. Patients should be medicated with prednisone 1-2 mg/kg per day or oral dexamethasone 0.15 mg/kg per day beginning before the first dose of antiparasitic drugs and continuing for at least 2 wk. Methotrexate can be used as a steroid-sparing agent in patients requiring prolonged antiinflammatory therapy.

Most patients with hydrocephalus require neurosurgical interventions. Some cases require emergent placement of a ventriculostomy, but most can be managed by cystectomy alone. For obstructive hydrocephalus caused by ventricular cysticercosis, many patients can be cured by minimally invasive surgery. Neuroendoscopy is the preferred approach to cysticerci in the lateral or third ventricle. Cysticerci in the fourth ventricle can be removed by either flexible endoscopy or via a suboccipital craniotomy Adherent cysticerci that cannot be removed can be treated by placement of a ventriculoperitoneal shunt. However, there is a high rate of shunt failure, which can be minimized somewhat by treatment with antiparasitic drugs plus corticosteroids.

Subarachnoid disease has a poor prognosis. However, recent studies suggest that the prognosis is much improved by aggressive therapy, including antiparasitic drugs, antiinflammatory treatment, and neurosurgical procedures for hydrocephalus (e.g., placement of a ventriculoperitoneal shunt). However, the dose and duration of antiparasitic and antiinflammatory therapy often need to be prolonged. Ocular cysticercosis is usually treated surgically, although there are reports of cure using medical therapy alone.

PREVENTION
In areas with evolved public health systems, cysticercosis can largely be eliminated by meat inspection, condemnation of infected meat, and thorough cooking of pork. This approach has not worked in countries where most meat is butchered informally. Mass chemotherapy for tape-worm carriers, mass treatment of pigs, and improved personal hygiene have decreased or eliminated transmission in some areas. Screening family members and those preparing food for index cases for cysticercosis has a very low yield, in part because of the poor sensitivity of current tests. Those who have noted passing material consistent with taeniasis should be treated with praziquantel regardless of the results of stool studies. Veterinary vaccines for several cestode infections have a high degree of efficacy and have a potential role in decreasing parasite transmission.

Bibliography is available at Expert Consult.
Bibliography

Chapter 304

Echinococcosis

*(Echinococcus granulosus* and *Echinococcus multilocularis*)

Philip R. Fischer, Miguel M. Cabada, and A. Clinton White Jr.

**ETIOLOGY**

Echinococcosis (hydatid disease or hydatidosis) is a widespread, serious human cestode infection (Fig. 304-1). Two major *Echinococcus* groups of species are responsible for distinct clinical presentations. *Echinococcus granulosus* and related species cause cystic hydatid disease. The organisms were, until recently, thought to be a single species, but recent molecular data have confirmed that there are a number of different species and genotypes in what was formally thought to be a single species. *Echinococcus multilocularis* causes alveolar hydatid disease. The adult parasites are a small (2-7 mm) tape-worm with only 2-6 segments that inhabit the intestines of dogs, wolves, dingoes, jackals, coyotes, and foxes. These carnivores pass the eggs in their stool, which contaminates the soil, pasture, and water, as well as their own fur. Domestic animals, such as sheep, goats, cattle, and camels, ingest *E. granulosus* complex eggs while grazing. Humans are also infected by consuming eggs by direct contact with infected dogs or from ova in the environment. The larvae hatch, penetrate the gut, and are carried by the vascular or lymphatic systems to the liver, lungs, and less commonly bones, brain, or heart.

The different species within the *E. granulosus* complex show significant variation in both ecology and genetics. One distinct variant is found in a sylvatic wolf/moose cycle in North America and Siberia. For *E. multilocularis*, the main intermediate hosts are small rodents. The rodents are consumed by foxes, wolves, and other natural predators. In Europe, contamination of gardens by fox excrement is a major risk factor for transmission. Ingestion of infected rodents by dogs can also facilitate transmissions to children.

**EPIDEMIOLOGY**

There is potential for transmission of this parasite to humans wherever dogs are allowed to ingest the entrails of herd animals. Cysts have been detected in up to 10% of the human population in northern Kenya and western China. Disease is highly endemic in the Middle East and Central Asia. In South America, the disease is prevalent in shepherding areas of the Andes, the beef-herding areas of the Brazilian/Argentine Pampas, and Uruguay. Among developed countries, the disease is recognized in Italy, Greece, Portugal, Spain, and Australia,
Distribution of *Echinococcus granulosus* and cystic echinococcosis (hydatidosis), worldwide, 2009

Figure 304-1 Worldwide distribution of cystic echinococcosis. (From Control of Neglected Tropical Diseases. © World Health Organization, 2011. Available at: http://gamapserver.who.int/mapLibrary/Files/Maps/Global_echinococcosis_2009.png)

and is reemergent in dogs in Great Britain. In North America, transmission rarely occurs through a sylvatic cycle in the Arctic, as well as in foci of the domestic cycle in sheep raising areas of western United States. Transmission of *E. multilocularis* occurs primarily in Central Europe, Siberia, Turkey, and China. Transmission is now rare in the Arctic regions of North America. Separate species, *Echinococcus vogel* and *Echinococcus oligarthrus*, cause polycystic disease similar to alveolar hydatidosis in northern South America.

**PATHOGENESIS**

*E. granulosus* complex parasites are often acquired in childhood, but liver cysts require many years to become large enough to detect or cause symptoms. In children, the lung is a common site, whereas in adults 70% of cysts develop in the liver. Cysts can also develop in bone, the genitourinary system, spleen, subcutaneous tissues, and brain. The host surrounds the primary cyst with a tough, fibrous capsule. Inside this capsule, the parasite produces a thick lamellar layer with the consistency of a soft-boiled egg white. Inside of the lamellar layer is the thin germinal layer of cells responsible for production of thousands of protoscoleces that remain attached to the wall or float free in the cyst fluid (Video 304-1). Smaller internal daughter cysts may develop within the primary cyst capsule. The fluid in a healthy cyst is clear, colorless, and watery. Rupture of the cyst, which can occur with trauma or during surgery, can be associated with an anaphylactic reaction. Protoscoleces released into the tissues can also develop into new cysts. *E. multilocularis* almost always involves the liver. The lesions grow very slowly and rarely present in children. The secondary reproductive units bud externally and are not confined within a single well-defined structure. Thus, the lesions are often confused with a malignancy. Furthermore, the cyst tissues are poorly demarcated from those of the host, making surgical removal difficult. The secondary cysts are also capable of distant metastatic spread. The growing cyst mass eventually replaces a significant portion of the liver and compromises adjacent tissues and structures.

**CLINICAL MANIFESTATIONS**

In the liver, cysts may remain asymptomatic, may regress spontaneously, or may produce nonspecific symptoms. Symptomatic cysts can cause increased abdominal girth, hepatomegaly, a palpable mass, vomiting, or abdominal pain. Serious complications result from compression of adjacent structures or spillage of cyst contents. Mass effects can be noted in the brain and bone. Anaphylaxis can occur with cyst rupture or spontaneous spillage, from trauma or intraoperatively.
Spillage can also be catastrophic long-term, because each protoscoloe can form a new cyst. Jaundice from cystic hydatid disease is rare. In the lung, cysts produce chest pain, cough, or hemoptysis. Fluid from partially ruptured cysts is often noted to be salty.

In alveolar hydatid disease, the proliferating mass may compromise hepatic tissue or the biliary system and causes progressive obstructive jaundice and hepatic failure. Symptoms also occur from expansion of extrahepatic foci.

**DIAGNOSIS**

Symptoms and signs are usually nonspecific (e.g., hepatomegaly or a palpable abdominal mass). Ultrasonography is the most valuable tool for both the diagnosis and treatment of cystic hydatid disease of the liver. The presence of internal membranes or echogenic cyst material (protoscoleces, termed hydatid sand) can be observed in real time to aid in the diagnosis. Ultrasonography can also be used for disease staging used to define optimal therapy (Fig. 304-2). Chest radiographs frequently reveal characteristic rounded masses (Fig. 304-3). Alveolar disease resembles a diffuse solid tumor. CT findings are similar to those of ultrasonography and may at times be useful in distinguishing alveolar from cystic hydatid disease in geographic regions where both occur (Fig. 304-4). CT or MRI is also important in planning a surgical intervention. Lung hydatid disease is usually apparent on chest radiograph (Fig. 304-3).

Serologic studies may be useful in confirming a diagnosis of cystic echinococcosis. The sensitivity is high for hepatic or bone disease, but the false-negative rate may be >50% with pulmonary or central nervous system infection.

**DIFFERENTIAL DIAGNOSIS**

Benign hepatic cysts are common but can be distinguished from cystic hydatid disease by the absence of a distinct wall, internal membranes, and hydatid sand. The density of bacterial hepatic abscesses is distinct from the watery cystic fluid characteristic of *E. granulosus* infection, but hydatid cysts may also be complicated by secondary bacterial infection. Alveolar echinococcosis is often confused with hepatoma or metastatic tumor.

**TREATMENT**

Management of cystic hydatid disease should be individualized and guided by disease stage. Approaches range from surgical resection for complicated disease to watchful waiting for cysts that are already degenerating. For small cystic lesions (cystic echinococcosis [CE] types 1 or 3; see Fig. 304-2) that are <5 cm in diameter, albendazole chemotherapy alone (15 mg/kg/day divided bid PO for 1-6 mo; maximum: 800 mg/day) may result in a high rate of cure. Adverse effects include occasional alopecia, mild gastrointestinal disturbance, and elevated transaminases on prolonged use. Because of leukopenia, the FDA recommends that blood counts be monitored at the beginning and every 2 wk during therapy. Chemotherapy may also be used for cysts that are not suitable to **PAIR** (percutaneous aspiration, instillation, and reaspiration) or operative management.

For larger CE1 and CE3 lesions, ultrasound- or CT-guided PAIR is the preferred therapy. Compared with surgical treatment alone, PAIR plus albendazole results in similar cyst disappearance with fewer adverse events and fewer days in the hospital. Spillage with PAIR is surprisingly uncommon, but prophylactic albendazole therapy is routinely administered more than 1 wk prior to PAIR and should be continued for at least 1 mo afterward. PAIR is contraindicated in pregnancy and for bile-stained cysts, which should not be injected with a scolicalid agent because of increased risk for biliary complications. In experienced centers, cysts with thick internal septation (CE2) can be managed using a trochar to break up the membranes and external drainage or with surgery.

Surgery is the treatment of choice for complicated cysts, including ruptured cysts, cysts communicating with the biliary tract, large pulmonary cysts, or cysts of the central nervous system or bones.

For conventional surgery, the inner cyst wall (only laminate and germinal layers are of parasite origin) can be easily peeled from the

![Figure 304-2 Ultrasound classification of cystic echinococcosis (CE) cysts. The WHO informal working group on echinococcosis classification differs from that of Gharbi and colleagues by the addition of a “cystic lesion” (CL) stage (undifferentiated) (not shown), and by reversing the order of CE types 2 and 3. CE3 transitional cysts may be differentiated into CE3a (with detached endocyst) and CE3b (predominantly solid with daughter vesicles). CE1 and CE3a are early stage cysts and CE4 and CE5 late stage cysts. (From McManus DP, Gray DJ, Zhang W, Yang Y: Diagnosis, treatment, and management of echinococcosis. BMJ 344:e3866, 2012, Fig. 4.)](image-url)
Infectious Diseases continued for 6-8 wk postoperatively. CE4 and CE5 cysts are in the process of degeneration and usually do not require specific therapy. They can be managed with serial imaging studies to document resolution (watch and wait). Small thoracic cysts may resolve with chemotherapy, but most cysts require operative removal.

Alveolar hydatidosis frequently requires radical surgery, including partial hepatectomy, lobectomy, or liver transplantation. Medical therapy with albendazole should be continued for 2 yr after presumably curative surgery. In patients who are not operative candidates or whose lesions are not amenable to surgical cure, albendazole long-term suppressive therapy should be used to slow the progression, but the infection generally recurs if albendazole is stopped.

PROGNOSIS
Factors predictive of success with chemotherapy are age of the cyst (<2 yr), low internal complexity of the cyst, and small size. The site of the cyst is not important, although cysts in bone respond poorly. For alveolar hydatidosis, if surgical removal is unsuccessful, the average mortality is 92% by 10 yr after diagnosis.

PREVENTION
Important measures to interrupt transmission include, above all, thorough handwashing, avoiding contact with dogs in endemic areas, boiling or filtering water when camping, proper disposal of animal carcasses, and proper meat inspection. Strict procedures for proper disposal of refuse from slaughterhouses must be instituted and followed so that dogs and wild carnivores do not have access to entrails. Other useful measures are control or treatment of the feral dog population and regular praziquantel treatment of pets and working dogs in endemic areas. Vaccines have been developed to prevent infection in grazing animals but are not widely used.

Bibliography is available at Expert Consult.

Figure 304-3 Serial chest x-rays of a young Kenyan woman with bilateral hydatid cysts. After 2 mo of albendazole therapy, sudden rupture of the right cyst was associated with massive aspiration and acute respiratory distress.

Figure 304-4 Abdominal CT revealed hepatomegaly and multiple (>20) liver cysts. (From Ben-Shimol S, Zelcer I: Liver hydatid cysts. J Pediatr 163:1792, 2013.)
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Clinical Manifestations of Gastrointestinal Disease

Chapter 305
Normal Digestive Tract Phenomena
Chris A. Liacouras

Gastrointestinal function varies with maturity; what is a physiologic event in a newborn or infant might be a pathologic symptom at an older age. A fetus can swallow amniotic fluid as early as 12 wk of gestation, but nutritive sucking in neonates first develops at about 34 wk of gestation. The coordinated oral and pharyngeal movements necessary for swallowing solids develop within the 1st few mo of life. Before this time, the tongue thrust is upward and outward to express milk from the nipple, instead of a backward motion, which propels solids toward the esophageal inlet. By 1 mo of age, infants appear to show preferences for sweet and salty foods. Infants’ interest in solids increases at approximately 4 mo of age. The recommendation to begin solids at 6 mo of age is based on nutritional and cultural concepts rather than maturation of the swallowing process (see Chapter 45). Infants swallow air during feeding, and burping is encouraged to prevent gaseous distension of the stomach.

A number of normal anatomic variations may be noted in the mouth. A short lingual frenulum ("tongue-tie") may be worrisome to parents but only rarely interferes with eating or speech, generally requiring no treatment. Surface furrowing of the tongue (a geographic or scrotal tongue) is usually a normal finding. A bifid uvula may be normal or associated with a submucous cleft of the soft palate.

Regurgitation, the result of gastroesophageal reflux, occurs commonly in the 1st yr of life. Effortless regurgitation can dribble out of an infant’s mouth but also may be forceful. In an otherwise healthy infant with regurgitation, volumes of emesis are commonly approximately 15-30 mL but occasionally are larger. Most often, the infant remains happy, although possibly hungry, after an episode of regurgitation. Episodes can occur from one to several times per day. Regurgitation gradually resolves in 80% of infants by 6 mo of age and in 90% by 12 mo. If complications develop or regurgitation persists, gastroesophageal reflux is considered pathologic rather than merely developmental and deserves further evaluation and treatment. Complications of gastroesophageal reflux include failure to thrive, pulmonary disease (apnea or aspiration pneumonitis), and esophagitis with its sequelae (see Chapters 323 and 324).

Infants and young children may be erratic eaters; this may be a worry to parents. A toddler might eat insatiably or refuse to consume food during a meal. Toddlers and young children also tend to eat only a limited variety of foods. Parents should be encouraged to view nutritional intake over several days and not be overly concerned about individual meals. Infancy and adolescence are periods of rapid growth; high nutrient requirements for growth may be associated with voracious appetites. The reduced appetite of toddlers and preschool children is often a worry to parents who are used to the relatively greater dietary intake during infancy. Demonstration of age-appropriate growth on a growth curve is reassuring.

The number, color, and consistency of stools can vary greatly in the same infant and between infants of similar age without apparent explanation. The earliest stools after birth consist of meconium, a dark, viscous material that is normally passed within the 1st 48 hr of life. With the onset of feeding, meconium is replaced by green-brown transition stools, often containing curds, and, after 4-5 days, by yellow-brown milk stools. Stool frequency is extremely variable in normal infants and can vary from none to 7 per day. Breastfed infants can have frequent small, loose stools early (transition stools), and then after 2-3 wk can have very infrequent soft stools. Some nursing infants might not pass any stool for 1-2 wk and then have a normal soft bowel movement. The color of stool has little significance except for the presence of blood or absence of bilirubin products (white-gray rather than yellow-brown). The presence of vegetable matter, such as peas or corn, in the stool of an older infant or toddler ingesting solids is normal and suggests poor chewing and not malabsorption. A pattern of intermittent loose stools, known as toddler’s diarrhea, occurs commonly between 1 and 3 yr of age. These otherwise healthy growing children often drink excessive carbohydrate-containing beverages. The stools typically occur during the day and not overnight. The volume of fluid intake is often excessive; limiting sugar and unabsorbable carbohydrate-containing beverages and increasing fat in the diet often leads to resolution of the pattern of loose stools.

A protuberant abdomen is often noted in infants and toddlers, especially after large feedings. This can result from the combination of weak abdominal musculature, relatively large abdominal organs, and lortedic stance. In the 1st yr of life, it is common to palpate the liver 1-2 cm below the right costal margin. The normal liver is soft in consistency and percuces to normal size for age. A Riedel lobe is a thin projection of the right lobe of the liver that may be palpated low in the right lateral abdomen. A soft spleen tip might also be palpable as a normal finding. In thin young children, the vertebral column is easily palpable, and an overlying structure may be mistaken for a mass. Pulsation of the aorta can be appreciated. Normal stool can often be palpated in the left lower quadrant in the descending or sigmoid colon.

Blood loss from the gastrointestinal tract is rare in normal, but swallowed blood may be misinterpreted as gastrointestinal bleeding. Maternal blood may be ingested at the time of birth or later by a nursing infant if there is bleeding near the mother’s nipple. Nasal or oropharyngeal bleeding is occasionally mistaken for gastrointestinal bleeding (see Chapter 103.4). Red dyes in foods or drinks can turn the stool red but do not produce a positive test result for occult blood.

Jaundice is common in neonates, especially among premature infants, and usually results from the inability of an immature liver to conjugate bilirubin, leading to an elevated indirect component (see Chapter 102.4). Persistent elevation of indirect bilirubin levels in nursing infants may be a result of breast milk jaundice, which is usually a benign entity in full-term infants. An elevated direct bilirubin is not normal and suggests liver disease, although in infants it may be a result of extrahepatic infection (urinary tract infection). The direct bilirubin fraction should account for no more than 15-20% of the total serum bilirubin. Elevations in direct bilirubin levels can follow indirect hyperbilirubinemia as the liver converts excessive indirect to direct bilirubin and the rate-limiting step in bilirubin excretion shifts from the glucuronidation of bilirubin to excretion of direct bilirubin into the bile canaliculus. Indirect hyperbilirubinemia, which occurs commonly in normal newborns, tends to tint the sclerae and skin golden yellow, whereas direct hyperbilirubinemia produces a greenish yellow hue.
Disorders of organs outside the gastrointestinal (GI) tract can produce symptoms and signs that mimic digestive tract disorders and should be considered in the differential diagnosis (Table 306-1). In children with normal growth and development, treatment may be initiated without a formal evaluation based on a presumptive diagnosis after taking a history and performing a physical examination. Poor weight gain or weight loss is often associated with a significant pathologic process and usually necessitates a more formal evaluation.

**DYSPHAGIA**

Difficulty in swallowing is termed *dysphagia*. Painful swallowing is termed *odynophagia*. *Globus* is the sensation of something stuck in the throat without a clear etiology. Swallowing is a complex process that starts in the mouth with mastication and lubrication of food that is formed into a bolus. The bolus is pushed into the pharynx by the tongue. The pharyngeal phase of swallowing is rapid and involves protective mechanisms to prevent food from entering the airway. The epiglottis is lowered over the larynx while the soft palate is elevated against the nasopharyngeal wall; respiration is temporarily arrested while the upper esophageal sphincter opens to allow the bolus to enter the esophagus. In the esophagus, peristaltic coordinated muscular contractions push the food bolus toward the stomach. The lower esophageal sphincter relaxes shortly after the upper esophageal sphincter, so liquids that rapidly clear the esophagus enter the stomach without resistance.

Dysphagia is classified as oropharyngeal dysphagia and esophageal dysphagia. Oropharyngeal dysphagia occurs when the transfer of the food bolus from the mouth to the esophagus is impaired (also termed *transfer dysphagia*). The striated muscles of the mouth, pharynx, and upper esophageal sphincter are affected in oropharyngeal dysphagia. Neurologic and muscular disorders can give rise to oropharyngeal dysphagia (Table 306-2). The most serious complication of oropharyngeal dysphagia is life-threatening aspiration.

A complex sequence of neuromuscular events is involved in the transfer of foods to the upper esophagus. Abnormalities of the muscles involved in the ingestion process and their innervation, strength, or coordination are associated with transfer dysphagia in infants and children. In such cases, an oropharyngeal problem is usually part of a more generalized neurologic or muscular problem (botulism, diphtheria, neuromuscular disease). Painful oral lesions, such as acute viral stomatitis or trauma, occasionally interfere with ingestion. If the nasal air passage is seriously obstructed, the need for respiration causes severe distress when sucking. Although severe structural, dental, and salivary abnormalities would be expected to create difficulties, ingestion proceeds relatively well in most affected children if they are hungry.

Esophageal dysphagia occurs when there is difficulty in transporting the food bolus down the esophagus. Esophageal dysphagia can result from neuromuscular disorders or mechanical obstruction (Table 306-3). Primary motility disorders causing impaired peristaltic function and dysphagia are rare in children. Achalasia is an esophageal motility disorder with associated inability of relaxation of the lower esophageal sphincter, and it rarely occurs in children. Motility of the distal esophagus is disordered after surgical repair of tracheoesophageal fistula or achalasia. Abnormal motility can accompany collagen vascular disorders. Mechanical obstruction can be intrinsic or extrinsic. Intrinsic structural defects cause a fixed impediment to the passage of food bolus because of a narrowing within the esophagus, as in a stricture, web, or tumor. Extrinsic obstruction is

### Table 306-1

<table>
<thead>
<tr>
<th>Some Nondigestive Tract Causes of Gastrointestinal Symptoms in Children</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ANOREXIA</strong></td>
</tr>
<tr>
<td>Systemic disease: inflammatory, neoplastic</td>
</tr>
<tr>
<td>Cardiorespiratory compromise</td>
</tr>
<tr>
<td>Iatrogenic: drug therapy, unpalatable therapeutic diets</td>
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<tr>
<td>Depression</td>
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<tr>
<td>Anorexia nervosa</td>
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<tr>
<td><strong>VOMITING</strong></td>
</tr>
<tr>
<td>Inborn errors of metabolism</td>
</tr>
<tr>
<td>Medications: erythromycin, chemotherapy, nonsteroidal anti-inflammatory drugs</td>
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<td>Increased intracranial pressure</td>
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<td>Brain tumor</td>
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<tr>
<td>Infection of the urinary tract</td>
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<tr>
<td>Labyrinthitis</td>
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<tr>
<td>Adrenal insufficiency</td>
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<tr>
<td>Pregnancy</td>
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<tr>
<td>Psychogenic</td>
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<tr>
<td>Abdominal migraine</td>
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<td>Toxins</td>
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<td>Renal disease</td>
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<td>Uremia</td>
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<td>Medications: antibiotics, cisapride</td>
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<td>Tumors: neuroblastoma</td>
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<td>Pericarditis</td>
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<td>Spina bifida</td>
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<td>Dehydration: diabetes insipidus, renal tubular lesions</td>
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<td>Medications: narcotics</td>
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<td>Lead poisoning</td>
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<td>Infant botulism</td>
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<td><strong>ABDOMINAL PAIN</strong></td>
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<td>Pelvonephritis, hydronephrosis, renal colic</td>
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<td>Pneumonia (lower lobe)</td>
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<td>Pelvic inflammatory disease</td>
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<td>Porphyria</td>
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<td>Angioedema</td>
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<td>Abdominal migraine</td>
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<td>School phobia</td>
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<td>Pelvic osteomyelitis or myositis</td>
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<td>Medications</td>
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<td><strong>ABDOMINAL DISTENTION OR MASS</strong></td>
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<td>Pregnancy</td>
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<td><strong>JAUNDICE</strong></td>
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<tr>
<td>Hypothyroidism</td>
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<tr>
<td>Panhypopituitarism</td>
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</tbody>
</table>

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Chapter 306

Major Symptoms and Signs of Digestive Tract Disorders

*Raman Sreedharan and Chris A. Liacouras*
Causes of Esophageal Dysphagia

NEUROMUSCULAR DISORDERS
- Cerebral palsy
- Brain tumors
- Cerebrovascular accidents
- Polio and postpolio syndromes
- Multiple sclerosis
- Myositis
- Dermatomyositis
- Myasthenia gravis
- Muscular dystrophies
- Acquired or inherited dystonia syndrome
- Dysautonomia

METABOLIC AND AUTOIMMUNE DISORDERS
- Hyperthyroidism
- Systemic lupus erythematosus
- Sarcoidosis
- Amyloidosis

INFECTION DISEASE
- Meningitis
- Botulism
- Diphtheria
- Lyme disease
- Neurosyphilis
- Viral infection: polio, Coxsackievirus, herpes, cytomegalovirus

STRUCTURAL LESIONS
- Inflammatory: abscess, pharyngitis
- Congenital web
- Dental problems
- Bullous skin lesions
- Plummer-Vinson syndrome
- Zenker diverticulum
- Extrinsic compression: osteophytes, lymph nodes, thyroid swelling

OTHER
- Corrosive injury
- Side effects of medications
- After surgery
- After radiation therapy


Vomiting, which denotes an active reflex process with an extensive differential diagnosis (Table 306-4).

ANOREXIA
Anorexia means prolonged lack of appetite. Hunger and satiety centers are located in the hypothalamus; it seems likely that afferent nerves from the GI tract to these brain centers are important determinants of the anorexia that characterizes many diseases of the stomach and intestine (see Chapter 47). Satiety is stimulated by distention of the stomach or upper small bowel, the signal being transmitted by sensory afferents, which are especially dense in the upper gut. Chemoreceptors in the intestine, influenced by the assimilation of nutrients, also affect afferent flow to the appetite centers. Impulses reach the hypothalamus from higher centers, possibly influenced by pain or the emotional disturbance of an intestinal disease. Other regulatory factors include hormones, ghrelin, leptin, and plasma glucose, which, in turn, reflect intestinal function (see Chapter 47).

VOMITING
Vomiting is a highly coordinated reflex process that may be preceded by increased salivation and begins with involuntary retching. Violent descent of the diaphragm and constriction of the abdominal muscles with relaxation of the gastric cardia actively force gastric contents back up the esophagus. This process is coordinated in the medullary vomiting center, which is influenced directly by afferent innervation and indirectly by the chemoreceptor trigger zone and higher central nervous system (CNS) centers. Many acute or chronic processes can cause vomiting (see Tables 306-1 and 306-4).

Vomiting caused by obstruction of the GI tract is probably mediated by intestinal visceral afferent nerves stimulating the vomiting center (Table 306-5). If obstruction occurs below the second part of the duodenum, vomiting is usually bile stained. Emesis can also become bile stained with repeated vomiting in the absence of obstruction when duodenal contents are refluxed into the stomach. Nonobstructive lesions of the digestive tract can also cause vomiting; this includes diseases of the upper bowel, pancreas, liver, or biliary tree. CNS or metabolic derangements can lead to severe, persistent emesis.

Cyclic vomiting is a syndrome with numerous episodes of vomiting interspersed with well intervals. The North American Society for Pediatric Gastroenterology, Hepatology and Nutrition consensus statement on the diagnosis and management of cyclic vomiting criteria are listed in Table 306-6. Rome III criteria for functional GI disorders have 2 criteria for cyclic vomiting in children, and both these criteria have to
### Table 306-4  
Differential Diagnosis of Emesis During Childhood

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<tr>
<th>INFANT</th>
<th>CHILD</th>
<th>ADOLESCENT</th>
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<tr>
<td></td>
<td>Anatomic obstruction*</td>
<td>Pregnancy</td>
</tr>
<tr>
<td></td>
<td>Eosinophilic esophagitis</td>
<td>Medications</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ipecac abuse, bulimia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Concussion</td>
</tr>
<tr>
<td>RARE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adrenogenital syndrome</td>
<td>Reye syndrome</td>
<td>Reye syndrome</td>
</tr>
<tr>
<td>Inborn errors of metabolism</td>
<td>Hepatitis</td>
<td>Hepatitis</td>
</tr>
<tr>
<td>Brain tumor (increased intracranial pressure)</td>
<td>Peptic ulcer</td>
<td>Peptic ulcer</td>
</tr>
<tr>
<td>Subdural hemorrhage</td>
<td>Pancreatitis</td>
<td>Pancreatitis</td>
</tr>
<tr>
<td>Food poisoning</td>
<td>Brain tumor</td>
<td>Brain tumor</td>
</tr>
<tr>
<td>Ruminaton</td>
<td>Increased intracranial pressure</td>
<td>Increased intracranial pressure</td>
</tr>
<tr>
<td>Renal tubular acidosis</td>
<td>Middle ear disease</td>
<td>Concussion</td>
</tr>
<tr>
<td>Ureteropelvic junction obstruction</td>
<td>Chemotherapy</td>
<td>Middle ear disease</td>
</tr>
<tr>
<td>Pseudoobstruction</td>
<td>Achalasia</td>
<td>Chemotherapy</td>
</tr>
<tr>
<td></td>
<td>Cyclic vomiting (migraine)</td>
<td>Cyclic vomiting (migraine)</td>
</tr>
<tr>
<td></td>
<td>Esophageal stricture</td>
<td>Biliary colic</td>
</tr>
<tr>
<td></td>
<td>Duodenal hematoma</td>
<td>Renal colic</td>
</tr>
<tr>
<td></td>
<td>Inborn error of metabolism</td>
<td>Diabetic ketoacidosis</td>
</tr>
<tr>
<td></td>
<td>Pseudoobstruction</td>
<td>Pseudoobstruction</td>
</tr>
</tbody>
</table>

*Includes malrotation, pyloric stenosis, intussusception, Hirschsprung disease.
†Meningitis, sepsis.
GERD, gastroesophageal reflux disease, inguinal hernia.

### Table 306-5  
Causes of Gastrointestinal Obstruction

<table>
<thead>
<tr>
<th>ESOPHAGUS</th>
<th>Ileal atresia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Congenital</strong></td>
<td>Meconium ileus</td>
</tr>
<tr>
<td>Esophageal atresia</td>
<td>Meckel diverticulum with volvulus or intussusception</td>
</tr>
<tr>
<td>Vascular rings</td>
<td>Inguinal hernia</td>
</tr>
<tr>
<td>Schatzki ring</td>
<td>Internal hernia</td>
</tr>
<tr>
<td>Tracheobronchial remnant</td>
<td>Intestinal duplication</td>
</tr>
<tr>
<td><strong>Acquired</strong></td>
<td>Pseudoobstruction</td>
</tr>
<tr>
<td>Esophageal stricture</td>
<td>Postsurgical adhesions</td>
</tr>
<tr>
<td>Foreign body</td>
<td>Crohn disease</td>
</tr>
<tr>
<td>Achalasia</td>
<td>Intussusception</td>
</tr>
<tr>
<td>Chagas disease</td>
<td>Distal ileal obstruction syndrome (cystic fibrosis)</td>
</tr>
<tr>
<td>Collagen vascular disease</td>
<td>Duodenal hematoma</td>
</tr>
<tr>
<td></td>
<td>Superior mesenteric artery syndrome</td>
</tr>
<tr>
<td>STOMACH</td>
<td></td>
</tr>
<tr>
<td><strong>Congenital</strong></td>
<td>COLON</td>
</tr>
<tr>
<td>Antral webs</td>
<td>Meconium plug</td>
</tr>
<tr>
<td>Pyloric stenosis</td>
<td>Hirschsprung disease</td>
</tr>
<tr>
<td><strong>Acquired</strong></td>
<td>Colonic atresia, stenosis</td>
</tr>
<tr>
<td>Bezoar, foreign body</td>
<td>Imperforate anus</td>
</tr>
<tr>
<td>Pyloric stricture (ulcer)</td>
<td>Rectal stenosis</td>
</tr>
<tr>
<td>Chronic granulomatous disease of childhood</td>
<td>Eosinophilic gastroenteritis</td>
</tr>
<tr>
<td>Eosinophilic gastroenteritis</td>
<td>Crohn disease</td>
</tr>
<tr>
<td>Crohn disease</td>
<td>Epidermolysis bullosa</td>
</tr>
<tr>
<td>SMALL INTESTINE</td>
<td></td>
</tr>
<tr>
<td><strong>Congenital</strong></td>
<td>SMALL INTESTINE</td>
</tr>
<tr>
<td>Duodenal atresia</td>
<td>Duodenal atresia</td>
</tr>
<tr>
<td>Annular pancreas</td>
<td>Annular pancreas</td>
</tr>
<tr>
<td>Malrotation/volvulus</td>
<td>Malrotation/volvulus</td>
</tr>
<tr>
<td>Malrotation/Ladd bands</td>
<td>Malrotation/Ladd bands</td>
</tr>
</tbody>
</table>

*Includes malrotation, pyloric stenosis, intussusception, Hirschsprung disease.
†Meningitis, sepsis.
GERD, gastroesophageal reflux disease, inguinal hernia.
be present for a diagnosis of cyclic vomiting: 2 or more periods of intense nausea and unremitting vomiting or retching lasting hours to days and return to usual state of health lasting weeks to months.

The onset of cyclic vomiting is usually between 2 and 5 yr of age but has been observed in infants and adults. The frequency of vomiting episodes is variable (average of 12 episodes per yr) with each episode typically lasting 2-3 days and 4 or more emesis episodes per hour. The episodes usually occur in the early hours of the morning or upon wakening. Patients can have a proadrome of nausea, pallor, intolerance of noise or light, lethargy, and headache. Epigastric pain, abdominal pain, diarrhea, and fever are seen in many patients, making the diagnosis difficult. Precipitants include infection, physical stress, and psychologic stress.

Several theories have been proposed as causative factors, including a migraine-related mechanism, mitochondrial disorders, and autonomic dysfunction. More than 80% of affected children have a 1st-degree relative with migraines; many patients develop migraines later in life. Many children show evidence for sympathetic autonomic dysfunction of sudomotor systems. The differential diagnosis includes GI anomalies (malrotation, duplication cysts, choledochal cysts, recurrent intussusceptions), CNS disorders (neoplasm, epilepsy, vestibular pathophysiology), nephrolithiasis, cholelithiasis, hydronephrosis, metabolic dysfunction of sudomotor systems. The differential diagnosis includes GI anomalies (malrotation, duplication cysts, choledochal cysts, recurrent intussusceptions), CNS disorders (neoplasm, epilepsy, vestibular pathophysiology), nephrolithiasis, cholelithiasis, hydronephrosis, metabolic dysfunction. 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### Table 306-6
Criteria for Cyclic Vomiting Syndrome

All of the criteria must be met for the consensus definition of cyclic vomiting syndrome:
- At least 5 attacks in any interval, or a minimum of 3 episodes during a 6-mo period
- Recurrent episodes of intense vomiting and nausea lasting 1 hr to 10 days and occurring at least 1 wk apart
- Stereotypical pattern and symptoms in the individual patient
- Vomiting during episodes occurs ≥ 4 times/hr for ≥ 1 hr
- Return to baseline health between episodes
- Not attributed to another disorder

### Table 306-7
Complications of Vomiting

<table>
<thead>
<tr>
<th>COMPLICATION</th>
<th>PATHOPHYSIOLOGY</th>
<th>HISTORY, PHYSICAL EXAMINATION, AND LABORATORY STUDIES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolic</td>
<td>Fluid loss in emesis</td>
<td>Dehydration</td>
</tr>
<tr>
<td></td>
<td>HCl loss in emesis</td>
<td>Alkalosis, hypochloremia</td>
</tr>
<tr>
<td></td>
<td>Na, K loss in emesis</td>
<td>Hyponatremia, hypokalemia</td>
</tr>
<tr>
<td></td>
<td>Alkalosis → Na into cells</td>
<td></td>
</tr>
<tr>
<td>Nutritional</td>
<td>Emesis of calories and nutrients</td>
<td>Malnutrition; “failure to thrive”</td>
</tr>
<tr>
<td></td>
<td>Anorexia for calories and nutrients</td>
<td></td>
</tr>
<tr>
<td>Mallory-Weiss tear</td>
<td>Retching → tear at lesser curve of gastroesophageal junction</td>
<td>Forceful emesis → hematemesis</td>
</tr>
<tr>
<td>Esophagitis</td>
<td>Chronic vomiting → esophageal acid exposure</td>
<td>Heartburn; Hemoccult + stool</td>
</tr>
<tr>
<td>Aspiration</td>
<td>Aspiration of vomitus, especially in context of obtubation</td>
<td>Pneumonia; neurologic dysfunction</td>
</tr>
<tr>
<td>Shock</td>
<td>Severe fluid loss in emesis or in accompanying diarrhea</td>
<td>Dehydration (accompanying diarrhea can explain acidosis?)</td>
</tr>
<tr>
<td></td>
<td>Severe blood loss in hematemesis</td>
<td>Blood volume depletion</td>
</tr>
<tr>
<td>Pneumomediastinum, pneumothorax</td>
<td>Increased intrathoracic pressure</td>
<td>Chest x-ray</td>
</tr>
<tr>
<td>Petechiae, retinal hemorrhages</td>
<td>Increased intrathoracic pressure</td>
<td>Normal platelet count</td>
</tr>
</tbody>
</table>

Osmotic diarrhea occurs after ingestion of a poorly absorbed solute. The solute may be one that is normally not well absorbed (magnesium, phosphate, lactulose, or sorbitol) or one that is not well absorbed because of a disorder of the small bowel (lactose with lactase deficiency or glucose with rotavirus diarrhea). Malabsorbed carbohydrate is fermented in the colon, and short-chain fatty acids are produced. Although short-chain fatty acids can be absorbed in the colon and used as an energy source, the net effect is increase in the osmotic solute load. This form of diarrhea is usually of lesser volume than a secretory diarrhea and stops with fasting. The osmolality of the stool will not be explained by the electrolytes, and the ion gap is >100 mOsm/kg or less. The ion gap is calculated by subtracting the concentration of electrolytes from total osmolality:

\[
\text{Ion gap} = \text{Stool osmolality} - ([\text{Stool Na} + \text{stool K}] \times 2)
\]

**Surface epithelium of the bowel and thereby stimulating intracellular accumulation of cyclic adenosine monophosphate or cyclic guanosine monophosphate. Some intraluminal fatty acids and bile salts cause the colonic mucosa to secrete through this mechanism. Diarrhea not associated with an exogenous secretagogue can also have a secretory component (congenital microvillus inclusion disease). Secretory diarrhea is usually of large volume and persists even with fasting.**
### Table 306-9  Supportive and Nonpharmacologic Therapies for Vomiting Episodes

<table>
<thead>
<tr>
<th>DISEASE</th>
<th>THERAPY</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>Treat cause</td>
</tr>
<tr>
<td></td>
<td>• Obstruction: operate</td>
</tr>
<tr>
<td></td>
<td>• Allergy: change diet (±steroids)</td>
</tr>
<tr>
<td></td>
<td>• Metabolic error: Rx defect</td>
</tr>
<tr>
<td></td>
<td>• Acid peptic disease: H2RAs, PPIs, etc.</td>
</tr>
</tbody>
</table>

**COMPLICATIONS**

- **Dehydration**
  - IV fluids, electrolytes
- **Hematemesis**
  - Transfuse, correct coagulopathy
- **Esophagitis**
  - H2RAs, PPIs
- **Malnutrition**
  - NG or NJ drip feeding useful for many chronic conditions
- **Meconium ileus**
  - Gastrografin enema
- **DIOS**
  - Gastrografin enema; balanced colonic lavage solution (e.g., GoLYTELY)
- **Intussusception**
  - Barium enema; air reduction enema
- **Hematemesis**
  - Endoscopic: injection sclerotherapy or banding of esophageal varices; injection therapy, fibrin sealant application, or heater probe electrocauterity for selected upper GI tract lesions
- **Sigmoid volvulus**
  - Colonoscopic decompression
- **Reflux**
  - Positioning; dietary measures (infants: rice cereal, 1 tbs/oz of formula)
- **Psychogenic components**
  - Psychotherapy; tricyclic antidepressants; anxiolytics (e.g., diazepam: 0.1 mg/kg PO tid-qid)

DIOS, distal intestinal obstruction syndrome; GI, gastrointestinal; H2RA, H2-receptor antagonist; NG, nasogastric; NJ, nasojejunal; PPIs, proton pump inhibitors; tbs, tablespoon.


### Table 306-10  Mechanisms of Diarrhea

<table>
<thead>
<tr>
<th>PRIMARY MECHANISM</th>
<th>DEFECT</th>
<th>STOOL EXAMINATION</th>
<th>EXAMPLES</th>
<th>COMMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Secretory</td>
<td>Decreased absorption, increased secretion, electrolyte transport</td>
<td>Watery, normal osmolality with ion gap &lt; 100 mOsm/kg</td>
<td>Cholera, toxigenic <em>Escherichia coli</em>, carcinoid, VIP, neuroblastoma, congenital chloride diarrhea, <em>Clostridium difficile</em>, cryptosporidiosis (AIDS)</td>
<td>Persists during fasting; bile salt malabsorption can also increase intestinal water secretion; no stool leukocytes</td>
</tr>
<tr>
<td>Osmotic</td>
<td>Maldigestion, transport defects ingestion of unabsorbable substances</td>
<td>Watery, acidic, and reducing substances; increased osmolality with ion gap &gt; 100 mOsm/kg</td>
<td>Lactase deficiency, glucose-galactose malabsorption, lactulose, laxative abuse</td>
<td>Stops with fasting; increased breath hydrogen with carbohydrate malabsorption; no stool leukocytes</td>
</tr>
<tr>
<td>Increased motility</td>
<td>Decreased transit time</td>
<td>Loose to normal-appearing stool, stimulated by gastrocolic reflex</td>
<td>Irritable bowel syndrome, thyrotoxicosis, postvagotomy dumping syndrome</td>
<td>Infection can also contribute to increased motility</td>
</tr>
<tr>
<td>Decreased motility</td>
<td>Defect in neuromuscular unit(s) stasis (bacterial overgrowth)</td>
<td>Loose to normal-appearing stool</td>
<td>Pseudoobstruction, blind loop</td>
<td>Possible bacterial overgrowth</td>
</tr>
<tr>
<td>Decreased surface area (osmotic, motility)</td>
<td>Decreased functional capacity</td>
<td>Watery</td>
<td>Short bowel syndrome, celiac disease, rotavirus enteritis</td>
<td>Might require elemental diet plus parenteral alimentation</td>
</tr>
<tr>
<td>Mucosal invasion</td>
<td>Inflammation, decreased colonic reabsorption, increased motility</td>
<td>Blood and increased WBCs in stool</td>
<td><em>Salmonella</em>, <em>Shigella</em> infection; amebiasis; <em>Yersinia</em>, <em>Campylobacter</em> infection</td>
<td>Dyentery evident in blood, mucus, and WBCs</td>
</tr>
</tbody>
</table>

VIP, vasoactive intestinal peptide; WBC, white blood cell.


Motility disorders can be associated with rapid or delayed transit and are not generally associated with large-volume diarrhea. Slow motility can be associated with bacterial overgrowth leading to diarrhea. The differential diagnosis of common causes of acute and chronic diarrhea is noted in Table 306-11.

### CONSTIPATION

Any definition of constipation is relative and depends on stool consistency, stool frequency, and difficulty in passing the stool. A normal child might have a soft stool only every 2nd or 3rd day without difficulty; this is not constipation. A hard stool passed with difficulty every 3rd day should be treated as constipation. Constipation can arise from defects either in filling or emptying the rectum (Table 306-12).

A nursing infant might have very infrequent stools of normal consistency; this is usually a normal pattern. True constipation in the neonatal period is most likely secondary to Hirschsprung disease, intestinal pseudoobstruction, or hypothyroidism.

Defective rectal filling occurs when colonic peristalsis is ineffective (in cases of hypothyroidism or opiate use and when bowel obstruction is caused either by a structural anomaly or by Hirschsprung disease).
Table 306-11  Differential Diagnosis of Diarrhea

<table>
<thead>
<tr>
<th>INFANT</th>
<th>CHILD</th>
<th>ADOLESCENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACUTE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Common</td>
<td>Gastroenteritis (viral &gt; bacterial &gt; protozoal)</td>
<td>Gastroenteritis (viral &gt; bacterial &gt; protozoal)</td>
</tr>
<tr>
<td>Systemic infection</td>
<td>Food poisoning</td>
<td>Food poisoning</td>
</tr>
<tr>
<td>Antibiotic associated</td>
<td>Systemic infection</td>
<td>Antibiotic associated</td>
</tr>
<tr>
<td>Overfeeding</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rare</td>
<td>Primary disaccharide deficiency</td>
<td>Toxic ingestion</td>
</tr>
<tr>
<td></td>
<td>Hirschsprung toxic colitis</td>
<td>Hemolytic uremic syndrome</td>
</tr>
<tr>
<td></td>
<td>Adrenogenital syndrome</td>
<td>Intussusception</td>
</tr>
<tr>
<td></td>
<td>Neonatal opiate withdrawal</td>
<td></td>
</tr>
<tr>
<td>CHRONIC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Common</td>
<td>Postinfectious secondary lactase deficiency</td>
<td>Postinfectious secondary lactase deficiency</td>
</tr>
<tr>
<td></td>
<td>Cow's milk or soy protein intolerance (allergy)</td>
<td>Irritable bowel syndrome</td>
</tr>
<tr>
<td></td>
<td>Chronic nonspecific diarrhea of infancy</td>
<td>Celiac disease</td>
</tr>
<tr>
<td></td>
<td>Excessive fruit juice (sorbitol) ingestion</td>
<td>Cystic fibrosis</td>
</tr>
<tr>
<td></td>
<td>Celiac disease</td>
<td>Lactose intolerance</td>
</tr>
<tr>
<td></td>
<td>Cystic fibrosis</td>
<td>Excessive fruit juice (sorbitol) ingestion</td>
</tr>
<tr>
<td></td>
<td>AIDS enteropathy</td>
<td>Giardiasis</td>
</tr>
<tr>
<td>Rare</td>
<td>Primary immune defects</td>
<td>Primary and acquired immune defects</td>
</tr>
<tr>
<td></td>
<td>Autoimmune enteropathy</td>
<td>Secretory tumors</td>
</tr>
<tr>
<td></td>
<td>IPEX and IPEX-like syndromes</td>
<td>Pseudobulbar oligosymptomatic polyneuropathy</td>
</tr>
<tr>
<td></td>
<td>Glucose-galactose malabsorption</td>
<td>Sucrase-isomaltase deficiency</td>
</tr>
<tr>
<td></td>
<td>Microvillus inclusion disease (microvillus atrophy)</td>
<td>Esoinophilic gastroenteritis</td>
</tr>
<tr>
<td></td>
<td>Congenital transport defects (chloride, sodium)</td>
<td>Secretory tumors</td>
</tr>
<tr>
<td></td>
<td>Primary bile acid malabsorption</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Factitious syndrome by proxy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hirschsprung disease</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Shwachman syndrome</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Secretory tumors</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Acrodermatitis enteropathica</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lymphangiectasia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Abetalipoproteinemia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Eosinophilic gastroenteritis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Short bowel syndrome</td>
<td></td>
</tr>
</tbody>
</table>


The resultant colonic stasis leads to excessive drying of stool and a failure to initiate reflexes from the rectum that normally trigger evacuation. Emptying the rectum by spontaneous evacuation depends on a defecation reflex initiated by pressure receptors in the rectal muscle. Stool retention, therefore, can also result from lesions involving these rectal muscles, the sacral spinal cord afferent and efferent fibers, or the muscles of the abdomen and pelvic floor. Disorders of anal sphincter relaxation can also contribute to fecal retention.

Constipation tends to be self-perpetuating, whatever its cause. Hard, large stools in the rectum become difficult and even painful to evacuate; thus, more retention occurs and a vicious circle ensues. Distention of the rectum and colon lessens the sensitivity of the defecation reflex and the effectiveness of peristalsis. Fecal impaction is common and leads to other problems. Eventually, watery content from the proximal colon might percolate around hard retained stool and pass per rectum unperceived by the child. This involuntary encopresis may be mistaken for diarrhea. Constipation itself does not have deleterious systemic organic effects, but urinary tract stasis can accompany severe long-standing cases and constipation can generate anxiety, having a marked emotional impact on the patient and family.

**ABDOMINAL PAIN**

There is considerable variation among children in their perception and tolerance for abdominal pain. This is one reason the evaluation of chronic abdominal pain is difficult. A child with functional abdomi-
Causes of Constipation

Major
The shifting (localization) of pain is a pointer suprapubic region. The shifting (localization) of pain is a pointer colon region, and pain from the transverse colon is usually felt in the right lower quadrant suggests appendicitis. Radiation of pain can be helpful in diagnosis; for example, in biliary colic the radiation of pain is toward the inferior angle of the right scapula, pancreatic pain radiated to the back, and the renal colic pain is radiated to the inguinal region on the same side.

Somatic pain is intense and is usually well localized. When the inflamed viscus comes in contact with the somatic organ like the parietal peritoneum or the abdominal wall, pain is localized to that site. Peritonitis gives rise to generalized abdominal pain with rigidity, involuntary guarding, rebound tenderness, and cutaneous hyperesthesia on physical examination.

Referred pain from extraintestinal locations, from shared central projections with the sensory pathway from the abdominal wall, can give rise to abdominal pain, as in pneumonia when the parietal pleural pain is referred to the abdomen.

Gastrointestinal Hemorrhage
Bleeding can occur anywhere along the GI tract, and identification of the site may be challenging (Table 306-15). Bleeding that originates in the esophagus, stomach, or duodenum can cause hematemesis. When exposed to gastric or intestinal juices, blood quickly darkens to resemble coffee grounds; massive bleeding is likely to be red. Red or maroon blood in stools, hematochezia, signifies either a distal bleeding site or massive hemorrhage above the distal ileum. Moderate to mild bleeding from sites above the distal ileum tends to cause blackened stools of tarry consistency (melena); major hemorrhages in the duodenum or above can also cause melena.

Erosive damage to the mucosa of the GI tract is the most common cause of bleeding, although variceal bleeding secondary to portal hypertension occurs often enough to require consideration. Prolapse gastropathy producing subepithelial hemorrhage and Mallory-Weiss lesions secondary to mucosal tears associated with esmes are causes of upper intestinal bleeds. Vascular malformations are a rare cause in children; they are difficult to identify. Upper intestinal bleeding is evaluated with esophagogastroduodenoscopy. Evaluation of the small intestine is facilitated by capsule endoscopy. The capsule-sized imaging device is swallowed in older children or placed endoscopically in younger children. Lower GI bleeding is investigated with a colonoscopy. In brisk intestinal bleeding of unknown location, a tagged red blood cell scan is helpful in locating the site of the bleeding. Occult blood in stool is usually detected by using commercially available fecal occult blood testing cards, which are based on a chemical reaction between the chemical guaiac and oxidizing action of a substrate (hemoglobin), giving a blue color. The guaiac test is very sensitive, but random testing can miss chronic blood loss, which can lead to iron-deficiency anemia. GI hemorrhage can produce hypotension and tachycardia but rarely causes GI symptoms; brisk duodenal or gastric bleeding can lead to nausea, vomiting, or diarrhea. The breakdown products of intraluminal blood might tip patients into hepatic coma if liver function is already compromised and can lead to elevation of serum bilirubin.

Abdominal Distention and Abdominal Masses
Enlargement of the abdomen can result from diminished tone of the wall musculature or from increased content: fluid, gas, or solid. Ascites, the accumulation of fluid in the peritoneal cavity, distends the abdomen both in the flanks and anteriorly when it is large in volume. This fluid shifts with movement of the patient and conducts a percussion wave. Ascitic fluid is usually a transudate with a low protein concentration resulting from reduced plasma colloid osmotic pressure of hypoalbuminemia and/or from raised portal venous pressure. In cases of portal hypertension, the fluid leak probably occurs from lymphatics on the liver surface and from visceral peritoneal capillaries, but ascites does not usually develop until the serum albumin level falls. Sodium excretion in the urine decreases greatly as the ascitic fluid accumulates and, thus, additional dietary sodium goes directly to the peritoneal space, taking with it more water. When ascitic fluid contains a high protein
### Table 306-13  Chronic Abdominal Pain in Children

<table>
<thead>
<tr>
<th>DISORDER</th>
<th>CHARACTERISTICS</th>
<th>KEY EVALUATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>NONORGANIC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Functional abdominal pain</td>
<td>Nonspecific pain, often periumbilical</td>
<td>Hx and PE; tests as indicated</td>
</tr>
<tr>
<td>Irritable bowel syndrome</td>
<td>Intermittent cramps, diarrhea, and constipation</td>
<td>Hx and PE; esophagogastrroduodenoscopy</td>
</tr>
<tr>
<td>Nonulcer dyspepsia</td>
<td>Peptic ulcer–like symptoms without abnormalities on evaluation of the upper GI tract</td>
<td>Hx; esophagogastrroduodenoscopy</td>
</tr>
<tr>
<td>GASTROINTESTINAL TRACT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic constipation</td>
<td>Hx of stool retention, evidence of constipation on examination</td>
<td>Hx and PE; plain x-ray of abdomen</td>
</tr>
<tr>
<td>Lactose intolerance</td>
<td>Symptoms may be associated with lactose ingestion; bloating, gas, cramps, and diarrhea</td>
<td>Trial of lactose-free diet; lactose breath hydrogen test</td>
</tr>
<tr>
<td>Parasite infection (especially Giardia)</td>
<td>Bloating, gas, cramps, and diarrhea</td>
<td>Stool evaluation for O&amp;P; specific immunoassays for Giardia</td>
</tr>
<tr>
<td>Excess fructose or sorbitol ingestion</td>
<td>Nonspecific abdominal pain, bloating, gas, and diarrhea</td>
<td>Large intake of apples, fruit juice, or candy or chewing gum sweetened with sorbitol</td>
</tr>
<tr>
<td>Crohn disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peptic ulcer</td>
<td>Burning or gnawing epigastric pain; worse on awakening or before meals; relieved with antacids</td>
<td>Esophagogastrroduodenoscopy, upper GI contrast x-rays, or MRI enteroscopy</td>
</tr>
<tr>
<td>Esophagitis</td>
<td>Epigastric pain with substernal burning</td>
<td>Esophagogastrroduodenoscopy</td>
</tr>
<tr>
<td>Meckel diverticulum</td>
<td>Periumbilical or lower abdominal pain; may have blood in stool (usually painless)</td>
<td>Meckel scan or enterolysis</td>
</tr>
<tr>
<td>Recurrent intussusception</td>
<td>Paroxysmal severe cramping abdominal pain; blood may be present in stool with episode</td>
<td>Identify intussusception during episode or lead point in intestine between episodes with contrast studies of GI tract PE, CT of abdominal wall Barium enema, CT</td>
</tr>
<tr>
<td>Internal, inguinal, or abdominal wall hernia</td>
<td>Dull abdomen or abdominal wall pain</td>
<td></td>
</tr>
<tr>
<td>Chronic appendicitis or appendiceal mucocoe</td>
<td>Recurrent RLQ pain; often incorrectly diagnosed, may be rare cause of abdominal pain</td>
<td></td>
</tr>
<tr>
<td>Gallbladder and Pancreas</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cholelithiasis</td>
<td>RUQ pain, might worsen with meals</td>
<td>Ultrasound of gallbladder</td>
</tr>
<tr>
<td>Choledochal cyst</td>
<td>RUQ pain, mass ± elevated bilirubin</td>
<td>Ultrasound or CT of RUQ</td>
</tr>
<tr>
<td>Recurrent pancreatitis</td>
<td>Persistent boring pain, might radiate to back, vomiting</td>
<td>Serum amylase and lipase ± serum trypsinogen; ultrasound, CT, or MRI-ERCP of pancreas</td>
</tr>
<tr>
<td>Genitourinary Tract</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>Dull suprapubic pain, flank pain</td>
<td>Urinalysis and urine culture; renal scan</td>
</tr>
<tr>
<td>Hydronephrosis</td>
<td>Unilateral abdominal or flank pain</td>
<td>Ultrasound of kidneys</td>
</tr>
<tr>
<td>Urolithiasis</td>
<td>Progressive, severe pain; flank to inguinal region to testicle</td>
<td>Urinalysis, ultrasound, IVP, CT</td>
</tr>
<tr>
<td>Other genitourinary disorders</td>
<td>Suprapubic or lower abdominal pain; genitourinary symptoms</td>
<td>Ultrasound of kidneys and pelvis; gynecologic evaluation</td>
</tr>
<tr>
<td>Miscellaneous Causes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal migraine</td>
<td>See text; nausea, family Hx migraine</td>
<td>Hx</td>
</tr>
<tr>
<td>Abdominal epilepsy</td>
<td>Might have seizure proadrome</td>
<td>EEG (can require &gt;1 study, including sleep-deprived EEG)</td>
</tr>
<tr>
<td>Gilbert syndrome</td>
<td>Mild abdominal pain (causal or coincidental?); slightly elevated unconjugated bilirubin</td>
<td>Serum bilirubin</td>
</tr>
<tr>
<td>Familial Mediterranean fever</td>
<td>Paroxysmal episodes of fever, severe abdominal pain, and tenderness with other evidence of polyserositis</td>
<td>Hx and PE during an episode, DNA diagnosis</td>
</tr>
<tr>
<td>Sickle cell crisis</td>
<td>Anemia</td>
<td>Hematologic evaluation</td>
</tr>
<tr>
<td>Lead poisoning</td>
<td>Vague abdominal pain ± constipation</td>
<td>Serum lead level</td>
</tr>
<tr>
<td>Henoch-Schönlein purpura</td>
<td>Recurrent, severe crampy abdominal pain, occult blood in stool, characteristic rash, arthritis</td>
<td>Hx, PE, urinalysis</td>
</tr>
<tr>
<td>Angioneurotic edema</td>
<td>Swelling of face or airway, crampy pain</td>
<td>Hx, PE, upper GI contrast x-rays, serum C1 esterase inhibitor</td>
</tr>
<tr>
<td>Acute intermittent porphyria</td>
<td>Severe pain precipitated by drugs, fasting, or infections</td>
<td>Spot urine for porphyrins</td>
</tr>
</tbody>
</table>

EEG, electroencephalogram; GI, gastrointestinal; Hx, history; IVP, intravenous pyelography; O&P, ova and parasites; PE, physical exam; RLQ, right lower quadrant; RUQ, right upper quadrant.
### Table 306-14

<table>
<thead>
<tr>
<th>DISEASE</th>
<th>ONSET</th>
<th>LOCATION</th>
<th>REFERRAL</th>
<th>QUALITY</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pancreatitis</td>
<td>Acute</td>
<td>Epigastric, left upper quadrant</td>
<td>Back</td>
<td>Constant, sharp, boring</td>
<td>Nausea, emesis, tenderness</td>
</tr>
<tr>
<td>Intestinal obstruction</td>
<td>Acute or gradual</td>
<td>Periumbilical-lower abdomen</td>
<td>Back</td>
<td>Alternating cramping (colic) and painless periods</td>
<td>Distention, obstipation, emesis, increased bowel sounds</td>
</tr>
<tr>
<td>Appendicitis</td>
<td>Acute</td>
<td>Periumbilical, then localized to lower right quadrant; generalized with peritonitis</td>
<td>Back or pelvis if retrocecal</td>
<td>Sharp, steady</td>
<td>Anorexia, nausea, emesis, local tenderness, fever with peritonitis</td>
</tr>
<tr>
<td>Intussusception</td>
<td>Acute</td>
<td>Periumbilical-lower abdomen</td>
<td>None</td>
<td>Cramping, with painless periods</td>
<td>Hematochezia, knees in pulled-up position</td>
</tr>
<tr>
<td>Urolithiasis</td>
<td>Acute, sudden</td>
<td>Back (unilateral)</td>
<td>Groin</td>
<td>Sharp, intermittent, cramping</td>
<td>Hematuria</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>Acute</td>
<td>Back</td>
<td>Bladder</td>
<td>Dull to sharp</td>
<td>Fever, costovertebral angle tenderness, dysuria, urinary frequency</td>
</tr>
</tbody>
</table>

### Table 306-15

<table>
<thead>
<tr>
<th>INFANT</th>
<th>COMMON</th>
<th>CHILD</th>
<th>ADOLESCENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacterial enteritis</td>
<td>Bacterial enteritis</td>
<td>Bacterial enteritis</td>
<td>Bacterial enteritis</td>
</tr>
<tr>
<td>Milk protein allergy intolerance</td>
<td>Anal fissure</td>
<td>Anal fissure</td>
<td>Anal fissure</td>
</tr>
<tr>
<td>Intussusception</td>
<td>Colonic polyps</td>
<td>Intussusception</td>
<td>Inflammatory bowel disease</td>
</tr>
<tr>
<td>Swallowed maternal blood</td>
<td>Peptic ulcer/gastritis</td>
<td>Swallowed epistaxis</td>
<td>Peptic ulcer/gastritis</td>
</tr>
<tr>
<td>Anal fissure</td>
<td>Prolapse (traumatic) gastropathy secondary to emesis</td>
<td>Prolapse (traumatic) gastropathy secondary to emesis</td>
<td>Peptic ulcer/gastritis</td>
</tr>
<tr>
<td>Lymphonodular hyperplasia</td>
<td>Mallory-Weiss syndrome</td>
<td>Mallory-Weiss syndrome</td>
<td>Peptic ulcer/gastritis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>RARE</th>
<th>Infant</th>
<th>Child</th>
<th>Adolescent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volvulus</td>
<td>Esophageal varices</td>
<td>Hemorrhoids</td>
<td></td>
</tr>
<tr>
<td>Necrotizing enterocolitis</td>
<td>Esophageal varices</td>
<td>Esophageal varices</td>
<td></td>
</tr>
<tr>
<td>Meckel diverticulum</td>
<td>Esophagitis</td>
<td>Esophagitis</td>
<td></td>
</tr>
<tr>
<td>Stress ulcer, gastritis</td>
<td>Meckel diverticulum</td>
<td>Pneumoperitoneum</td>
<td></td>
</tr>
<tr>
<td>Coagulation disorder (hemorrhagic disease of newborn)</td>
<td>Meckel diverticulum</td>
<td>Esophageal varices</td>
<td></td>
</tr>
<tr>
<td>Esophagitis</td>
<td>Lymphonodular hyperplasia</td>
<td>Telangiectasia-angiodysplasia</td>
<td></td>
</tr>
<tr>
<td>Foreign body</td>
<td>Henoch-Schönlein purpura</td>
<td>Telangiectasia-angiodysplasia</td>
<td></td>
</tr>
<tr>
<td>Hemangioma, arteriovenous malformation</td>
<td>Hemangioma, arteriovenous malformation</td>
<td>Telangiectasia-angiodysplasia</td>
<td></td>
</tr>
<tr>
<td>Sexual abuse</td>
<td>Sexual abuse</td>
<td>Telangiectasia-angiodysplasia</td>
<td></td>
</tr>
<tr>
<td>Hemolytic-uremic syndrome</td>
<td>Hemolytic-uremic syndrome</td>
<td>Telangiectasia-angiodysplasia</td>
<td></td>
</tr>
<tr>
<td>Inflammatory bowel disease</td>
<td>Inflammatory bowel disease</td>
<td>Telangiectasia-angiodysplasia</td>
<td></td>
</tr>
<tr>
<td>Coagulopathy</td>
<td>Coagulopathy</td>
<td>Telangiectasia-angiodysplasia</td>
<td></td>
</tr>
<tr>
<td>Duplication cyst</td>
<td>Duplication cyst</td>
<td>Telangiectasia-angiodysplasia</td>
<td></td>
</tr>
</tbody>
</table>

An abdominal organ can enlarge diffusely or be affected by a discrete mass. In the digestive tract, such discrete masses can occur in the lumen, wall, omentum, or mesentery. In a constipated child, mobile, non-tender fecal masses are often found. Congenital anomalies, cysts, or inflammatory processes can affect the wall of the gut. Gut wall neoplasms are extremely rare in children. The pathologic enlargement of liver, spleen, bladder, and kidneys can give rise to abdominal distention.

**JAUNDICE**

See Chapters 102.3 and 356.

_Bibliography is available at Expert Consult._
Bibliography


Section 2
The Oral Cavity

Chapter 307
Development and Developmental Anomalies of the Teeth
Norman Tinanoff

INITIATION
The primary teeth form in dental crypts that arise from a band of epithelial cells incorporated into each developing jaw. By 12 wk of fetal life, each of these epithelial bands (dental laminae) has 5 areas of rapid growth on each side of the maxilla and the mandible, seen as rounded, bud-like enlargements. Organization of adjacent mesenchyme takes place in each area of epithelial growth, and the 2 elements together are the beginning of a tooth.

After the formation of these crypts for the 20 primary teeth, another generation of tooth buds forms lingually (toward the tongue); these will develop into the succeeding permanent incisors, canines, and premolars that eventually replace the primary teeth. This process takes place from approximately 5 mo of gestation for the central incisors to approximately 10 mo of age for the 2nd premolars. The permanent 1st, 2nd, and 3rd molars, on the other hand, arise from extension of the dental laminae distal to the 2nd primary molars; buds for these teeth develop at approximately 4 mo of gestation, 1 yr of age, and 4-5 yr of age, respectively.

HISTODIFFERENTIATION–MORPHODIFFERENTIATION
As the epithelial bud proliferates, the deeper surface invaginates and a mass of mesenchyme becomes partially enclosed. The epithelial cells differentiate into the ameloblasts that lay down an organic matrix that forms enamel; the mesenchyme forms the dentin and dental pulp.

CALCIFICATION
After the organic matrix has been laid down, the deposition of the inorganic mineral crystals takes place from several sites of calcification that later coalesce. The characteristics of the inorganic portions of a tooth can be altered by disturbances in formation of the matrix, decreased availability of minerals, or the incorporation of foreign materials. Such disturbances can affect the color, texture, or thickness of the tooth surface. Calcification of primary teeth begins at 3-4 mo in utero and concludes postnatally at approximately 12 mo with mineralization of the 2nd primary molars (Table 307-1).

ERUPTION
At the time of tooth bud formation, each tooth begins a continuous movement toward the oral cavity. Table 307-1 lists the times of eruption of the primary and permanent teeth.

ANOMALIES ASSOCIATED WITH TOOTH DEVELOPMENT
Both failures and excesses of tooth initiation are observed. Developmentally missing teeth can result from environmental insult, a genetic defect involving only teeth, or the manifestation of a syndrome. Anodontia, or absence of teeth, occurs when no tooth buds form (ectodermal dysplasia, or familial missing teeth) or when there is a disturbance of a normal site of initiation (the area of a palatal cleft). The teeth that are most commonly absent are the 3rd molars, the maxillary lateral incisors, and the mandibular 2nd premolars.

If the dental lamina produces more than the normal number of buds, supernumerary teeth occur, most often in the area between the maxillary central incisors. Because they tend to disrupt the position and eruption of the adjacent normal teeth, their identification by radiographic examination is important. Supernumerary teeth also occur with cleidocranial dysplasia (see Chapter 311) and in the area of cleft palates.

Twining, in which 2 teeth are joined together, is most often observed in the mandibular incisors of the primary dentition. It can result from gemination, fusion, or concrescence. Gemination is the result of the division of 1 tooth germ to form a bifid crown on a single root with a common pulp canal; an extra tooth appears to be present in the dental arch. Fusion is the joining of incompletely developed teeth that, owing to pressure, trauma, or crowding, continue to develop as 1 tooth. Fused teeth are sometimes joined along their entire length; in other cases, a single wide crown is supported on 2 roots. Concrescence is the attachment of the roots of closely approximated adjacent teeth by an excessive deposit of cementum. This type of twinning, unlike the others, is found most often in the maxillary molar region.

Disturbances during differentiation can result in alterations in dental morphology, such as macrodontia (large teeth) or microdontia (small teeth). The maxillary lateral incisors can assume a slender, tapering shape (peg-shaped laterals).

<table>
<thead>
<tr>
<th>Table 307-1</th>
<th>Calciﬁcation, Crown Completion, and Eruption</th>
</tr>
</thead>
<tbody>
<tr>
<td>TOOTH</td>
<td>FIRST EVIDENCE OF CALCIFICATION</td>
</tr>
<tr>
<td>PRIMARY DENTITION</td>
<td></td>
</tr>
<tr>
<td>Maxillary</td>
<td></td>
</tr>
<tr>
<td>Central incisor</td>
<td>3-4 mo in utero</td>
</tr>
<tr>
<td>Lateral incisor</td>
<td>4.5 mo in utero</td>
</tr>
<tr>
<td>Canine</td>
<td>5.5 mo in utero</td>
</tr>
<tr>
<td>First molar</td>
<td>5 mo in utero</td>
</tr>
<tr>
<td>Second molar</td>
<td>6 mo in utero</td>
</tr>
<tr>
<td>Mandibular</td>
<td></td>
</tr>
<tr>
<td>Central incisor</td>
<td>4.5 mo in utero</td>
</tr>
<tr>
<td>Lateral incisor</td>
<td>4.5 mo in utero</td>
</tr>
<tr>
<td>Canine</td>
<td>5 mo in utero</td>
</tr>
<tr>
<td>First molar</td>
<td>5 mo in utero</td>
</tr>
<tr>
<td>Second molar</td>
<td>6 mo in utero</td>
</tr>
<tr>
<td>PERMANENT DENTITION</td>
<td></td>
</tr>
<tr>
<td>Maxillary</td>
<td></td>
</tr>
<tr>
<td>Central incisor</td>
<td>3-4 mo</td>
</tr>
<tr>
<td>Lateral incisor</td>
<td>10 mo</td>
</tr>
<tr>
<td>Canine</td>
<td>4.5 mo</td>
</tr>
<tr>
<td>First premolar</td>
<td>1.5-1½ yr</td>
</tr>
<tr>
<td>Second premolar</td>
<td>2-2½ yr</td>
</tr>
<tr>
<td>First molar</td>
<td>At birth</td>
</tr>
<tr>
<td>Second molar</td>
<td>2.5-3 yr</td>
</tr>
<tr>
<td>Third molar</td>
<td>7-9 yr</td>
</tr>
<tr>
<td>Mandibular</td>
<td></td>
</tr>
<tr>
<td>Central incisor</td>
<td>3-4 mo</td>
</tr>
<tr>
<td>Lateral incisor</td>
<td>3-4 mo</td>
</tr>
<tr>
<td>Canine</td>
<td>4.5 mo</td>
</tr>
<tr>
<td>First premolar</td>
<td>1½-2 yr</td>
</tr>
<tr>
<td>Second premolar</td>
<td>2½-2.5 yr</td>
</tr>
<tr>
<td>First molar</td>
<td>At birth</td>
</tr>
<tr>
<td>Second molar</td>
<td>2.5-3 yr</td>
</tr>
<tr>
<td>Third molar</td>
<td>8-10 yr</td>
</tr>
</tbody>
</table>

Modified from Logan WHG, Kronfeld R: Development of the human jaws and surrounding structures from birth to age 15 years, J Am Dent Assoc 20:379, 1939.
Amelogenesis imperfecta represents a group of hereditary conditions that manifest in enamel defects of the primary and permanent teeth without evidence of systemic disorders (Fig. 307-1). The teeth are covered by only a thin layer of abnormally formed enamel through which the yellow underlying dentin is seen. The primary teeth are generally affected more than the permanent teeth. Susceptibility to caries is low, but the enamel is subject to destruction from abrasion. Complete coverage of the crown may be indicated for dentin protection, to reduce tooth sensitivity, and for improved appearance.

Dentinogenesis imperfecta, or hereditary opalescent dentin, is a condition analogous to amelogenesis imperfecta in which the odontoblasts fail to differentiate normally, resulting in poorly calcified dentin (Fig. 307-2). This autosomal dominant disorder can also occur in patients with osteogenesis imperfecta. The enamel-dentin junction is altered, causing enamel to break away. The exposed dentin is then susceptible to abrasion, in some cases worn to the gingiva. The teeth are opaque and pearly, and the pulp chambers are generally obliterated by calcification. Both primary and permanent teeth are usually involved. If there is excessive wear of the teeth, selected complete coverage of the teeth may be indicated to prevent further tooth loss and improve appearance.

Localized disturbances of calcification that correlate with periods of illness, malnutrition, premature birth, or birth trauma are common. Hypocalcification appears as opaque white patches or horizontal lines on the teeth; hypoplasia is more severe and manifests as pitting or areas devoid of enamel. Systemic conditions, such as renal failure and cystic fibrosis, are associated with enamel defects. Local trauma to the primary incisors can also affect calcification of permanent incisors.

Fluorosis (mottled enamel) can result from systemic fluoride consumption > 0.05 mg/kg/day during enamel formation. This high fluoride consumption can be caused by residing in an area of high fluoride content of the drinking water (>2.0 ppm), swallowing excessive fluoridated toothpaste, or inappropriate fluoride prescriptions. Excessive fluoride during enamel formation affects ameloblastic function, resulting in inconspicuous white, lacy patches on the enamel to severe brownish discoloration and hypoplasia. The latter changes are usually seen with fluoride concentrations in the drinking water > 5.0 ppm.

Discolored teeth can result from incorporation of foreign substances into developing enamel. Neonatal hyperbilirubinemia can produce blue to black discoloration of the primary teeth. Porphyria produces a red-brown discoloration. Tetracyclines are extensively incorporated into bones and teeth and, if administered during the period of formation of enamel, can result in brown-yellow discoloration and hypoplasia of the enamel. Such teeth fluoresce under ultraviolet light. The period at risk extends from approximately 4 mo of gestation to 7 yr of life. Repeated or prolonged therapy with tetracycline carries the highest risk.

Delayed eruption of the 20 primary teeth can be familial or indicate systemic or nutritional disturbances such as hypopituitarism, hypothyroidism, cleidocranial dysplasia, trisomy 21, and multiple syndromes. Failure of eruption of single or small groups of teeth can arise from local causes such as malpositioned teeth, supernumerary teeth, cysts, or retained primary teeth. Premature loss of primary teeth is most commonly caused by premature eruption of the permanent teeth. If the entire dentition is advanced for age and sex, precocious puberty or hyperthyroidism should be considered.

Natal teeth are observed in approximately 1 in 2,000 newborn infants usually in the position of the mandibular central incisors. Natal teeth are present at birth, whereas neonatal teeth erupt in the 1st mo of life. Attachment of natal and neonatal teeth is generally limited to the gingival margin, with little root formation or bony support. They may be a supernumerary or a prematurely erupted primary tooth. A radiograph can easily differentiate between the two conditions. Natal teeth are associated with cleft palate, Pierre Robin syndrome, Ellis-van Creveld syndrome, Hallermann-Streiff syndrome, pachyonychia congenita, and other anomalies. A family history of natal teeth or premature eruption is present in 15-20% of affected children.

Natal or neonatal teeth occasionally result in pain and refusal to feed and can produce maternal discomfort because of abrasion or biting of the nipple during nursing. If the tooth is mobile there is a danger of detachment, with aspiration of the tooth. Because the tongue lies between the alveolar processes during birth, it can become lacerated (Riga-Fede disease). Decisions regarding extraction of prematurely erupted primary teeth must be made on an individual basis.

Exfoliation failure occurs when a primary tooth is not shed before the eruption of its permanent successor. Most often the primary tooth exfoliates eventually, but in some cases, the primary tooth needs to be extracted. This occurs most commonly in the mandibular incisor region.

Bibliography is available at Expert Consult.
Bibliography
Disorders of the teeth and surrounding structures can occur in isolation or in combination with other systemic conditions (Table 308-1). Most commonly, medical conditions that occur during tooth development can affect tooth formation or appearance. Damage to teeth during their development is permanent.

Table 308-1 Dental Problems Associated with Selected Medical Conditions

<table>
<thead>
<tr>
<th>MEDICAL CONDITION</th>
<th>COMMON ASSOCIATED DENTAL OR ORAL FINDINGS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cleft lip and palate</td>
<td>Missing teeth, extra (supernumerary) teeth, shifting of arch segments, feeding difficulties, speech problems</td>
</tr>
<tr>
<td>Kidney failure</td>
<td>Mottled enamel (permanent teeth), facial dysmorphology</td>
</tr>
<tr>
<td>Cystic fibrosis</td>
<td>Stained teeth with extensive medication, mottled enamel</td>
</tr>
<tr>
<td>Immunosuppression</td>
<td>Oral candidiasis with potential for systemic candidiasis, cyclosporine-induced gingival hyperplasia</td>
</tr>
<tr>
<td>Low birthweight</td>
<td>Palatal groove, narrow arch with prolonged oral intubation; enamel defects of primary teeth</td>
</tr>
<tr>
<td>Heart defects with susceptibility to bacterial endocarditis</td>
<td>Bacteremia from dental procedures or trauma</td>
</tr>
<tr>
<td>Neutrophil chemotactic deficiency</td>
<td>Juvenile periodontitis (loss of supporting bone around teeth)</td>
</tr>
<tr>
<td>Juvenile diabetes (uncontrolled)</td>
<td>Juvenile periodontitis</td>
</tr>
<tr>
<td>Neuromotor dysfunction</td>
<td>Oral trauma from falling; malocclusion (open bite); gingivitis from lack of hygiene</td>
</tr>
<tr>
<td>Prolonged illness (generalized) during tooth formation</td>
<td>Enamel hypoplasia of crown portions forming during illness</td>
</tr>
<tr>
<td>Seizures</td>
<td>Gingival enlargement if phenytoin is used</td>
</tr>
<tr>
<td>Maternal infections</td>
<td>Syphilis: abnormally shaped teeth</td>
</tr>
<tr>
<td>Vitamin D–dependent rickets</td>
<td>Enamel hypoplasia</td>
</tr>
</tbody>
</table>
Malocclusion
Norman Tinanoff

The oral cavity is essentially a masticatory instrument. The purpose of the anterior teeth is to bite off portions of large amounts of food. The posterior teeth reduce foodstuff to a soft, moist bolus. The cheeks and tongue force the food onto the areas of tooth contact. Establishing a proper relationship between the mandibular and maxillary teeth is important for physiologic and cosmetic reasons.

VARIATIONS IN GROWTH PATTERNS
Growth patterns are classified into 3 main types of occlusion, determined when the jaws are closed and the teeth are held together (Fig. 309-1). According to the Angle Classification of Malocclusion, in class I occlusion (normal), the cusps of the posterior mandibular teeth interdigitate ahead of and inside of the corresponding cusps of the opposing maxillary teeth. This relationship provides a normal facial profile.

In class II malocclusion, “buck teeth,” the cusps of the posterior mandibular teeth are behind and inside the corresponding cusps of the maxillary teeth. This common occlusal disharmony is found in ~45% of the population. The facial profile can give the appearance of a “receding chin” (retrognathia) (mandibular deficiency) or protruding front teeth. The resultant increased space between upper and lower anterior teeth encourage finger sucking and tongue-thrust habits. Additionally, children with pronounced class II malocclusions are at greater risks of damage to the incisors as a consequence of trauma. Treatment includes orthodontic retraction of the maxilla or stimulation of the mandible.

In class III malocclusion, “underbite,” the cusps of the posterior mandibular teeth interdigitate a tooth or more ahead of their opposing maxillary counterparts. The anterior teeth appear in cross bite with the mandibular incisors protruding beyond the maxillary incisors. The facial profile gives the appearance of a “protruding chin” (prognathia) with or without an appearance of maxillary deficiency. If necessary, treatment includes mandibular excess reduction osteotomy or orthodontic maxillary facial protrusion.

CROSSBITE
Normally, the mandibular teeth are in a position just inside the maxillary teeth, so that the outside mandibular cusps or incisal edges meet the central portion of the opposing maxillary teeth. A reversal of this relation is referred to as a crossbite. Crossbites can be anterior, involving the incisors; can be posterior, involving the molars; or can involve single or multiple teeth.

Figure 309-1 Angle classification of occlusion. The typical correspondence between the facial-jaw profile and molar relationship is shown.
OPEN AND CLOSED BITES
If the posterior mandibular and maxillary teeth make contact with each other, but the anterior teeth are still apart, the condition is called an open bite. Open bites can result from skeletal growth pattern or digit sucking. If digit sucking is terminated before skeletal and dental growth is complete, the open bite might resolve naturally. If mandibular anterior teeth occlude inside the maxillary anterior teeth in an overclosed position, the condition is referred to as a closed or deep bite.

Treatment of open and closed bites consists of orthodontic correction, generally performed in the preteen or teenage years. Some cases require orthognathic surgery to position the jaws optimally in a vertical direction.

DENTAL CROWDING
Overlap of incisors can result when the jaws are too small or the teeth are too large for adequate alignment of the teeth. Growth of the jaws is mostly in the posterior aspects of the mandible and maxilla, and therefore inadequate space for the teeth at 7 or 8 yr of age will not resolve with growth of the jaws. Spacing in the primary dentition is normal and favorable for adequate alignment of successor teeth.

DIGIT SUCKING
Various and conflicting etiologic theories and recommendations for correction have been proposed for digit sucking in children. Prolonged digit sucking can cause flaring of the maxillary incisor teeth, an open bite, and a posterior crossbite. The prevalence of digit sucking decreases steadily from the age of 2 yr to ≈10% by the age of 5 yr. The earlier the habit is discontinued after the eruption of the permanent maxillary incisors (age 7–8 yr), the greater the likelihood that there will be lessening effects on the dentition.

A variety of treatments have been suggested, from behavioral modification to insertion of an appliance with extensions that serves as a reminder when the child attempts to insert the digit. The greatest likelihood of success occurs in cases in which the child desires to stop. Stopping of the habit will not rectify a malocclusion caused by a prior deviant growth pattern.
Clefts of the lip and palate are distinct entities closely related embryologically, functionally, and genetically. It is thought that cleft of the lip appears because of hypoplasia of the mesenchymal layer, resulting in a failure of the medial nasal and maxillary processes to join. Cleft of the palate appears to represent failure of the palatal shelves to approximate or fuse.

INCIDENCE AND EPIDEMIOLOGY
The incidence of cleft lip with or without cleft palate is approximately 1 in 750 white births; the incidence of cleft palate alone is approximately 1 in 2,500 white births. Clefts of the lip are more common in males. Possible causes include maternal drug exposure, a syndrome-malformation complex, or genetic factors. Although clefts of lips and palates appear to occur sporadically, the presence of susceptible genes appears important. There are approximately 400 syndromes associated with cleft lip and palates. There are families in which a cleft lip or palate, or both, is inherited in a dominant fashion (van der Woude syndrome), and careful examination of parents is important to distinguish this type from others, because the recurrence risk is 50%. Ethnic factors also affect the incidence of cleft lip and palate; the incidence is highest among Asians (~1 in 500) and Native Americans (~1 in 300), and lowest among blacks (~1 in 2,500). Cleft lip may be associated with other cranial facial anomalies, whereas cleft palate may be associated with central nervous system anomalies.

CLINICAL MANIFESTATIONS
Cleft lip can vary from a small notch in the vermilion border to a complete separation involving skin, muscle, mucosa, tooth, and bone. Clefts of the lip may be unilateral (more often on the left side) or bilateral and can involve the alveolar ridge (Fig. 310-1).

Isolated cleft palate occurs in the midline and might involve only the uvula or can extend into or through the soft and hard palates to the incisive foramen. When associated with cleft lip, the defect can involve the midline of the soft palate and extend into the hard palate on one or both sides, exposing one or both of the nasal cavities as a unilateral or bilateral cleft palate. The palate can also have a submucosal cleft indicated by a bifid uvula, partial separation of muscle with intact mucosa, or a palpable notch at the posterior of the palate.

TREATMENT
A complete program of habilitation for the child with a cleft lip or palate can require years of special treatment by a team consisting of a pediatrician, plastic surgeon, otolaryngologist, oral and maxillofacial surgeon, pediatric dentist, prosthodontist, orthodontist, speech therapist, geneticist, medical social worker, psychologist, and public health nurse.

The immediate problem in an infant born with a cleft lip or palate is feeding. Although some advocate the construction of a plastic obturator to assist in feedings, most believe that with the use of soft artificial nipples with large openings, a squeezable bottle, and proper instruction, feeding of infants with clefts can be achieved.

Surgical closure of a cleft lip is usually performed by 3 mo of age, when the infant has shown satisfactory weight gain and is free of any oral, respiratory, or systemic infection. Modification of the Millard rotation–advancement technique is the most commonly used technique; a staggered suture line minimizes notching of the lip from retraction of scar tissue. The initial repair may be revised at 4 or 5 yr of age. Corrective surgery on the nose may be delayed until adolescence. Nasal surgery can also be performed at the time of the lip repair. Cosmetic results depend on the extent of the original deformity, healing potential of the individual patient, absence of infection, and the skill of the surgeon.

Because clefts of the palate vary considerably in size, shape, and degree of deformity, the timing of surgical correction should be individualized. Criteria such as width of the cleft, adequacy of the existing palatal segments, morphology of the surrounding areas (width of the oropharynx), and neuromuscular function of the soft palate and pharyngeal walls affect the decision. The goals of surgery are the union of the cleft segments, intelligible and pleasant speech, reduction of nasal regurgitation, and avoidance of injury to the growing maxilla.

In an otherwise healthy child, closure of the palate is usually done before 1 yr of age to enhance normal speech development. When surgical correction is delayed beyond the 3rd yr, a contoured speech bulb can be attached to the posterior of a maxillary denture so that contractions of the pharyngeal and velopharyngeal muscles can bring tissues into contact with the bulb to accomplish occlusion of the nasopharynx and help the child develop intelligible speech.

A cleft palate usually crosses the alveolar ridge and interferes with the formation of teeth in the maxillary anterior region. Teeth in the cleft area may be displaced, malformed, or missing. Missing teeth or teeth that are nonfunctional are replaced by prosthetic devices.

POSTOPERATIVE MANAGEMENT
During the immediate postoperative period, special nursing care is essential. Gentle aspiration of the nasopharynx minimizes the chances of the common complications of atelectasis or pneumonia. The primary considerations in postoperative care are maintenance of a clean suture line and avoidance of tension on the sutures. The infant is fed with a
Velopharyngeal dysfunction may also be demonstrated radiographically. The head should be carefully positioned to obtain a true lateral view; one film is obtained with the patient at rest and another during continuous phonation of the vowel "u" as in "boom." The soft palate contacts the posterior pharyngeal wall in normal function, whereas in velopharyngeal dysfunction such contact is absent.

In selected cases of velopharyngeal dysfunction, the palate may be retropositioned or pharyngoplasty may be performed using a flap of tissue from the posterior pharyngeal wall. Dental speech appliances have also been used successfully. The type of surgery used is best tailored to the findings on nasoendoscopy.

Bibliography is available at Expert Consult.

Mead Johnson bottle and the arms are restrained with elbow cuffs. A fluid or semifluid diet is maintained for 3 wk. The patient’s hands, toys, and other foreign bodies must be kept away from the surgical site.

**SEQUELAE**

Recurrent otitis media and subsequent hearing loss are frequent with cleft palate. Displacement of the maxillary arches and malposition of the teeth usually require orthodontic correction. Misarticulations and velopharyngeal dysfunction are often associated with cleft lip and palate and may be present or persist because of physiologic dysfunction, anatomic insufficiency, malocclusion, or inadequate surgical closure of the palate. Such speech is characterized by the emission of air from the nose and by a hypernasal quality with certain sounds or by compensatory misarticulations (glottal stops). Before and sometimes after palatal surgery, the speech defect is caused by inadequacies in function of the palatal and pharyngeal muscles. The muscles of the soft palate and the lateral and posterior walls of the nasopharynx constitute a valve that separates the nasopharynx from the oropharynx during swallowing and in the production of certain sounds. If the valve does not function adequately, it is difficult to build up enough pressure in the mouth to make such explosive sounds as p, b, d, t, h, v, f, and s, or the sibilants s, sh, and ch, and such words as "cats," "boats," and "sisters" are not intelligible. After operation or the insertion of a speech appliance, speech therapy is necessary.

**VELOPHARYNGEAL DYSFUNCTION**

The speech disturbance characteristic of the child with a cleft palate can also be produced by other osseous or neuromuscular abnormalities where there is an inability to form an effective seal between oropharynx and nasopharynx during swallowing or phonation. In a child who has the potential for abnormal speech, adenoidectomy can precipitate overt hypernasality. If the neuromuscular function is adequate, compensation in palatopharyngeal movement might take place and the speech defect might improve, although speech therapy is necessary. In other cases, slow involution of the adenoids can allow gradual compensation in palatal and pharyngeal muscular function. This might explain why a speech defect does not become apparent in some children who have a submucous cleft palate or similar anomaly predisposing to palatopharyngeal incompetence.

**Clinical Manifestations**

Although clinical signs vary, the symptoms of velopharyngeal dysfunction are similar to those of a cleft palate. There may be hypernasal speech (especially noted in the articulation of pressure consonants such as p, b, d, t, h, v, f, and s); conspicuous constricting movement of the nares during speech; inability to whistle, gargle, blow out a candle, or inflate a balloon; loss of liquid through the nose when drinking with the head down; otitis media; and hearing loss. Oral inspection might reveal a cleft palate or a relatively short palate with a large oropharynx; absent, grossly asymmetric, or minimal muscular activity of the soft palate and pharynx during phonation or gagging; or a submucous cleft.

Velopharyngeal dysfunction may also be demonstrated radiographically. The head should be carefully positioned to obtain a true lateral view; one film is obtained with the patient at rest and another during continuous phonation of the vowel "u" as in "boom." The soft palate contacts the posterior pharyngeal wall in normal function, whereas in velopharyngeal dysfunction such contact is absent.

In selected cases of velopharyngeal dysfunction, the palate may be retropositioned or pharyngoplasty may be performed using a flap of tissue from the posterior pharyngeal wall. Dental speech appliances have also been used successfully. The type of surgery used is best tailored to the findings on nasoendoscopy.

Bibliography is available at Expert Consult.
Bibliography
Many syndromes have distinct or accompanying facial, oral, and dental manifestations (see Apert syndrome, Chapter 591.12; Crouzon disease, Chapter 591.12; Down syndrome, Chapter 81.2).

Osteogenesis imperfecta is often accompanied by effects on the teeth, termed dentinogenesis imperfecta (see Chapter 307, Fig. 307-2). Depending on the severity of presentation, treatment of the dentition varies from routine preventive and restorative monitoring to covering affected posterior teeth with stainless steel crowns, to prevent further tooth loss and improve appearance. Dentinogenesis imperfecta can also occur in isolation without the bony effects.

Another syndrome, cleidocranial dysplasia, has orofacial features such as frontal bossing, hypoplastic maxilla and supernumerary teeth. The primary teeth can be over retained and the permanent teeth remain unerupted. Supernumerary teeth are common, especially in the premolar area. Extensive dental rehabilitation may be needed to correct severe tooth crowding, unerupted and supernumerary teeth.

Ectodermal dysplasias (see Chapter 649) are a heterogeneous group of conditions in which oral manifestations range from little or no involvement (the dentition is completely normal) to cases in which the teeth can be totally or partially absent or malformed. Because alveolar bone does not develop in the absence of teeth, the alveolar processes can be either totally or partially absent, and the resultant overclosure of the mandible causes the lips to protrude. Facial development is otherwise not disturbed. Teeth, when present, can range from normal to small and conical. If aplasia of the buccal and labial salivary glands
is present, dryness and irritation of the oral mucosa can occur. People with ectodermal dysplasia might need partial or full dentures, even at a very young age. The vertical height between the jaws is thus restored, improving the position of the lips and facial contours as well as restoring masticatory function.

Pierre Robin syndrome consists of micrognathia usually accompanied by a high arched or cleft palate (Fig. 311-1). The tongue is usually of normal size, but the floor of the mouth is foreshortened. The air passages can become obstructed, particularly on inspiration, usually requiring treatment to prevent suffocation. The infant should be maintained in a prone or partially prone position so that the tongue falls forward to relieve respiratory obstruction. Some patients require tracheostomy. Mandibular distraction procedures in the neonate can improve mandibular size, enhance respiration, and facilitate oral feedings.

Sufficient spontaneous mandibular growth can take place within a few months to relieve the potential airway obstruction. Often the growth of the mandible achieves a normal profile in 4-6 yr. Of children with Pierre Robin syndrome, 30-50% have Stickler syndrome, an autosomal dominant condition that includes other findings such as prominent joints, arthritis, hypotonia, hypermobile joints, mitral valve prolapse, hearing loss, and ocular problems (myopia, glaucoma, cataracts, retinal detachment). Mutations are noted in the genes that produce types II, IX, and XI collagen in many, but not all, patients with Stickler syndrome. Other syndromes are associated with Pierre Robin syndrome including 22Q11.2 deletion syndrome (Velo-cardio-facial syndrome). Hemifacial microsomia presentation can be quite variable but is usually characterized by unilateral hypoplasia of the mandible and can be associated with partial paralysis of the facial nerve, underdeveloped ear, and blind fistulas between the angles of the mouth and the ears. Severe facial asymmetry and malocclusion can develop because of the absence or hypoplasia of the mandibular condyle on the affected side. Congenital condylar deformity tends to increase with age. Early craniofacial surgery may be indicated to minimize the deformity. This disorder can be associated with ocular and vertebral anomalies (oculo-auriculo-vertebral spectrum, including Goldenhar syndrome); therefore, radiographs of the vertebrae and ribs should be considered to determine the extent of skeletal involvement.

**Bibliography is available at Expert Consult.**
Bibliography

ETIOLOGY
The development of dental caries depends on interrelationships among the tooth surface, dietary carbohydrates, and specific oral bacteria. Organic acids produced by bacterial fermentation of dietary carbohydrates reduce the pH of dental plaque adjacent to the tooth to a point where demineralization occurs. The initial demineralization appears as an opaque white spot lesion on the enamel, and with progressive loss of tooth mineral, cavitation of the tooth occurs (Fig. 312-1).

The group of microorganisms, mutans streptococci, is associated with the development of dental caries. These bacteria have the ability to adhere to enamel, produce abundant acid, and survive at low pH. Once the enamel surface cavitates, other oral bacteria (lactobacilli) can colonize the tooth, produce acid, and foster further tooth demineralization. Demineralization from bacterial acid production is determined by the frequency of carbohydrate consumption and by the type of carbohydrate. Sucrose is the most cariogenic sugar because one of its by-products during bacterial metabolism is glucan, a polymer that enables bacteria to adhere more readily to tooth structures. Dietary behaviors, such as consuming sweetened beverages in a nursing bottle or frequently consuming sticky candies, increase the cariogenic potential of foods because of the long retention of sugar in the mouth.

EPIDEMIOLOGY
The incidence of dental caries has decreased in developed countries in the past 30 yr but has not decreased and remains highly prevalent among low-income children and children from developing countries. More than half of the children in the United States have dental caries, with most of those having caries primarily in the pits and fissures of the occlusal (biting) surfaces of the molar teeth.

CLINICAL MANIFESTATIONS
Dental caries of the primary dentition usually begins in the pits and fissures. Small lesions may be difficult to diagnose by visual inspection,
but larger lesions are evident as darkened or cavitated lesions on the tooth surfaces (Fig. 312-2). Rampant dental caries in infants and toddlers, referred to as early childhood caries, is the result of early colonization of the child with cariogenic bacteria and the frequent ingestion of sugar, either in the bottle or in solid foods. The carious process in this situation is initiated earlier and consequently can affect the maxillary incisors first and then progress to the molars as they erupt.

The prevalence of early childhood caries is 30-50% in children from low socioeconomic backgrounds and as high as 70% in some Native American groups. Besides high frequency of sugar consumption and colonization with cariogenic bacteria, other enabling factors include low socioeconomic status of the family, other family member with carious teeth, recent immigrant status of the child, and the visual presence of dental plaque on the child’s teeth. Children who develop caries at a young age are known to be at high risk for developing further caries as they get older. Therefore, the appropriate prevention of early childhood caries can result in the elimination of major dental problems in toddlers and less decay in later childhood.

**COMPLICATIONS**

Left untreated, dental caries usually destroy most of the tooth and invade the dental pulp (pulpitis) and significant pain. Pulpitis can progress to pulp necrosis, with bacterial invasion of the alveolar bone causing a dental abscess (Fig. 312-4). Infection of a primary tooth can disrupt normal development of the successor permanent tooth. In some cases, this process leads to sepsis and infection of the facial space.

**TREATMENT**

The age at which dental caries occurs is important in dental management. Children younger than 3 yr of age lack the developmental ability...
to cooperate with dental treatment and often require sedation, or general anesthesia to repair carious teeth. After age 4 yr, children can generally cope with dental restorative care with the use of local anesthesia.

Dental treatment, using silver amalgam, plastic composite, or stainless steel crowns, can restore most teeth affected with dental caries. If caries involves the dental pulp, a partial removal of the pulp (pulpotomy) or complete removal of the pulp (pulpectomy) may be required. If a tooth requires extraction, a space maintainer may be indicated to prevent migration of teeth, which subsequently leads to malposition of permanent successor teeth.

Clinical management of the pain and infection associated with untreated dental caries varies with the extent of involvement and the medical status of the patient. Dental infection localized to the dentoalveolar unit can be managed by local measures (extraction, pulpectomy). Oral antibiotics are indicated for dental infections associated with fever, cellulitis, and facial swelling, or if it is difficult to anesthetize the tooth in the presence of inflammation. Penicillin is the antibiotic of choice, except in patients with a history of allergy to this agent. Clindamycin and erythromycin are suitable alternatives. Oral analgesics, such as ibuprofen, are usually adequate for the pain control.

**PREVENTION**
Because they are seeing infants and toddlers on a periodicity schedule, physicians have an important role in screening children younger than 3 yr of age for dental caries; providing preventive instructions; applying preventive measures, such as fluoride varnish; and referring the child to a dentist if problems exist.

**Fluoride**
The most effective preventive measure against dental caries is communal water supplies with optimal fluoride content. Water fluoridation at the level of 0.7-1.2 mg fluoride per liter (ppm F) was introduced in the United States in the 1940s. Because fluoride from water supplies is now one of several sources of fluoride, the Department of Health and Human Services proposes to not have a fluoride range, but instead to limit the recommendation to the lower limit of 0.7 ppm F. The rationale is to balance the benefits of preventing dental caries with reducing the chance of fluorosis. Children who reside in areas with fluoride-deficient water supplies and are at risk for caries benefit from dietary fluoride supplements (Table 312-1). If the patient uses a private water supply, it is necessary to get the water tested for fluoride levels before prescribing fluoride supplements. To avoid potential overdoses, no fluoride prescription should be written for more than a total of 120 mg of fluoride. However, because of confusion regarding fluoride supplements among practitioners and parents, association of supplements with fluorosis, and lack of parent compliance with the daily administration, supplements may no longer be the first-line approach for preventing caries in preschool-aged children.

Topical fluoride on a daily basis can be achieved by using fluoridated toothpaste. Supervised use of less than a “pea-sized” amount of toothpaste (approximately 0.25 g) on the toothbrush in children younger than 6 yr of age reduces the risk of fluorosis. Children younger than 4 yr of age should brush with less than a “smear or grain-sized” amount of fluoridated toothpaste. Professional topical fluoride applications performed semiannually reportedly reduce caries by approximately 30%. Fluoride varnish is ideal for professional applications in preschool children because of ease of use, even with non–dental health providers, and its safety because of single-dose dispensers. Products that are available now come in containers of 0.25, 0.4, or 0.6 mL of varnish, corresponding to 5.6, 9.0, and 13.6 mg fluoride, respectively. Fluoride varnish should be administered twice a year for preschool children at moderate caries risk and 4 times a year for children at high caries risk.

**Oral Hygiene**
Daily brushing, especially with fluoridated toothpaste, helps prevent dental caries. Most children younger than 8 yr of age do not have the coordination required for adequate tooth brushing. Accordingly, parents should assume responsibility for the child’s oral hygiene, with the degree of parental involvement appropriate to the child’s changing abilities.

**Diet**
Frequent consumption of sweetened fruit drinks is not generally recognized by parents for its high cariogenic potential. Consuming sweetened beverages in a nursing bottle or sippy cup should be discouraged, and special efforts made to instruct parents that their child should only consume sweetened beverages at meal times and not exceed 6 oz per day.

**Dental Sealant**
Plastic dental sealants have been shown to be effective in preventing caries on the pit and fissure of the primary and permanent molars. Sealants are most effective when placed soon after teeth erupt and used in children with deep grooves and fissures in the molar teeth.

*Bibliography is available at Expert Consult.*

### Table 312-1 Supplemental Fluoride Dosage Schedule

<table>
<thead>
<tr>
<th>AGE</th>
<th>FLUORIDE IN HOME WATER</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;0.3 (ppm)</td>
</tr>
<tr>
<td>6 mo-3 yr</td>
<td>0.25*</td>
</tr>
<tr>
<td>3-6 yr</td>
<td>0.50</td>
</tr>
<tr>
<td>6-16 yr</td>
<td>1.00</td>
</tr>
</tbody>
</table>

*Milligrams of fluoride per day.*
Bibliography
The periodontium includes the gingiva, alveolar bone, cementum, and periodontal ligament (see Fig. 312-3).

GINGIVITIS
Poor oral hygiene results in the accumulation of dental plaque at the tooth–gingival interface that activates an inflammatory response, expressed as localized or generalized reddening and swelling of the gingiva. More than half of American school children experience gingivitis. In severe cases, the gingiva spontaneously bleeds and there is oral malodor. Treatment is proper oral hygiene (careful tooth brushing and flossing); complete resolution can be expected. Fluctuations in hormonal levels during the onset of puberty can increase inflammatory response to plaque. Gingivitis in healthy children is unlikely to progress to periodontitis (inflammation of the periodontal ligament resulting in loss of alveolar bone).

AGGRESSIVE PERIODONTITIS IN CHILDREN (PREPUBERTAL PERIODONTITIS)
Periodontitis in children before puberty is a rare disease that often begins between the time of eruption of the primary teeth and the age of 4 or 5 yr. The disease occurs in localized and generalized forms. There is rapid bone loss, often leading to premature loss of primary teeth. It is often associated with systemic problems, including
neutropenia, leukocyte adhesion or migration defects, hypophosphatasia, Papillon-Lefèvre syndrome, leukemia, and histiocytosis X. In many cases, however, there is no apparent underlying medical problem. Nonetheless, diagnostic work-ups are necessary to rule out underlying systemic disease.

Treatment includes aggressive professional teeth cleaning, strategic extraction of affected teeth, and antibiotic therapy. There are few reports of long-term successful treatment to reverse bone loss surrounding primary teeth.

**AGGRESSIVE PERIODONTITIS IN ADOLESCENTS (LOCALIZED JUVENILE PERIODONTITIS)**

Aggressive periodontitis in adolescents is characterized by rapid alveolar bone loss, especially around the primary incisors and 1st molars. Overall prevalence in the United States is <1%, but the prevalence among African-Americans is reportedly 2.5%. This form of periodontitis is associated with a strain of *Aggregatibacter (Actinobacillus)* bacteria. In addition, the neutrophils of patients with aggressive periodontitis can have chemotactic or phagocytic defects. If left untreated, affected teeth lose their attachment and can exfoliate. Treatment varies with the degree of involvement. Patients whose disease is diagnosed at onset are usually managed by surgical or nonsurgical debridement in conjunction with antibiotic therapy. Prognosis depends on the degree of initial involvement and compliance with therapy.

**TEETHING**

Teething can lead to intermittent localized discomfort in the area of erupting primary teeth, irritability, low-grade fevers, and excessive salivation; many children have no apparent difficulties. Treatment of symptoms includes oral analgesics and ice rings for the child to “gum.” Similar manifestations can also arise when the 1st permanent molars erupt at about age 6 yr.

**CYCLOSPORINE- OR PHENYTOIN-INDUCED GINGIVAL OVERGROWTH**

The use of cyclosporine to suppress organ rejection or phenytoin for anticonvulsant therapy, and in some cases calcium channel blockers, is associated with generalized enlargement of the gingiva. Phenytoin and its metabolites have a direct stimulatory action on gingival fibroblasts, resulting in accelerated synthesis of collagen. Phenytoin induces less gingival hyperplasia in patients who maintain meticulous oral hygiene.

Gingival hyperplasia occurs in 10-30% of patients treated with phenytoin. Severe manifestations can include gross enlargement of the gingiva, sometimes covering the teeth; edema and erythema of the gingiva; secondary infection, resulting in abscess formation; migration of teeth; and inhibition of exfoliation of primary teeth and subsequent impaction of permanent teeth. Treatment should be directed toward prevention and, if possible, discontinuation of cyclosporine or phenytoin. Patients undergoing long-term treatment with these drugs should receive frequent dental examinations and oral hygiene care. Severe forms of gingival overgrowth are treated by gingivectomy, but the lesion recurs if drug use is continued.

**ACUTE PERICORONITIS**

Acute inflammation of the flap of gingiva that partially covers the crown of an incompletely erupted tooth is common in mandibular permanent molars. Accumulation of debris and bacteria between the gingival flap and tooth precipitates the inflammatory response. A variant of this condition is a gingival abscess caused by entrapment of bacteria because of orthodontic bands or crowns. Trismus and severe pain may be associated with the inflammation. Untreated cases can result in facial space infections and facial cellulitis.

Treatment includes local debridement and irrigation, warm saline rinses, and antibiotic therapy. When the acute phase has subsided, resection of the gingival flap prevents recurrence. Early recognition of the partial impaction of mandibular 3rd molars and their subsequent extraction prevents these areas from developing pericoronitis.

**NECROTIZING PERIODONTAL DISEASE (ACUTE NECROTIZING ULCERATIVE GINGIVITIS)**

Necrotizing periodontal disease, in the past sometimes referred to as “trench mouth,” is a distinct periodontal disease associated with oral spirochetes and fusobacteria. It is not clear, however, whether bacteria initiate the disease or are secondary. It rarely develops in healthy children in developed countries, with a prevalence in the United States of <1%, but is seen more often in children and adolescents from developing areas of Africa, Asia, and South America. In certain African countries, where affected children usually have protein malnutrition, the lesion can extend into adjacent tissues, causing necrosis of facial structures (cancrum oris, or noma).

Clinical manifestations of necrotizing periodontal disease include necrosis and ulceration of gingiva between the teeth, an adherent grayish pseudomembrane over the affected gingiva, oral malodor, cervical lymphadenopathy, malaise, and fever. The condition may be mistaken for acute herpetic gingivostomatitis. Dark-field microscopy of debris obtained from necrotizing lesions demonstrates dense spirochete populations.

Treatment of necrotizing periodontal disease is divided into an acute management with local debridement, oxygenating agents (direct application of 10% carbamide peroxide in anhydrous glycerol qid), and analgesics. Dramatic resolution usually occurs within 48 hr. If a patient is febrile, antibiotics (penicillin or metronidazole) may be an important adjunctive therapy. A second phase of treatment may be necessary if the acute phase of the disease has caused irreversible morphologic damage to the periodontium. The disease is not contagious.

*Bibliography is available at Expert Consult.*
Bibliography
Traumatic oral injuries may be categorized into 3 groups: injuries to teeth, injuries to soft tissue (contusions, abrasions, lacerations, punctures, avulsions, and burns), and injuries to jaw (mandibular and/or maxillary fractures).

**INJURIES TO TEETH**

Approximately 10% of children between 18 mo and 18 yr of age sustain significant tooth trauma. There appear to be 3 age periods of greatest predilection: toddlers (1-3 yr), usually from falls or child abuse; school-age children (7-10 yr), usually from bicycle and playground accidents; and adolescents (16-18 yr), often the result of fights, athletic injuries, and automobile accidents. Injuries to teeth are more common among children with protruding front teeth. Children with craniofacial abnormalities or neuromuscular deficits are also at increased risk for dental injury. Injuries to teeth can involve the hard dental tissues, the dental pulp (nerve), and injuries to the periodontal structure (surrounding bone and attachment apparatus) (Fig. 314-1 and Table 314-1).

Fractures of teeth may be uncomplicated (confined to the hard dental tissues) or complicated (involving the pulp). Exposure of the pulp results in its bacterial contamination, which can lead to infection and pulp necrosis. Such pulp exposure complicates therapy and can lower the likelihood of a favorable outcome.

The teeth most often affected are the maxillary incisors. Uncomplicated crown fractures are treated by covering exposed dentin and by placing an aesthetic restoration. Complicated crown fractures involving the tooth pulp usually require **endodontic therapy** (root canal). Crown-root fractures and root fractures usually require extensive...
dental therapy. Such injuries in the primary dentition can interfere with normal development of the permanent dentition, and therefore significant injuries of the primary incisor teeth are usually managed by extraction.

Traumatic oral injuries should be referred to a dentist as soon as possible. Even when the teeth appear intact, a dentist should promptly evaluate the patient. Baseline data (radiographs, mobility patterns, responses to specific stimuli) enable the dentist to assess the likelihood of future complications.

**INJURIES TO PERIODONTAL STRUCTURES**

Trauma to teeth with associated injury to periodontal structures that hold the teeth usually manifests as mobile or displaced teeth. Such injuries are more common in the primary than in the permanent dentition. Categories of trauma to the periodontium include concussion, subluxation, intrusive luxation, extrusive luxation, and avulsion.

**Concussion**

Injuries that produce minor damage to the periodontal ligament are termed concussions. Teeth sustaining such injuries are not mobile or displaced but react markedly to percussion (gentle hitting of the tooth with an instrument). This type of injury usually requires no therapy and resolves without complication. Primary incisors that sustain concussion can change color, indicating pulpal degeneration, and should be evaluated by a dentist.

**Subluxation**

Subluxated teeth exhibit mild to moderate horizontal mobility and/or vertical mobility. Hemorrhage is usually evident around the neck of the tooth at the gingival margin. There is no displacement of the tooth. Many subluxated teeth need to be immobilized by splints to ensure adequate repair of the periodontal ligament. Some of these teeth develop pulp necrosis.

**Intrusion**

Intruded teeth are pushed up into their socket, sometimes to the point where they are not clinically visible. Intruded primary incisors can give the false appearance of being avulsed (knocked out). To rule out avulsion, a dental radiograph is indicated (Figs. 314-2 and 314-3).

**Extrusion**

Extrusion injury is characterized by displacement of the tooth from its socket. The tooth is usually displaced to the lingual (tongue) side, with fracture of the wall of the alveolar socket. These teeth need immediate treatment; the longer the delay, the more likely the tooth will be fixed in its displaced position. Therapy is directed at reduction (repositioning the tooth) and fixation (splinting). The pulp of such teeth often becomes necrotic and requires endodontic therapy. Extrusive luxation in the primary dentition is usually managed by extraction because

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**Table 314-1** Injuries to Crowns of Teeth

<table>
<thead>
<tr>
<th>TYPE OF TRAUMA</th>
<th>DESCRIPTION</th>
<th>TREATMENT AND REFERRAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enamel infraction (crazing)</td>
<td>Incomplete fracture of enamel without loss of tooth structure</td>
<td>Initially might not require therapy but should be assessed periodically by dentist</td>
</tr>
<tr>
<td>Enamel fractures</td>
<td>Fracture of only the tooth enamel</td>
<td>Tooth may be smoothed or treated to replace fragment</td>
</tr>
<tr>
<td>Enamel and dentin fracture</td>
<td>Fracture of enamel and dentinal layer of the tooth.</td>
<td>Refer as soon as possible. Area should be treated to preserve the integrity of the underlying pulp</td>
</tr>
<tr>
<td>Enamel, dentin fracture</td>
<td>Bacterial contamination can lead to pulpal necrosis and periapical abscess</td>
<td>Refer immediately. The dental therapy of choice depends on the extent of injury, the condition of the pulp, the development of the tooth, time elapsed from injury, and any other injuries to the supporting structures. Therapy is directed toward minimizing contamination in an effort to improve the prognosis</td>
</tr>
</tbody>
</table>

complications of reduction and fixation can result in problems with development of permanent teeth.

**Avulsion**

If avulsed permanent teeth are replanted as soon as possible after injury, there is a good chance that normal reattachment will follow and the tooth will have a good prognosis. However, if the tooth is in a dry environment for longer than 1 hr, the ligament that holds the tooth in place has little chance for survival and failure (root resorption, ankylosis) is common. Parents confronted with this emergency situation can be instructed to do the following:

- Find the tooth.
- Briefly rinse the tooth. (Do not scrub the tooth. Do not touch the root. After plugging the sink drain, hold the tooth by the crown and rinse it under running tap water.)
- Insert the tooth into the socket. (Gently place it back into its normal position. Do not be concerned if the tooth extrudes slightly. If the parent or child is too apprehensive for replantation of the tooth, the tooth should be placed in cold cow’s milk or other cold isotonic solution.)
- Go directly to the dentist. (In transit, the child should hold the tooth in its socket with a finger. The parent should buckle a seatbelt around the child and drive safely.)

After the tooth is replanted, it must be immobilized to facilitate reattachment; endodontic therapy is always required. The initial signs of complications associated with replantation can appear as early as 1 wk after trauma or as late as several years later. Close dental follow-up is indicated for at least 1 yr.

**PREVENTION**

To minimize the likelihood of dental injuries:

- Every child or adolescent who engages in contact sports should wear a mouth guard, which may be constructed by a dentist or purchased at any athletic goods store.
- Helmets with face guards should be worn by children or adolescents with neuromuscular problems or seizure disorders to protect the head and face during falls.
- Helmets should also be used during biking, skiing, skating, and skateboarding.
- All children or adolescents with protruding incisors should be evaluated by a pediatric dentist or orthodontist.

**ADDITIONAL CONSIDERATIONS**

Children who experience dental trauma might also have sustained head or neck trauma, and therefore neurologic assessment is warranted. Tetanus prophylaxis should be considered with any injury that disrupts the integrity of the oral tissues. The possibility of child abuse should always be considered.

*Bibliography is available at Expert Consult.*
Bibliography
Chapter 315
Common Lesions of the Oral Soft Tissues
Norman Tinanoff

OROPHARYNGEAL CANDIDIASIS
Oropharyngeal infection with *Candida albicans* (thrush, moniliasis) (see Chapter 234.1) is common in neonates from contact with the organism in the birth canal or breast. The lesions of oropharyngeal candidiasis (OPC) appear as white plaques covering all or part of the oropharyngeal mucosa. These plaques are removable from the underlying surface, which is characteristically inflamed and has pinpoint hemorrhages. The diagnosis is confirmed by direct microscopic examination on potassium hydroxide smears and culture of scrapings from lesions. OPC is usually self-limited in the healthy newborn infant, but topical application of nystatin to the oral cavity of the baby and to the nipples of breastfeeding mothers will hasten recovery.

OPC is also a major problem during myelosuppressive therapy. Systemic candidiasis, a major cause of morbidity and mortality during myelosuppressive therapy, develops almost exclusively in patients who have had prior oropharyngeal, esophageal, or intestinal candidiasis. This observation implies that prevention of OPC should reduce the incidence of systemic candidiasis. The use of oral rinses of 0.2% chlorhexidine solution plus systemic antifungals may be effective in preventing OPC, systemic candidiasis, or candidal esophagitis.

APHTHOUS ULCERS
The aphthous ulcer (canker sore) is a distinct oral lesion, prone to recurrence; Table 315-1 notes the differential diagnosis. Aphthous ulcers are reported to develop in 20% of the population. Their etiology is unclear, but allergic or immunologic reactions, emotional stress, genetics, and injury to the soft tissues in the mouth have been implicated. Aphthous-like lesions may be associated with inflammatory bowel disease, Behçet disease, gluten-sensitive enteropathy, periodic fever-aphthae-pharyngitis-adenitis syndrome, Sweet syndrome, HIV infection (especially if ulcers are large and slow to heal), and cyclic neutropenia. Clinically, these ulcers are characterized by well-circumscribed, ulcerative lesions with a white necrotic base surrounded by a red halo. The lesions last 10-14 days and heal without scarring. Nonprescription palliative therapies, such as benzocaine and topical lidocaine, are effective, as are topical steroids. Tetracycline has benefit with severe outbreaks, but caution is necessary in pregnant women and young children to prevent tetracycline tooth staining during a child’s tooth development.

HERPETIC GINGIVOSTOMATITIS
After an initial incubation period of approximately 1 wk, the initial infection with herpes simplex virus manifests as fever and malaise, usually in a child younger than 5 yr (see Chapter 252). The oral cavity can show various expressions, including the gingiva becoming erythematous, mucosal hemorrhages, and clusters of small vesicles erupting throughout the mouth. There is often involvement of the mucocutaneous margin and perioral skin (Fig. 315-1). The oral symptoms generally are accompanied by fever, lymphadenopathy, and difficulty eating and drinking. The symptoms usually regress within 2 wk without scarring. Fluids should be encouraged because the child may become dehydrated. Analgesics and anesthetic rinses can make the child more comfortable. Oral acyclovir if taken within the 1st 3 days of symptoms may be beneficial in shortening the duration of
symptoms. Caution should be exercised to prevent autoinoculation or transmission of infection to the eyes.

**RECURRENT HERPES LABIALIS**

Approximately 90% of the population develops antibodies to herpes simplex virus. In periods of quiescence, the virus is thought to remain latent in sensory neurons. Unlike primary herpetic gingivostomatitis, which manifests as multiple painful vesicles on the lips, tongue, palate, gingiva, and mucosa, recurrent herpes is generally limited to the lips. Other than the annoyance of causing pain and an unattractive appearance, there are generally no systemic symptoms. Reactivation of the virus is thought to be the result of exposure to ultraviolet light, tissue trauma, stress, or fevers. There is little advantage of antiviral therapy over palliative therapies in an otherwise healthy patient affected by recurrent herpes.

**BOHN NODULES**

Bohn nodules are small developmental anomalies located along the buccal and lingual aspects of the mandibular and maxillary ridges and in the hard palate of the neonate. These lesions arise from remnants of mucous gland tissue. Treatment is not necessary, because the nodules disappear within a few weeks.

**DENTAL LAMINA CYSTS**

Dental lamina cysts are small cystic lesions located along the crest of the mandibular and maxillary ridges of the neonate. These lesions arise from epithelial remnants of the dental lamina. Treatment is not necessary; they disappear within a few weeks.

**FORDYCE GRANULES**

Almost 80% of adults have multiple yellow-white granules in clusters or plaque-like areas on the oral mucosa, most commonly on the buccal mucosa or lips. They are aberrant sebaceous glands. The glands are present at birth, but they can hypertrophy and first appear as discrete yellowish papules during the preadolescent period in approximately 50% of children. No treatment is necessary.

**PARULIS**

The parulis (gum boil) is a soft reddish papule located adjacent to the root of a chronically abscessed tooth. It occurs at the end-point of a draining dental sinus tract. Treatment consists of diagnosing which tooth is abscessed and extracting it or performing root canal on the offending tooth.

**CHEILITIS**

This dryness of the lips followed by scaling and cracking and accompanied by a characteristic burning sensation is common in children. Cheilitis may be caused by sensitivity to contact substances, lip licking, vitamin deficiency, weakened immune system, or fungal or bacterial infections. Cheilitis often occurs in association with fever. Treatment may include antifungal or antibacterial agents and frequent application of petroleum jelly.

**ANKYLOGLOSSIA**

Ankyloglossia or “tongue-tie” is characterized by an abnormally short lingual frenum that can hinder the tongue movement but rarely interferes with feeding or speech. The frenum might spontaneously lengthen as the child gets older. If the extent of the ankyloglossia is severe, speech may be affected and surgical correction may be indicated.

**GEOGRAPHIC TONGUE**

Geographic tongue (migratory glossitis) is a benign and asymptomatic lesion and is characterized by 1 or more smooth, bright red patches, often showing a yellow, gray, or white membranous margin on the dorsum of an otherwise normally roughened tongue. The condition has no known cause, and no treatment is indicated (see Chapter 664).

**FISSURED TONGUE**

The fissured tongue (scrotal tongue) is a malformation manifested clinically by numerous small furrows or grooves on the dorsal surface (see Chapter 664). If the tongue is painful, brushing the tongue or irrigating with water can reduce the bacteria in the fissures.

<table>
<thead>
<tr>
<th>CONDITION</th>
<th>Differential Diagnosis of Oral Ulceration</th>
<th>COMMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>COMMON</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aphthous (canker sore)</td>
<td>Painful, circumscribed lesions; recurrences</td>
<td></td>
</tr>
<tr>
<td>Traumatic</td>
<td>Accidents, chronic cheek biter, or after dental local anesthesia</td>
<td></td>
</tr>
<tr>
<td>Hand, foot, mouth disease</td>
<td>Painful; lesions on tongue, anterior oral cavity, hands, and feet</td>
<td></td>
</tr>
<tr>
<td>Herpangina</td>
<td>Painful; lesions confined to soft palate and oropharynx</td>
<td></td>
</tr>
<tr>
<td>Herpetic gingivostomatitis</td>
<td>Vesicles on mucocutaneous borders; painful, febrile</td>
<td></td>
</tr>
<tr>
<td>Recurrent herpes labialis</td>
<td>Vesicles on lips; painful</td>
<td></td>
</tr>
<tr>
<td>Chemical burns</td>
<td>Alkali, acid, aspirin; painful</td>
<td></td>
</tr>
<tr>
<td>Heat burns</td>
<td>Hot food, electrical</td>
<td></td>
</tr>
<tr>
<td>UNCOMMON</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutrophil defects</td>
<td>Agranulocytosis, leukemia, cyclic neutropenia; painful</td>
<td></td>
</tr>
<tr>
<td>Systemic lupus erythematosus</td>
<td>Recurrent, may be painless</td>
<td></td>
</tr>
<tr>
<td>Behçet syndrome</td>
<td>Resembles aphthous lesions; associated with genital ulcers, uveitis</td>
<td></td>
</tr>
<tr>
<td>Necrotizing ulcerative gingivostomatitis</td>
<td>Vincent stomatitis; painful</td>
<td></td>
</tr>
<tr>
<td>Syphilis</td>
<td>Chancre or gumma; painless</td>
<td></td>
</tr>
<tr>
<td>Oral Crohn disease</td>
<td>Aphthous-like; painful</td>
<td></td>
</tr>
<tr>
<td>Histoplasmosis</td>
<td>Lingual</td>
<td></td>
</tr>
<tr>
<td>Pemphigus</td>
<td>May be isolated to the oral cavity</td>
<td></td>
</tr>
<tr>
<td>Stevens-Johnson syndrome</td>
<td>May be isolated or appear initially in the oral cavity</td>
<td></td>
</tr>
</tbody>
</table>

**Figure 315-1** Herpetic gingivostomatitis. Lip erosions with multiple perioral herpetic lesions involving the mucocutaneous borders. *(From Paller AS, Mancini AJ, editors: Hurwitz clinical pediatric dermatology, ed 3, Philadelphia, 2006, WB Saunders, p. 398.)*
With the exception of mumps (see Chapter 248), disease of the salivary glands is rare in children. Bilateral enlargement of the submaxillary glands can occur in AIDS, cystic fibrosis, Epstein-Barr virus infection, and malnutrition, and, transiently, during acute asthmatic attacks. Chronic vomiting can be accompanied by enlargement of the parotid glands. Benign salivary gland hypertrophy has been associated with endocrinopathies: thyroid disease, diabetes, and Cushing syndrome. Infiltrative disease or tumors are uncommon; red flags include facial nerve palsy, rapid growth, fixed skin, paresthesias, ulceration, or a history of radiation to the head or neck region.

PAROTITIS
Acute parotitis is often caused by blockage, with further inflammation due to bacterial infection. The blockage may be due to a salivary stone or mucous plug. Stones can be removed by physical manipulation, surgery, or lithotripsy. Recurrent parotitis is an idiopathic swelling of the parotid gland that can occur in otherwise healthy children. The swelling is usually unilateral, but both glands can be involved simultaneously or alternately. There is little pain; the swelling is limited to the gland and usually lasts 2-3 wk. Treatment may include local heat, massaging the gland, and antibiotics. Suppurative parotitis is usually caused by *Staphylococcus aureus*. It is usually unilateral and may be accompanied by fever. The gland becomes swollen, tender, and painful. Suppurative parotitis responds to antibacterial therapy based on culture obtained from the Stensen duct or by surgical drainage. Viral causes of parotitis include mumps (often in epidemics), EBV, human herpes virus 6, enteroviruses, and HIV.

RANULA
A ranula is a cyst associated with a major salivary gland in the sublingual area. It is a large, soft, mucus-containing swelling in the floor of the mouth. It occurs at any age, including infancy. The cyst should be excised, and the severed duct should be exteriorized.

MUCOCELE
Mucocle is a salivary gland lesion caused by a blockage of a salivary gland duct. It is most common on the lower lip and has the appearance of a fluid-filled vesicle or a fluctuant nodule with the overlying mucosa normal in color. Treatment is surgical excision, with removal of the involved accessory salivary gland.

CONGENITAL LIP PITS
Congenital lip pits are caused by fistulous tracts that lead to embedded mucous glands in the lower lip. They leak saliva, especially with salivary stimulation. Lip pits can be isolated anomalies, or they can be found in patients with cleft lip or palate. Treatment is surgical excision of the glandular tissue.

ERUPTION CYST
Eruption cyst is a smooth, painless swelling over the erupting tooth. If bleeding occurs in the cyst space, it may appear blue or blue-black. In most cases, no treatment is indicated and the cyst resolves with the full eruption of the tooth.

XEROSTOMIA
Also known as dry mouth, xerostomia may be associated with fever, dehydration, anticholinergic drugs, chronic graft-versus-host disease, Mikulicz disease (leukemia infiltrates), Sjögren syndrome, or tumoricidal doses of radiation when the salivary glands are within the field. Long-term xerostomia is a high-risk factor for dental caries.
Bibliography
The panoramic radiograph provides a single tomographic image of the upper and lower jaw, including all the teeth and supporting structures. The x-ray tube rotates about the patient’s head with reciprocal movement of the film or image receptor during the exposure. The panoramic image shows the teeth, mandibular bodies, rami, and condyles; maxillary sinuses; and a majority of the facial buttresses. Such images are used to show abnormalities of tooth number, development and eruption pattern, cystic and neoplastic lesions, bone infections, and fracture, as well as dental caries and periodontal disease (Fig. 317-1).

Cephalometric radiographs are posteroanterior and lateral skull films that are taken using a cephalostat (head positioner) and employ techniques that clearly demonstrate the facial skeleton and soft facial tissues. Similar protocols for positioning children are used throughout the world. From these images, cranial and facial points and planes can be determined and compared with standards derived from thousands of images. A child’s facial growth can be assessed serially when cephalometric radiographs are taken sequentially. Relationships among the maxilla, mandible, cranial base, and facial skeleton can be determined in a quantitative manner. Additionally, the alignment of the teeth and the relation of the teeth to the supporting bone can be serially measured.

Intraoral dental radiographs are highly detailed, direct-exposure films that demonstrate sections of the child’s teeth and supporting bone structures. The film or image receptor is placed lingual to the teeth,
Figure 317-1 A panoramic radiograph of a 10 yr old child showing extensive dental caries of the 1st permanent molars (arrows), as well as normal structures: erupted 1st permanent molar, unerupted 2nd molar, and unerupted 3rd molar; erupted incisors (EI), unerupted premolars (UP), and erupted primary canines (pc).

and the x-ray beam is directed through the teeth and supporting structures. The resulting images are used to detect dental caries, loss of alveolar bone (periodontal disease), abscesses at the roots of the teeth, and trauma to the teeth and alveolar bone and to demonstrate the developmental status of permanent teeth within the bone.
The esophagus is a hollow muscular tube, separated from the pharynx above and the stomach below by 2 tonically closed sphincters. Its primary function is to convey ingested material from the mouth to the stomach. Largely lacking digestive glands and enzymes, and exposed only briefly to nutrients, it has no active role in digestion.

EMBRYOLOGY
The esophagus develops from the postpharyngeal foregut and can be distinguished from the stomach in the 4 wk old embryo. At the same time, the trachea begins to bud just anterior to the developing esophagus; the resulting laryngotracheal groove extends and becomes the lung. Disturbance of this stage can result in congenital anomalies such as tracheoesophageal fistula. The length of the esophagus is 8-10 cm at birth and doubles in the 1st 2-3 yr of life, reaching approximately 25 cm in the adult. The abdominal portion of the esophagus is as large as the stomach in an 8 wk old fetus but gradually shortens to a few millimeters at birth, attaining a final length of approximately 3 cm by a few years of age. This intraabdominal location of both the distal esophagus and the lower esophageal sphincter (LES) is an important antireflux mechanism, because increases in intraabdominal pressure are also transmitted to the sphincter, augmenting its defense. Swallowing can be seen in utero as early as 16-20 wk of gestation, helping to circulate the amniotic fluid; polyhydramnios is a hallmark of lack of normal swallowing or of esophageal or upper gastrointestinal tract obstruction. Sucking and swallowing are not fully coordinated before 34 wk of gestation, a contributing factor for feeding difficulties in premature infants.

ANATOMY
The luminal aspect of the esophagus is covered by thick, protective, nonkeratinized stratified squamous epithelium, which abruptly changes to simple columnar epithelium at the stomach’s upper margin, at the gastroesophageal junction (GEJ). This squamous epithelium is relatively resistant to damage by gastric secretions (in contrast to the ciliated columnar epithelium of the respiratory tract), but chronic irritation by gastric contents can result in morphometric changes (thickening of the basal cell layer and lengthening of papillary ingrowth into the epithelium) and subsequent metaplasia of the cells lining the lower esophagus from squamous to columnar. Deeper layers of the esophageal wall are composed successively of lamina propria, muscularis mucosae, submucosa, and the 2 layers of muscularis propria (circular surrounded by longitudinal). The 2 delimiting sphincters of the esophagus, the upper esophageal sphincter (UES) at the criocopharyngeus muscle and the LES at the GEJ, constrict the esophageal lumen at its proximal and distal boundaries. The muscularis propria of the upper third of the esophagus is predominantly striated, and that of the lower two-thirds is smooth muscle. Clinical conditions involving striated muscle (criocopharyngeal dysfunction, cerebral palsy) affect the upper esophagus, whereas those involving smooth muscle (achalasia, reflux esophagitis) affect the lower esophagus. The muscular LES and the mucosal “Z-line” of the GEJ may be discrepant up to several centimeters.

FUNCTION
The esophagus can be divided into 3 areas: the UES, the esophageal body, and the LES. At rest, the tonic LES pressure is normally approximately 20 mm Hg; values <10 mm Hg are usually considered abnormal, although it seems that competence against retrograde flow of gastric material is maintained if the LES pressure is >5 mm Hg. The LES pressure rises during intragastric pressure amplifications, whether caused by gastric contractions, abdominal wall muscle contractions (“straining”), or external pressure applied to the abdominal wall. It also rises in response to cholinergic stimuli, gastrin, gastric alkalization, and certain drugs (bethanechol, metoclopramide, cisapride). The UES pressure is more variable and often higher than that of the LES; it decreases almost to zero during deep sleep and it increases markedly during stress and straining. The UES and LES relax briefly to allow material to pass through during swallowing, belching, reflux, and vomiting. They can contract in response to subthreshold levels of reflux (esophagoglottal closure reflex).

Swallowing is initiated by elevation of the tongue, propelling the bolus into the pharynx. The larynx elevates and moves anteriorly, pulling open the relaxing UES, while the opposed aryepiglottic folds close. The epiglottis drops back to cover the larynx and direct the bolus over the larynx and into the UES. The soft palate occludes the nasopharynx. The primary peristalsis thus initiated is a contraction originating in the oropharynx that clears the esophagus aborally (Fig. 318-1). The LES tonically contracted as a barrier against gastroesophageal reflux (GER), relaxes as swallowing is initiated, at nearly the same time as the UES relaxation. The LES relaxation persists considerably longer, until the peristaltic wave traverses it and closes it. The normal esophageal peristaltic speed is approximately 3 cm/sec; the wave takes 4 sec or longer to traverse the 12 cm esophagus of a young infant and considerably longer in a larger child. Facial stimulation by a puff of air can induce swallowing and esophageal peristalsis in healthy young infants, a reflex termed the Santmyer swallow.

In addition to relaxing to move swallowed material past the GEJ into the stomach, the LES normally relaxes to vent swallowed air or to allow retrograde expulsion of material from the stomach. Perhaps as an extension of these functions, the normal LES also permits physiologic reflux episodes, brief events that occur approximately 5 times in the
first postprandial hour, particularly in the awake state, but are otherwise uncommon. **Transient LES relaxation**, not associated with swallowing, is the major mechanism underlying pathologic reflux (see Fig. 318-1).

The close linkage of the anatomy of the upper digestive and respiratory tracts has mandated intricate functional protections of the respiratory tract during retrograde movement of gastric contents as well as during swallowing. The protective functions include the LES tone, the bolstering of the LES by the surrounding diaphragmatic crura, and the “backup protection” of the LES tone. Secondary peristalsis, akin to primary peristalsis but without an oral component, originates in the upper esophagus, triggered mainly by GER, and thereby also clears refluxed gastric contents from the esophagus. Another protective reflex is the “pharyngeal swallow” (initiated above the esophagus, but without lingual participation). Multiple levels of protection against aspiration include the rhythmic coordination of swallowing and breathing and a series of protective reflexes with esophagopharyngeal afferents and efferents that close the LES or larynx. These reflexes include the esophago-UES contractile reflex, the pharyngo-UES contractile reflex, the esophagotracheal closure reflex, and 2 pharyngoglottal adduction reflexes. The last 2 reflexes have chemoreceptors on the laryngeal surface of the epiglottis and mechanoreceptors on the aryepiglottic folds as their sites of stimulus. It is likely that interactions between the esophagus and the respiratory tract, which cause extraesophageal manifestations of gastroesophageal reflux disease (GERD), will be explained by subtle abnormalities in these protective reflexes.

**318.1 Common Clinical Manifestations and Diagnostic Aids**

Seema Khan and Susan R. Orenstein

**COMMON CLINICAL MANIFESTATIONS**

Manifestations of esophageal disorders include pain, obstruction or difficulty swallowing, abnormal retrograde movement of gastric contents (reflux, regurgitation, or vomiting), or bleeding; esophageal disease can also engender respiratory symptoms. Pain in the chest unrelated to swallowing (heartburn) can be a sign of esophagitis, but similar pain might also represent cardiac, pulmonary, or musculoskeletal disease or visceral hyperalgesia. Pain during swallowing (odynophagia) localizes the disease more discretely to the pharynx and esophagus and often represents inflammatory mucosal disease. Complete esophageal obstruction can be produced acutely by esophageal foreign bodies, including food impactions; can be congenital, as in esophageal atresia; or can evolve over time as a peptic stricture occludes the esophagus. Difficulty swallowing (dysphagia) can be produced by incompletely occlusive esophageal obstruction (by extrinsic compression, intrinsic narrowing, or foreign bodies) but can also result from dysmotility of the esophagus (whether primary/idiopathic or secondary to systemic disease). Inflammatory lesions of the esophagus without obstruction or dysmotility are a third cause of dysphagia; eosinophilic esophagitis, most often afflicting older boys, is relatively common.

The most common esophageal disorder in children is GERD, which is from retrograde return of gastric contents into the esophagus. Esophagitis can be caused by GERD, by eosinophilic disease, by infection, or by caustic substances. Esophageal bleeding can result from severe esophagitis that produces erosions or ulcerations and can manifest as anemia or Hemoccult-positive stools. More acute or severe bleeding can be from ruptured esophageal varices. The resulting hematemesis must be differentiated from more distal bleeding (gastric ulcer) and from more proximal bleeding (a nosebleed or hemoptysis).

Respiratory symptoms of esophageal disease can result from luminal contents incorrectly being directed into the respiratory tract or to reflexive respiratory responses to esophageal stimuli.

**DIAGNOSTIC AIDS**

The esophagus can be evaluated by radiography, endoscopy, histology, scintigraphy, manometry, pH-metry (linked as indicated with other polysomnography), and multichannel intraluminal impedance. Contrast (usually barium) radiographic study of the esophagus usually incorporates fluoroscopic imaging over time so that motility and anatomy can be assessed. Although most often requested to evaluate for GERD, it is neither sensitive nor specific for this purpose; it can detect complications of GERD (stricture or hiatal hernia) or conditions mimicking GERD (pyloric stenosis or malrotation with intermittent volvulus).

Barium fluoroscopy is optimal for evaluating for structural anomalies, such as duplications, strictures, or external esophageal compression by an aberrant blood vessel, or for causes of dysmotility, such as achalasia. Modifications of the routine barium fluoroscopic study are used in special situations. When an “H-type” tracheoesophageal fistula is suspected, the test is most sensitive if the radiologist, with the patient prone, distends the esophagus with barium via a nasogastric tube. The videofluoroscopic evaluation of swallowing performed with varying consistencies of barium (“modified barium swallow,” oropharyngeal videofluorosgram, or “cookie swallow”) optimally evaluates children with dysphagia by demonstrating incoordination of the pharyngeal and esophageal phases of swallowing and any associated aspiration.

In some centers, fiberoptic endoscopic evaluation of swallowing uses nasopharyngeal endoscopy to visualize the pharynx and larynx during swallowing of dye-enhanced foods when dysphagia, laryngeal penetration, or aspiration are suspected. This is often combined with sensory testing of the laryngeal adductor reflex in response to a calibrated puff of air through the endoscope to the arytenoids, generating the composite fiberoptic endoscopic evaluation of swallowing sensory testing.

**Figure 318-1** A continuous tracing of esophageal motility showing 2 swallows, as indicated by the pharyngeal contraction associated with relaxation of the upper esophageal sphincter (UES) and followed by peristalsis in the body of the esophagus. The lower esophageal sphincter (LES) also displays a transient relaxation (arrow) unassociated with a swallow. There is an episode of gastroesophageal reflux (*) recorded by a pH probe at the time of the transient LES relaxation. (Courtesy of John Dent, FRACP, PhD, and Geoffrey Davidson, MD.)
that examines the mechanisms of any aspiration that is present. Endoscopy allows direct visualization of esophageal mucosa and helps therapeutically in the removal of foreign bodies and treatment of esophageal varices. Endoscopy also allows biopsy samples to be taken, thus improving the diagnosis of “endoscopy-negative” GERD, differentiating GERD from eosinophilic esophagitis, and identifying viral or fungal causes of esophagitis.

Radionuclide scintigraphy scans are helpful in evaluating the efficiency of peristalsis and demonstrating reflux episodes. They can be specific, although not very sensitive, for aspiration and can quantify gastric emptying, thus hinting at a cause for GERD. The related radionuclide salivagram can demonstrate aspiration of even minute amounts of saliva.

Esophageal manometry evaluates for dysmotility from the pharynx to the stomach; by synchronized quantitative pressure measurements along the esophagus, it detects and characterizes dysfunctions sometimes missed radiographically. Manometry is often challenging in young infants, and sphincters are optimally evaluated with special Dent sleeves, rather than the simple ports available for the esophageal body.

Extended pH monitoring of the distal esophagus is a sensitive test for acidic GER episodes that can quantify duration and degree of acidity, but not volume, of the reflux episodes. It is linked with polysomnography (a “pneumogram”) when GER is suspected to cause apnea or similar symptoms.

Multichannel intraluminal impedance is a method for pH-independent detection of bolus movements in the esophagus; with a pH probe incorporated, it can distinguish between acid and nonacid liquid and gaseous reflux, the proximal extent of reflux, and several aspects of esophageal function, such as direction of bolus flow, duration of bolus presence, and bolus clearance.
Bibliography
Esophageal atresia (EA) is the most common congenital anomaly of the esophagus, with a prevalence of 1.7 per 10,000 live births. Of these, >90% have an associated tracheoesophageal fistula (TEF). In the most common form of EA, the upper esophagus ends in a blind pouch and the TEF is connected to the distal esophagus (type C). Figure 319-1 shows the types of EA and TEF and their relative frequencies. The exact cause is still unknown; associated features include advanced maternal age, European ethnicity, obesity, low socioeconomic status, and tobacco smoking. This defect has survival rates of >90%, owing largely to improved neonatal intensive care, earlier recognition, and appropriate intervention. Infants weighing <1,500 g at birth and those with severe cardiac anomalies have the highest risk for mortality. Fifty percent of infants are nonsyndromic without other anomalies, and the rest have associated anomalies, most often associated with the VATER or VACTERL (vertebral, anorectal, [cardiac], tracheal, esophageal, renal, radial, [limb]) syndrome. Cardiac and vertebral anomalies are seen in 32% and 24%, respectively. These syndromes generally are associated with normal intelligence. Despite low concordance among twins and the low incidence of familial cases, genetic factors have a role in the pathogenesis of TEF in some patients as suggested by discrete mutations in syndromic cases: Feingold syndrome (N-MYC), CHARGE syndrome (coloboma of the eye, central nervous system anomalies; heart defects; atresia of the choanae; retardation of growth and/or development; genital and/or urinary defects [hypogonadism]; ear anomalies and/or deafness) (CHD7), and anophthalmia-esophageal-genital syndrome (SOX2).

**PRESENTATION**
The neonate with EA typically has frothing and bubbling at the mouth and nose after birth as well as episodes of coughing, cyanosis, and respiratory distress. Feeding exacerbates these symptoms, causes regurgitation, and can precipitate aspiration. Aspiration of gastric contents via a distal fistula causes more damaging pneumonitis than aspiration of pharyngeal secretions from the blind upper pouch. The infant with an isolated TEF in the absence of EA (“H-type” fistula) might come to medical attention later in life with chronic respiratory problems, including refractory bronchospasm and recurrent pneumonias.

**DIAGNOSIS**
In the setting of early-onset respiratory distress, the inability to pass a nasogastric or orogastric tube in the newborn suggests EA. Perinatal radiographic findings of absence of the infant stomach bubble and maternal polyhydramnios might alert the physician to EA. Plain radiography in the evaluation of respiratory distress might reveal a coiled feeding tube in the esophageal pouch and/or an air-distended stomach, indicating the presence of a coexisting TEF (Fig. 319-2). Conversely, pure EA can manifest as an airless scaphoid abdomen. In isolated TEF (H type), an esophagogram with contrast medium injected under pressure can demonstrate the defect (Fig. 319-3). Alternatively, the orifice may be detected at bronchoscopy or when methylene blue dye injected into the endotracheal tube during endoscopy is observed in the esophagus during forced inspiration.

**MANAGEMENT**
Initially, maintaining a patent airway, pre-operative proximal pouch decompression to prevent aspiration of secretions and use of antibiotics to prevent consequent pneumonia are paramount. Prone positioning minimizes movement of gastric secretions into a distal fistula, and esophageal suctioning minimizes aspiration from a blind pouch. Endotracheal intubation with mechanical ventilation is to be avoided if possible because it can worsen distention of abdominal viscera. Surgical ligation of the TEF and primary end-to-end anastomosis of the esophagus via right-sided thoracotomy constitute the current standard surgical approach. In the premature or otherwise complicated infant, a primary closure may be delayed by temporizing with fistula ligation and gastrostomy tube placement. If the gap between the atretic ends of the esophagus is >3-4 cm, primary repair cannot be done; options include using gastric, jejunal, or colonic segments interposed as a neoesophagus. Careful search must be undertaken for the common associated cardiac and other anomalies. Thoracoscopic surgical repair is now considered feasible and associated with favorable long-term outcomes.

**OUTCOME**
The majority of children with EA and TEF grow up to lead normal lives, but complications are often challenging, particularly during the 1st 5 yr of life. Complications of surgery include anastomotic leak, refistulization, and anastomotic stricture. Gastroesophageal reflux...
disease, resulting from intrinsic abnormalities of esophageal function, often combined with delayed gastric emptying, contributes to management challenges in many cases. Gastroesophageal reflux disease contributes significantly to the respiratory disease (reactive airway disease) that often complicates EA and TEF and also worsens the frequent anastomotic strictures after repair of EA.

Many patients have an associated tracheomalacia that improves as the child grows.

Bibliography is available at Expert Consult.

### 319.2 Laryngotracheoesophageal Clefts

**Seema Khan and Susan R. Orenstein**

Laryngotracheoesophageal clefts are uncommon anomalies that result when the septum between the esophagus and trachea fails to develop fully, leading to a common channel defect between the pharyngoesophagus and laryngotracheal lumen, thus making the laryngeal closure incompetent during swallowing or reflux. Other developmental anomalies, such as EA and TEF, are seen in 20% of patients with clefts. The severity of presenting symptoms depends on the type of cleft; they are commonly classified as 4 types (I-IV) according to the inferior extent of the cleft. Early in life, the infant presents with stridor, choking, cyanosis, aspiration of feedings, and recurrent chest infections. The diagnosis is difficult and usually requires direct endoscopic visualization of the larynx and esophagus. When contrast radiography is used,
Bibliography


Bibliography
Obstructing lesions classically produce dysphagia to solids earlier and more noticeably than to liquids and can manifest when the infant liquid diet begins to incorporate solids; this is in contrast to dysphagia from dysmotility, in which swallowing of liquids is affected as early as, or earlier than, solids. In most instances of dysphagia, evaluation begins with fluoroscopy, which may include videofluoroscopic evaluation of swallowing, particularly if aspiration is a primary symptom. Secondary studies are often endoscopic if intrinsic obstruction is suspected or manometric if dysmotility is suspected; other imaging studies may be used in particular cases. Congenital lesions can require surgery, whereas
webs and peptic strictures might respond adequately to endoscopic (or bougie) dilation. Peptic strictures, once dilated, should prompt consideration of fundoplication for ongoing prophylaxis.

**EXTRINSIC**

Esophageal duplication cysts are the most commonly encountered foregut duplications. These cysts are lined by intestinal epithelium, have a well-developed smooth muscle wall, and are attached to the normal gastrointestinal tract. Most of these affect the distal half of the esophagus on the right side. The most common presentation is respiratory distress caused by compression of the adjacent airways. Dysphagia is a common symptom in older children. Upper gastrointestinal bleeding can occur as a result of acid-secreting gastric mucosa in the duplication wall. Neuroenteric cysts might contain glial elements and are associated with vertebral anomalies. Diagnosis is made using modalities, such as barium swallow, chest CT, and MRI, or endosonography. Treatment is surgical; laparoscopic approach to excision is also possible.

Enlarged mediastinal or subcarinal lymph nodes, caused by infection (tuberculosis, histoplasmosis) or neoplasm (lymphoma), are the most common external masses that compress the esophagus and produce obstructive symptoms. Vascular anomalies can also compress the esophagus; dysphagia lusoria is a term denoting the dysphagia produced by a developmental vascular anomaly, which is often an aberrant right subclavian artery or right-sided or double aortic arch (see Chapter 432.1).

**INTRINSIC**

Intrinsic narrowing of the esophageal lumen can be congenital or acquired. The etiology is suggested by the location, the character of the lesion, and the clinical situation. The lower esophagus is the most common location for peptic strictures, which are generally somewhat ragged and several cm long. Thin membranous rings, including the Schatzki ring at the squamocolumnar junction, can also occlude this area. In the midesophagus, congenital narrowing may be associated with the esophageal atresia–tracheoesophageal fistula complex, in which some of the lesions might incorporate cartilage and might be impossible to dilate safely; alternatively, reflux esophagitis can induce a ragged and extensive narrowing that appears more proximal than the usual peptic stricture, often because of an associated hiatal hernia. Congenital webs or rings can narrow the upper esophagus. The upper esophagus can also be narrowed by an inflammatory stricture occurring after a caustic ingestion or due to epidermolysis bullosa. Cricopharyngeal achalasia can appear radiographically as a cricopharyngeal “bar” posteriorly in the upper esophagus. Eosinophilic esophagitis is one of the most common causes for esophageal obstructive symptoms. Although the pathogenesis of obstructive eosinophilic esophagitis is not yet completely explained and seems to vary among individual patients, endoscopy or radiology demonstrates stricture formation in some children with eosinophilic esophagitis, and in others a noncompliant esophagus is evident, with thickened wall layers demonstrable by ultrasonography.

*Bibliography is available at Expert Consult.*
Bibliography
Dysmotility

Seema Khan and Susan R. Orenstein

UPPER ESOPHAGEAL AND UPPER ESOPHAGEAL SPHINCTER DYSMOTILITY (STRIATED MUSCLE)

Cricopharyngeal achalasia signifies a failure of complete relaxation of the upper esophageal sphincter (UES), whereas cricopharyngeal incoordination occurs in infancy and remits spontaneously in the 1st yr of life if nutrition is maintained despite the dysphagia. In children, treatment options for non-self-limited cricopharyngeal achalasia consist of dilation, botox injection, and transcervical myotomy. It is important to evaluate such children thoroughly, including cranial MRI to detect Arnold-Chiari malformations, which can manifest in this way but are best treated by cranial decompression, rather than esophageal surgery. Cricopharyngeal spasm may be severe enough to produce posterior pharyngeal (Zenker) diverticulum above the obstructive sphincter; this entity occurs rarely in children.

Systemic causes of swallowing dysfunction that can affect the oropharynx, UES, and upper esophagus include cerebral palsy, Arnold-Chiari malformations, syringomyelia, bulbar palsy or cranial nerve defects (Möbius syndrome, transient infantile paralysis of the superior laryngeal nerve), transient pharyngeal muscle dysfunction, spinal muscular atrophy (including Werdnig-Hoffmann disease), muscular dystrophy, multiple sclerosis, infections (botulism, tetanus, poliomyelitis, diphtheria), inflammatory and autoimmune diseases (dermatomyositis, myasthenia gravis, polynuertis, scleroderma), and familial dysautonomia. All of these can produce dysphagia. Medications (nitrazepam, benzodiazepines) and tracheostomy can adversely affect the function of the UES and thereby produce dysphagia.

LOWER ESOPHAGEAL AND LOWER ESOPHAGEAL SPHINCTER DYSFUNCTION (SMOOTH MUSCLE)

Causes of dysphagia resulting from more distal primary esophageal dysmotility include achalasia, diffuse esophageal spasm, nutcracker esophagus, and hypertensive lower esophageal sphincter (LES); all but achalasia are rare in children. Secondary causes include Hirschsprung disease, pseudoobstruction, inflammatory myopathies, scleroderma, and diabetes.

Achalasia is a primary esophageal motor disorder of unknown etiology characterized by loss of LES relaxation and loss of esophageal peristalsis, both contributing to a functional obstruction of the distal esophagus. Degenerative, autoimmune (antibodies to Auerbach plexus), and infectious (Chagas disease caused by Trypanosoma cruzi) factors are possible causes. In rare cases, achalasia is familial or part of the achalasia, alacrima, and adrenal insufficiency, known as triple A syndrome or Allgrove syndrome. Pseudoachalasia refers to achalasia caused by various forms of cancer via obstruction of the gastroesophageal junction, infiltration of the submucosa and muscularis of the LES, or as part of the paraneoplastic syndrome with formation of anti-Hu antibodies. Pathologically, in achalasia, inflammation surrounds ganglion cells, which are decreased in number. There is selective loss of postganglionic inhibitory neurons that normally lead to sphincter relaxation, leaving postganglionic cholinergic neurons unopposed. This imbalance produces high basal LES pressures and insufficient LES relaxation. The loss of esophageal peristalsis can be a secondary phenomenon.

Achalasia manifests with regurgitation and dysphagia for solids and liquids and may be accompanied by undernutrition or chronic cough; retained esophageal food can produce esophagitis. The presentations of chronic regurgitation/vomiting with weight loss, and chronic cough have led to misdiagnoses of anorexia nervosa and asthma, respectively. The mean age in children is 8.8 yr, with a mean duration of symptoms before diagnosis of 23 mo; it is uncommon before school age. Chest radiograph shows an air-fluid level in a dilated esophagus. Barium fluoroscopy reveals a smooth tapering of the lower esophagus leading to the closed LES, resembling a bird’s beak (Fig. 321-1). Loss of primary peristalsis in the distal esophagus with retained food and poor emptying are often present. Manometry is the most sensitive diagnostic test; it reveals the defining features of aperistalsis in the
distal esophageal body and incomplete or absent LES relaxation, often
accompanied by high pressure LES and low-amplitude esophageal
body contractions.

The goals of achalasia therapy are relief of symptoms, improvement
of esophageal emptying, and prevention of megaesophagus. The 2 most
effective treatment options are pneumatic dilation and laparoscopic or
surgical (Heller) myotomy. Pneumatic dilation is the initial treatment
of choice, and does not preclude a future myotomy. Surgeons often
supplement a myotomy with an antireflux procedure to prevent the
gastroesophageal reflux disease that otherwise often ensues when the
spincter is rendered less competent. Laparoscopic myotomy is a par-
ticularly effective procedure in adolescent and young adult males.
Peroral endoscopic myotomy may be a feasible, safe, and an effective
alternative to the laparoscopic method. Calcium channel blockers
(nifedipine) and phosphodiesterase inhibitors offer temporary relief of
dysphagia. Endoscopic injection of the LES with botulinum toxin
counterbalances the selective loss of inhibitory neurotransmitters by
inhibiting the release of acetylcholine from nerve terminals and may
be an effective therapy. Botulinum toxin is effective in 50-65% of
patients and is expensive; half the patients might require a repeat injec-
tion within 1 yr. Most eventually require dilation or surgery.

**Diffuse esophageal spasm** causes chest pain and dysphagia and
affects adolescents and adults. It is diagnosed **manometrically** and can
be treated with nitrates or calcium-channel-blocking agents.

**Gastroesophageal reflux disease** constitutes the most common
cause of nonspecific abnormalities of esophageal motor function,
probably through the effect of the esophageal inflammation on the
musculature.

*Bibliography is available at Expert Consult.*

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*Figure 321-1* Barium esophagogram of a patient with achalasia
demonstrating dilated esophagus and narrowing at the lower esopha-
geal spincter. Note retained secretions layered on top of barium in
the esophagus.
Bibliography


Herniation of the stomach through the esophageal hiatus can occur as a common sliding hernia (type 1), in which the gastroesophageal junction slides into the thorax, or it can be paraesophageal (type 2), in which a portion of the stomach (usually the fundus) is insinuated next to the esophagus inside the gastroesophageal junction in the hiatus (Figs. 322-1 and 322-2). A combination of sliding and paraesophageal types (type 3) is present in some patients. Sliding hernias are often associated with gastroesophageal reflux, especially in developmentally delayed children. The relationship to hiatal hernias in adults is unclear. Diagnosis is usually made by an upper gastrointestinal series and upper endoscopy. Medical treatment is not directed at the hernia but at the gastroesophageal reflux, unless failure of medical therapy prompts correction of the hernia at the time of fundoplication.

A paraesophageal hernia can be an isolated congenital anomaly or associated with gastric volvulus, or it may be encountered after fundoplication for gastroesophageal reflux, especially if the edges of a dilated esophageal diaphragmatic hiatus have not been approximated. Fullness after eating and upper abdominal pain are the usual symptoms. Infarction of the herniated stomach is rare.
Gastroesophageal reflux disease (GERD) is the most common esophageal disorder in children of all ages. Gastroesophageal reflux (GER) signifies the retrograde movement of gastric contents across the lower esophageal sphincter (LES) into the esophagus, which occurs physiologically every day in all infants, older children, and adults. Physiologic GER is exemplified by the effortless regurgitation of normal infants. The phenomenon becomes pathologic GERD in infants and children who manifest or report bothersome symptoms because of frequent or persistent GER, producing esophagitis-related symptoms, or extraesophageal presentations, such as respiratory symptoms or nutritional effects.

**PATHOPHYSIOLOGY**

Factors determining the esophageal manifestations of reflux include the duration of esophageal exposure (a product of the frequency and duration of reflux episodes), the causticity of the refluxate, and the susceptibility of the esophagus to damage. The LES, defined as a high-pressure zone by manometry, is supported by the crura of the diaphragm at the gastroesophageal junction, together with valve-like functions of the esophagogastric junction anatomy, form the antireflux barrier. In the context of even the normal intraabdominal pressure augmentations that occur during daily life, the frequency of reflux episodes is increased by insufficient LES tone, by abnormal frequency of LES relaxations, and by hiatal herniation that prevents the LES pressure from being proportionately augmented by the crura during abdominal straining. Normal intraabdominal pressure augmentations may be further exacerbated by straining or respiratory efforts. The duration of reflux episodes is increased by lack of swallowing (e.g., during sleep) and by defective esophageal peristalsis. Vicious cycles ensue because chronic esophagitis produces esophageal peristaltic dysfunction (low-amplitude waves, propagation disturbances), decreased LES tone, and inflammatory esophageal shortening that induces hiatal herniation, all worsening reflux.

**Transient LES relaxation (TLESR)** is the primary mechanism allowing reflux to occur, and is defined as simultaneous relaxation of both LES and the surrounding crura. TLESRs occur independent of swallowing, reduce LES pressure to 0-2 mm Hg (above gastric), and last 10-60 sec; they appear by 26 wk of gestation. A vagovagal reflex, composed of afferent mechanoreceptors in the proximal stomach, a brainstem pattern generator, and efferents in the LES, regulates TLESRs. Gastric distention (postprandially, or from abnormal gastric emptying or air swallowing) is the main stimulus for TLESRs. Whether GERD is caused by a higher frequency of TLESRs or by a greater incidence of reflux during TLESRs is debated; each is likely in different persons. Straining during a TLESR makes reflux more likely, as do positions that place the gastroesophageal junction below the air-fluid interface in the stomach. Other factors influencing gastric pressure–volume dynamics, such as increased movement, straining, obesity, large-volume or hyperosmolar meals, gastroparesis, a large sliding hiatal hernia, and increased respiratory effort (coughing, wheezing) can have the same effect.

**EPIDEMIOLOGY AND NATURAL HISTORY**

Infant reflux becomes evident in the 1st few mo of life, peaks at 4 mo, and resolves in up to 88% by 12 mo and in nearly all by 24 mo. Symptoms in **older children** tend to be chronic, waxing and waning, but completely resolving in no more than half, which resembles adult patterns (Table 323-1). The histologic findings of esophagitis persist in infants who have naturally resolving symptoms of reflux. GERD likely has genetic predispositions: family clustering of GERD symptoms, endoscopic esophagitis, hiatal hernia, Barrett esophagus, and adenocarcinoma have been identified. As a continuously variable and common disorder, complex inheritance involving multiple genes and environmental factors is likely. Genetic linkage is indicated by the strong evidence of GERD in studies with monozygotic twins. A pediatric autosomal dominant form with otolaryngologic and respiratory manifestations has been located to chromosome 13q14, and the locus is termed GERD1.

**CLINICAL MANIFESTATIONS**

Most of the common clinical manifestations of esophageal disease can signify the presence of GERD and are generally thought to be mediated by the pathogenesis involving acid GER (Table 323-2). Although less noxious for the esophageal mucosa, nonacid reflux events are recognized to play an important role in extraesophageal disease manifestations. **Infantile reflux** manifests more often with regurgitation (especially postprandially), signs of esophagitis (irritability, arching, choking, gagging, feeding aversion), and resulting failure to thrive; symptoms resolve spontaneously in the majority of infants by 12-24 mo. **Older children** can have regurgitation during the preschool years; this complaint diminishes somewhat as children age, and complaints of abdominal and chest pain supervene in later childhood and adolescence. Occasional children present with food refusal or neck contortions (arching, turning of head) designated **Sandifer syndrome**. The respiratory presentations are also age dependent: GERD in infants can manifest as obstructive apnea or as stridor or lower airway disease in which reflux complicates primary airway disease such as laryngomalacia or bronchopulmonary dysplasia. Otitis media, sinusitis, lymphoid hyperplasia, hoarseness, vocal cord nodules, and laryngeal edema have all been associated with GERD. Airway manifestations in older children are more commonly related to asthma or to otolaryngologic disease such as laryngitis or sinusitis. Despite the high prevalence of GERD symptoms in asthmatic children, data showing direction of causality are conflicting.

**DIAGNOSIS**

For most of the typical GERD presentations, particularly in older children, a thorough history and physical examination suffice initially to reach the diagnosis. This initial evaluation aims to identify the pertinent positives in support of GERD and its complications and the negatives that make other diagnoses unlikely. The history may be facilitated and standardized by questionnaires (e.g., the Infant Gastroesophageal Reflux Questionnaire, the I-GERQ, and its derivative, the I-GERQ-R), which also permit quantitative scores to be evaluated for their diagnostic discrimination and for evaluative assessment of improvement or worsening of symptoms. The clinician should be alerted to the possibility of other important diagnoses in the presence of any alarm or warning signs: bilious emesis, frequent projectile emesis, gastrointestinal bleeding, lethargy, organomegaly, abdominal distention, micro or macrocephaly, hepatosplenomegaly, failure to thrive, diarrhea, fever, bulging fontanelle, and seizures. The important differential diagnoses to consider in the evaluation of an infant or a child with chronic vomiting are milk and other food allergies, eosinophilic esophagitis, pyloric stenosis, intestinal obstruction (especially malrotation with intermittent volvulus), nonsesophageal inflammatory diseases, infections, inborn errors of metabolism, hydrenephrosis, increased intracranial pressure, ruminination, and bulimia. Focused diagnostic testing, depending on the presentation and the differential diagnosis, can then supplement the initial examination.

Most of the esophageal tests are of some use in particular patients with suspected GERD. **Contrast (usually barium) radiographic** study of the esophagus and upper gastrointestinal tract is performed in children with vomiting and dysphagia to evaluate for achalasia, esophageal strictures and stenosis, hiatal hernia, and gastric outlet or intestinal obstruction (Fig. 323-1). It has poor sensitivity and specificity in the diagnosis of GERD as a result of its limited duration and the inability
Table 323-1  Symptoms According to Age

<table>
<thead>
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<th>CHILDREN</th>
<th>ADOLESCENTS AND ADULTS</th>
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<td>+</td>
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<tr>
<td>Heartburn/pyrosis</td>
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<td>+</td>
<td>+++</td>
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<tr>
<td>Epigastric pain</td>
<td>?</td>
<td>+</td>
<td>++</td>
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<tr>
<td>Chest pain</td>
<td>?</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>?</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Dental erosions/water brush</td>
<td>?</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Hoarseness/globus pharyngeus</td>
<td>?</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Chronic asthma/sinusitis</td>
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<td>+</td>
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<tr>
<td>Laryngostenosis/vocal nodule problems</td>
<td>–</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Stenosis</td>
<td>–</td>
<td>(+)</td>
<td>+</td>
</tr>
<tr>
<td>Barrett/esophageal adenocarcinoma</td>
<td>–</td>
<td>(+)</td>
<td>+</td>
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+++ Very common; ++ common; + possible; (+) rare; – absent; ? unknown; ALTE, apparent life-threatening event.


to differentiate physiologic GER from GERD. Furthermore, contrast radiography neither accurately assesses mucosal inflammation nor correlates with severity of GERD.

Extended esophageal pH monitoring of the distal esophagus, no longer considered the sine qua non of a GERD diagnosis, provides a quantitative and sensitive documentation of acidic reflux episodes, the most important type of reflux episodes for pathologic reflux. The distal esophageal pH probe is placed at a level corresponding to 87% of the nares-LES distance, based on regression equations using the patient’s height, on fluoroscopic visualization, or on manometric identification of the LES. Normal values of distal esophageal acid exposure (pH < 4) are generally established as <5-8% of the total monitored time, but these quantitative normals are insufficient to establish or disprove a diagnosis of pathologic GERD. The most important indications for esophageal pH monitoring are for assessing efficacy of acid suppression during treatment, evaluating apneic episodes in conjunction with a pneumogram and perhaps impedance, and evaluating atypical GERD presentations such as chronic cough, stridor, and asthma. Dual pH probes, adding a proximal esophageal probe to the standard distal one, are used in the diagnosis of extraesophageal GERD, identifying upper esophageal acid exposure times of 1% of the total time as threshold values for abnormality.

Endoscopy allows diagnosis of erosive esophagitis (Fig. 323-2) and complications such as strictures or Barrett esophagus; esophageal biopsies can diagnose histologic reflux esophagitis in the absence of erosions while simultaneously eliminating allergic and infectious causes. Endoscopy is also used therapeutically to dilate reflux-induced strictures. Radionucleotide scintigraphy using technetium can demonstrate aspiration and delayed gastric emptying when these are suspected.

The multichannel intraluminal impedance is a cumbersome test, but with potential applications both for diagnosing GERD and for understanding esophageal function in terms of bolus flow, volume clearance, and (in conjunction with manometry) motor patterns associated with GERD. Owing to the multiple sensors and a distal pH sensor, it is possible to document acidic reflux (pH < 4), weakly acidic reflux (pH 4-7), and weakly alkaline reflux (pH > 7) with multichannel intraluminal impedance. It is an important tool in those with respiratory symptoms, particularly for the determination of nonacid reflux, but must be cautiously applied in routine clinical evaluation because of limited evidence-based parameters for GERD diagnosis and symptom association.

Laryngotracheobronchoscopy evaluates for visible airway signs that are associated with extraesophageal GERD, such as posterior laryngeal inflammation and vocal cord nodules; it can permit diagnosis of silent aspiration (during swallowing or during reflux) by bronchoalveolar lavage with subsequent quantification of lipid-laden macrophages in airway secretions. Detection of pepsin in tracheal fluid is a
marker of reflux-associated aspiration of gastric contents. Esophageal manometry permits evaluation for dysmotility, particularly in preparation for antireflux surgery.

**Empirical antireflux therapy**, using a time-limited trial of high-dose proton pump inhibitor (PPI), is a cost-effective strategy for diagnosis in adults; although not formally evaluated in older children, it has also been applied to this age group. Failure to respond to such empirical treatment, or a requirement for the treatment for prolonged periods, mandates formal diagnostic evaluation.

**MANAGEMENT**

Conservative therapy and lifestyle modifications that form the foundation of GERD therapy can be effectively implemented through education and reassurance for parents. Dietary measures for infants include normalization of any abnormal feeding techniques, volumes, and frequencies. Thickening of feeds or use of commercially prethickened formulas increases the percentage of infants with no regurgitation, decreases the frequency of daily regurgitation and emesis, and increases the infant's weight gain. However, caution should be exercised when managing preterm infants because of the possible association between xanthan gum-based thickened feeds and necrotizing enterocolitis. The evidence does not clearly favor 1 type of thickener over another; the addition of a Tbsp of rice cereal per oz of formula results in a greater caloric density (30 kcal/oz) and reduced crying time, although it might not modify the number of nonregurgitant reflux episodes. A short trial of a hypoallergenic diet in infants may be used to exclude milk or soy protein allergy before pharmacotherapy. A combination of modified feeding volumes, hydrolyzed infant formulas, proper positioning, and avoidance of smoke exposure satisfactorily improve GERD symptoms in 24-59% infants with GERD. Older children should be counseled to

**Table 323-2**

<table>
<thead>
<tr>
<th>Symptoms</th>
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<tbody>
<tr>
<td>Recurrent regurgitation with or without vomiting</td>
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<tr>
<td>Weight loss or poor weight gain</td>
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<tr>
<td>Irritability in infants</td>
</tr>
<tr>
<td>Ruminative behavior</td>
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<tr>
<td>Heartburn or chest pain</td>
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<tr>
<td>Hematemesis</td>
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<tr>
<td>Dysphagia, odynophagia</td>
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<tr>
<td>Wheezing</td>
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<tr>
<td>Stridor</td>
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<tr>
<td>Cough</td>
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<tr>
<td>Hoarseness</td>
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<table>
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<tr>
<th>Signs</th>
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<tr>
<td>Esophagitis</td>
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<tr>
<td>Esophageal stricture</td>
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<tr>
<td>Barrett esophagus</td>
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<td>Laryngeal/pharyngeal inflammation</td>
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<tr>
<td>Recurrent pneumonia</td>
</tr>
<tr>
<td>Anemia</td>
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<tr>
<td>Dental erosion</td>
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<tr>
<td>Feeding refusal</td>
</tr>
<tr>
<td>Dystonic neck posturing (Sandifer syndrome)</td>
</tr>
<tr>
<td>Apnea spells</td>
</tr>
<tr>
<td>Apparent life-threatening events</td>
</tr>
</tbody>
</table>


**Figure 323-1** Barium esophagogram demonstrating free gastroesophageal reflux. Note stricture caused by peptic esophagitis. Longitudinal gastric folds above the diaphragm indicate the unusual presence of an associated hiatal herna.

**Figure 323-2** Endoscopic image of a normal esophagus **(A)** and erosive peptic esophagitis **(B)**.
avoid acidic or reflux-inducing foods (tomatoes, chocolate, mint) and beverages (juices, carbonated and caffeinated drinks, alcohol). Weight reduction for obese patients and elimination of smoke exposure are other crucial measures at all ages.

Positioning measures are particularly important for infants, who cannot control their positions independently. Seated position worsens infant reflux and should be avoided in infants with GERD. Esophageal pH monitoring demonstrates more reflux episodes in infants in supine and side positions compared with the prone position, but evidence that the supine position reduces the risk of sudden infant death syndrome has led the American Academy of Pediatrics and the North American Society of Pediatric Gastroenterology and Nutrition to recommend supine positioning during sleep. When the infant is awake and observed, prone position and upright carried position can be used to minimize reflux. Lying in the flat supine position and semi-seated positions (e.g., car seats, infant carriers) in the postpartum period are considered provocative positions for GER and therefore should be avoided. The efficacy of positioning for older children is unclear, but some evidence suggests a benefit to left side position and head elevation during sleep. The head should be elevated by elevating the head of the bed, rather than using excess pillows, to avoid abdominal flexion and compression that might worsen reflux.

Pharmacotherapy is directed at ameliorating the acidity of the gastric contents or at promoting their aboral movement, and should be considered for those symptomatic infants and children who are either highly suspected or proven to have GERD. Antacids are the most commonly used antireflux therapy and are readily available over the counter. They provide rapid but transient relief of symptoms by acid neutralization. The long-term regular use of antacids cannot be recommended because of side effects of diarrhea (magnesium antacids) and constipation (aluminum antacids) and rare reports of more serious side effects of chronic use.

Histamine-2 receptor antagonists (H2RAs: cimetidine, famotidine, nizatidine, and ranitidine) are widely used antisecretory agents that act by selective inhibition of histamine receptors on gastric parietal cells. There is a definite benefit of H2RAs in treatment of mild-to-moderate reflux esophagitis. H2RAs have been recommended as first-line therapy because of their excellent overall safety profile, but they are superseded by PPIs in this role, as increased experience with pediatric use and safety, FDA approval, and pediatric formulations and dosing are available.

PPIs (omeprazole, lansoprazole, pantoprazole, rabeprazole, and esomeprazole) provide the most potent antireflux effect by blocking the hydrogen–potassium adenosine triphosphatase channels of the final common pathway in gastric acid secretion. PPIs are superior to H2RAs in the treatment of severe and erosive esophagitis. Pharmacodynamic studies indicate that children require higher doses of PPIs than adults on a per-weight basis. The use of PPIs to treat infants and children deemed to have GERD on the basis of symptoms is now the standard of care. An important systematic review of the efficacy and safety of PPI therapy in pediatric GERD reveals no clear benefit for PPI over placebo use in suspected infantile GERD (crying, arching behavior). Limited pediatric data are available to draw definitive conclusions about potential complications implicated with PPI use, such as respiratory infections, Clostridium difficile infection, bone fractures (noted in adults), and hypomagnesemia.

Prokinetic agents available in the United States include metoclopramide (dopamine-2 and 5-HT, antagonist), bethanechol (cholinergic agonist), and erythromycin (motilin receptor agonist). Most of these increase LES pressure; some improve gastric emptying or esophageal clearance. None affects the frequency of TLESRs. The available controlled trials have not demonstrated much efficacy for GERD. In 2009, the FDA announced a black box warning for metoclopramide, linking its chronic use (longer than 3 mo) with tardive dyskinesia, the rarely reversible movement disorder. Baclofen is a centrally acting γ-aminobutyric acid agonist that decreases reflux by decreasing TLESRs in healthy adults and in a small number of neurologically impaired children with GERD. New agents of great interest include peripherally acting γ-aminobutyric acid agonists devoid of central side effects, and metabotropic glutamate receptor 5 antagonists that are reported to reduce TLESRs but are as yet inadequately studied for this indication in children.

Surgery, usually fundoplication, is effective therapy for intractable GERD in children, particularly those with refractory esophagitis or strictures and those at risk for significant morbidity from chronic pulmonary disease. It may be combined with a gastrostomy for feeding or venting. The availability of potent acid-suppressing medication mandates more-rigorous analysis of the relative risks (or costs) and benefits of this relatively irreversible therapy in comparison to long-term pharmacotherapy. Some of the risks of fundoplication include a wrap that is “too tight” (producing dysphagia or gas-bloat) or “too loose” (and thus incompetent). Surgeons may choose to perform a “tight” (360 degrees, Nissen) or variations of a “loose” (<360 degrees, Thal, Toupet, Boix-Ochoa) wrap, or to add a gastric drainage procedure (pyloroplasty) to improve gastric emptying, based on their experience and the patient’s disease. Preoperative accuracy of diagnosis of GERD and the skill of the surgeon are 2 of the most important predictors of successful outcome. Long-term studies suggest that fundoplications often become incompetent in children, as in adults, with reflux recurrence rates of up to 14% for Nissen and up to 20% for loose wraps; this fact currently combines with the potency of PPI therapy that is now available to shift practice toward long-term pharmacotherapy in many cases. Fundoplication procedures may be performed as open operations, by laparoscopy, or by endoluminal (gastroplication) techniques. Pediatric experience is limited with endoscopic application of radiofrequency therapy (Stretta procedure) to a 2-3 cm area of the LES and cardia to create a high-pressure zone to reduce reflux.

Bibliography is available at Expert Consult.

323.1 Complications of Gastroesophageal Reflux Disease

Seema Khan and Susan R. Orenstein

ESOPHAGEAL: ESOPHAGITIS AND SEQUELAE—STRICUTURE, BARRETT ESOPHAGUS, ADENOCARCINOMA

Esophagitis can manifest as irritability, arching, and feeding aversion in infants; chest or epigastric pain in older children; and, rarely, as hematemesis, anemia, or Sandifer syndrome at any age. Erosive esophagitis is found in approximately 12% of children with GERD symptoms and is more common in boys, older children, neurologically abnormal children, children with severe chronic respiratory disease, and in those with hiatal hernia. Prolonged and severe esophagitis leads to formation of strictures, generally located in the distal esophagus, producing dysphagia, and requiring repeated esophageal dilations and often fundoplication. Long-standing esophagitis predisposes to metaplastic transformation of the normal esophageal squamous epithelium into intestinal columnar epithelium, termed Barrett esophagus, a precursor of esophageal adenocarcinoma. A large multicenter prospective study of 840 consecutive children who underwent elective endoscopies reported a 25.7% prevalence for reflux esophagitis, and a mere 0.12% for Barrett esophagus in children without neurologic disorders or tracheoesophageal anomalies. Both Barrett esophagus and adenocarcinoma occur more in white males and in those with increased duration, frequency, and severity of reflux symptoms. This transformation increases with age to plateau in the 5th decade; adenocarcinoma is thus rare in childhood. Barrett esophagus, uncommon in children, warrants periodic surveillance biopsies, aggressive pharmacotherapy, and fundoplication for progressive lesions.

NUTRITIONAL

Esophagitis and regurgitation may be severe enough to induce failure to thrive because of caloric deficits. Enteral (nasogastric or nasojejunal, or percutaneous gastric or jejunal) or parenteral feedings are sometimes required to treat such deficits.
Bibliography

EXTRAESOPHAGEAL: RESPIRATORY ("ATYPICAL") PRESENTATIONS

GERD should be included in the differential diagnosis of children with unexplained or refractory otolaryngologic and respiratory complaints. GERD can produce respiratory symptoms by direct contact of the refluxed gastric contents with the respiratory tract (aspiration, laryngeal penetration, or microaspiration) or by reflexive interactions between the esophagus and respiratory tract (inducing laryngeal closure or bronchospasm). Often, GERD and a primary respiratory disorder, such as asthma, interact and a vicious cycle between them worsens both diseases. Many children with these extraesophageal presentations do not have typical GERD symptoms, making the diagnosis difficult. These atypical GERD presentations require a thoughtful approach to the differential diagnosis that considers a multitude of primary otolaryngologic (infections, allergies, postnasal drip, voice overuse) and pulmonary (asthma, cystic fibrosis) disorders. Therapy for the GERD must be more intense (usually incorporating a PPI) and prolonged (usually at least 3–6 mo). Subspecialist assistance from the perspective of the airway disease (otolaryngology, pulmonology) and the reflux disease (gastroenterology) is often warranted for specialized diagnostic testing and for optimizing intensive management.

APNEA AND STRIDOR

These upper airway presentations have been linked with GERD in case reports and epidemiologic studies; temporal relationships between them and reflux episodes have been demonstrated in some patients by esophageal pH–multichannel intraluminal impedance studies, and a beneficial response to therapy for GERD provides further support in a number of case series. An evaluation of 1,400 infants with apnea attributed the apnea to GERD in 50%, but other studies have failed to find an association. Apnea and apparent life-threatening event caused by reflux is generally obstructive, owing to laryngospasm that may be conceived of as an abnormally intense protective reflex. At the time of such apnea, infants have often been provocatively positioned (supine or flexed seated), have been recently fed, and have shown signs of obstructive apnea, with unproductive respiratory efforts. The evidence suggests that for the large majority of infants presenting with apnea and an apparent life-threatening event, GERD is not causal. Stridor triggered by reflux generally occurs in infants anatomically predisposed toward stridor (laryngomalacia, micrognathia). Spasmodic croup, an episodic frightening upper airway obstruction, can be an analogous condition in older children. Esophageal pH probe studies might fail to demonstrate linkage of these manifestations with reflux owing to the buffering of gastric contents by infant formula and the episodic nature of the conditions. Pneumograms can fail to identify apnea if they are not designed to identify obstructive apnea by measuring nasal airflow.

Reflux laryngitis and other otolaryngologic manifestations (also known as laryngopharyngeal reflux) can be attributed to GERD. Hoarseness, voice fatigue, throat clearing, chronic cough, pharyngitis, sinusitis, otitis media, and a sensation of globus have been cited. Laryngopharyngeal signs of GERD include edema and hyperemia (of the posterior surface), contact ulcers, granulomas, polyps, subglottic stenosis, and interarytenoid edema. The paucity of well-controlled evaluations of the association contributes to the skepticism with which these associations may be considered. Other risk factors irritating the upper respiratory passages can predispose some patients with GERD to present predominantly with these complaints.

Many studies have reported a strong association between asthma and reflux as determined by history, pH–multichannel intraluminal impedance, endoscopy, and esophageal histology. GERD symptoms are present in an average of 23% (19–80%) of children with asthma as observed in a systematic review of 19 studies examining the prevalence of GERD in asthmatics. The review also reported abnormal pH results in 63%, and esophagitis in 35% of asthmatic children. However, this association does not clarify the direction of causality in individual cases and thus does not indicate which patients with asthma are likely to benefit from anti-GERD therapy. Children with asthma who are particularly likely to have GERD as a provocative factor are those with symptoms of reflux disease, those with refractory or steroid-dependent asthma, and those with nocturnal worsening of asthma. Endoscopic evaluation that discloses esophageal sequelae of GERD provides an impetus to embark on the aggressive (high dose and many months’ duration) therapy of GERD.

Dental erosions constitute the most common oral lesion of GERD, the lesions being distinguished by their location on the lingual surface of the teeth. The severity seems to correlate with the presence of reflux symptoms and the presence of an acidic milieu as the result of reflux in the proximal esophagus and oral cavity. The other common factors that can produce similar dental erosions are juice consumption and bulimia.

Bibliography is available at Expert Consult.
Bibliography
Eosinophilic Esophagitis (EoE) is a chronic esophageal disorder characterized by infiltration of the esophageal epithelium by eosinophils, typically in a density exceeding 15 per high-power field. While infants and toddlers present commonly with vomiting, feeding problems, and poor weight gain, older children and adolescents usually experience solid food dysphagia with occasional food impactions or strictures and may complain of chest or epigastric pain. Most patients are male. The mean age at diagnosis is 7 yr (range: 1-17 yr), and the duration of symptoms is 3 yr. Many patients have other atopic diseases (or a positive family history) and associated food allergies; laboratory abnormalities can include peripheral eosinophilia and elevated immunoglobulin E (IgE) levels. The pathogenesis involves mainly T-helper type 2 cytokine-mediated pathways leading to production of a potent eosinophil chemoattractant, eotaxin-3, by esophageal epithelium. Endoscopically, the esophagus presents a granular, furrowed, ringed, or exudative appearance (Fig. 324-1); esophageal histology reveals eosinophilia, with cutpoints for diagnosis variably chosen at 15-20/high-power field. Up to 30% children with EoE have grossly normal esophageal mucosa. EoE is differentiated from gastroesophageal reflux disease by its general lack of erosive esophagitis, its greater eosinophil density, and its normal esophageal pH-multichannel intraluminal impedance results. A favorable response to proton pump inhibitor therapy should no longer be considered diagnostic of gastroesophageal reflux disease, as a subgroup of EoE patients with normal esophageal pH-multichannel intraluminal impedance also demonstrate histologic response, and constitute a proton pump inhibitor–responsive EoE group. This response may be because of an antieosinophil effect of the proton pump inhibitor class that is mediated by inhibition of eotaxin-3 secretion. Gastroesophageal reflux disease may be an important coexisting diagnosis. Evaluation of EoE should include a thorough search for food and environmental allergies via skin prick (IgE mediated) and patch (non–IgE mediated) tests.
followed by progressive retrosternal pain, odynophagia, and dysphagia. Endoscopy shows a focal lesion often localized to one of the anatomic narrowed regions of the esophagus or to an unsuspected pathologic narrowing. Treatment is supportive; lacking much evidence, antacids, topical anesthetics, and bland or liquid diets are often used.

*Bibliography is available at Expert Consult.*

**Figure 324-1** Endoscopic image of eosinophilic esophagitis with characteristic mucosal appearance of furrowing and white specks.

**Treatment** involves dietary restrictions that take one of 3 forms: elimination diets guided by circumstantial evidence and food allergy test results; “6 food elimination diet” removing the major food allergens (milk, soy, wheat, egg, peanuts and tree nuts, seafood); and elemental diet composed exclusively of an amino acid–based formula. Successful clinical and histologic remission is observed in 70-98% patients. Topical and systemic corticosteroids have been used successfully for nonresponders and for nonallergic (“primary”) EoE, with symptomatic and histologic remission rates reaching 90%. Therapies under investigation include anti–interleukin-5 antibody (mepolizumab, reslizumab). Little is yet known about its natural history, but it seems that EoE is a chronic remitting and relapsing disorder with a potential for complications such as stricture formation.

**INFECTIVE ESOPHAGITIS**
Uncommon, and most often affecting immunocompromised children, infective esophagitis is caused by fungal agents, such as *Candida* and *Torulopsis glabrata*; viral agents, such as herpes simplex, cytomegalovirus, HIV, and varicella zoster; and, rarely, bacterial infections, including diphtheria and tuberculosis. The typical presenting signs and symptoms are odynophagia, dysphagia, and retrosternal pain; there may also be fever, nausea, and vomiting. Candida is the leading cause of infective esophagitis in immunocompetent and immunocompromised children, and presents with concurrent oropharyngeal infection in the majority of immunocompromised patients. Esophageal viral infections can also manifest in immunocompetent hosts as an acute febrile illness. Infectious esophagitis, like other forms of esophageal inflammation, occasionally progresses to esophageal stricture. Diagnosis of infectious esophagitis is made by endoscopy, usually notable for white plaques in candida, multiple superficial ulcers in herpes simplex virus, and single deep ulcer in cytomegalovirus, and histopathologic examination; adding polymerase chain reaction, tissue-viral culture, and immunocytochemistry enhances the diagnostic sensitivity and precision. Treatment is with appropriate antimicrobial agents, analgesics, and antacids.

**“PILL” ESOPHAGITIS**
This acute injury is produced by contact with a damaging agent. Medications implicated in “pill” esophagitis include tetracycline, potassium chloride, ferrous sulfate, nonsteroidal antiinflammatory medications, and alendronate. Most often the offending tablet is ingested at bedtime with inadequate water. This practice often produces acute discomfort
Bibliography
Chapter 325

**Esophageal Perforation**

Seema Khan and Susan R. Orenstein

The majority of esophageal perforations in children are from blunt trauma (automobile injury, gunshot wounds, child abuse) or are iatrogenic. Cardiac massage, the Heimlich maneuver, nasogastric tube placement, traumatic laryngoscopy or endotracheal intubation, excessively vigorous postpartum suctioning of the airway during neonatal resuscitation, difficult upper endoscopy, sclerotherapy of esophageal varices, esophageal compression by a cuffed endotracheal tube, and dilation for therapy of achalasia and strictures have all been implicated. Esophageal rupture has followed forceful vomiting in patients with anorexia and has followed esophageal injury due to caustic ingestion, foreign body ingestion, food impactions, pill esophagitis, or eosinophilic esophagitis. Drinking cold, carbonated beverages rapidly is also known to cause esophageal perforation.

Spontaneous esophageal rupture (Boerhaave syndrome) is less common and is associated with sudden increases in intraesophageal pressure wrought by situations such as vomiting, coughing, or straining at stool. Children and adults with eosinophilic esophagitis have also been described with Boerhaave syndrome in the setting of forceful emesis in the aftermath of esophageal food impaction. In older children, as in adults, the tear occurs on the distal left lateral esophageal wall, because the smooth muscle layer here is weakest; in neonates (neonatal Boerhaave syndrome), spontaneous rupture is on the right.

Symptoms of esophageal perforation include pain, neck tenderness, dysphagia, subcutaneous crepitus, fever, and tachycardia; several patients with cervical perforations have displayed cold water polydipsia in an attempt to soothe pain in the throat. Perforations in the proximal thoracic esophagus tend to create signs (pneumothorax, effusions) in the left chest, whereas the signs of distal tears are more often on the right. Cervical spine and chest radiographs are often diagnostic, showing mediastinal widening or paracervical free air. If these x-rays are normal, an esophagogram using water-soluble contrast media should be performed, but esophagograms miss >30% of cervical perforations. Therefore, a negative water-soluble contrast esophagogram should be followed by a barium study; the greater density of barium can better demonstrate a small defect, though with a higher risk of inflammatory mediastinitis. Endoscopy may also be useful but carries a 30% false-negative rate. CT of the chest can assist in difficult cases.

Treatment must be individualized. Small tears in contained perforations with minimal mediastinal contamination in hemodynamically stable patients can be treated conservatively with broad-spectrum antibiotics, nothing given orally, gastric drainage, and parenteral nutrition. Chest exploration and direct surgical repair is infrequently indicated these days. Mortality rates range between 20% and 28%, with poor prognosis correlated with delayed diagnosis and interventions.

Bibliography is available at Expert Consult.
Bibliography
Esophageal varices form in adults with portal hypertension with hepatic venous pressure gradient above 10 mm Hg and pose a risk for bleeding at above 12 mm Hg (see Chapter 367). Spontaneous decompression of this hypertension through portosystemic collateral circulation via the coronary vein, in conjunction with the left gastric veins, gives rise to esophageal varices. Most esophageal varices are “uphill varices”; less commonly, those that arise in the absence of portal hypertension and with superior vena cava obstruction are “downhill varices.” Their treatment is directed at the underlying cause of the superior vena cava abnormality. Hemorrhage from esophageal varices is the major cause of morbidity and mortality from portal hypertension. Presentation is with significant hematemesis and melena; whereas most patients have liver disease, some children with entities such as extrahepatic portal venous thrombosis might have been previously asymptomatic. Any child with hematemesis and splenomegaly should be presumed to have esophageal variceal bleeding until proved otherwise.

Upper endoscopy is the preferred diagnostic test for esophageal varices, as it provides definitive diagnosis and delineation of details that aid in predicting the risk for bleeding, as well as in enabling therapy for acute bleeding episodes via either sclerotherapy or band ligation. A report comprising a large series of children with biliary atresia and portal hypertension described endoscopic findings of large varices, red marks, and the presence of gastric varices as predictive of bleeding. Non-invasive methods of evaluating varices include barium contrast studies, ultrasound, computerized tomography, magnetic resonance, and elastography, but they are not recommended for routine diagnostic evaluation because of suboptimal accuracy compared to endoscopy.

Primary prophylaxis with the goal of preventing an initial hemorrhage can decrease the incidence of esophageal bleeding; the various modalities used are nonselective β blockade (e.g., propranolol or nadolol), sclerotherapy, ligation, and portosystemic shunt surgery. Treated patients can bleed from congestive gastropathy, and no improvement in survival rate may be seen. Endoscopic variceal ligation in adults reduces the risk of first-time variceal bleeding when compared with untreated controls as well as patients treated with β blockade; a decrease in mortality is only noted in comparison to the control group (see Chapter 367). The management of acute variceal bleeding must include attention to hemodynamic stability through blood transfusion, vasoactive drugs (e.g., octreotide), short-term antibiotic use, and endoscopy to perform ligation or sclerotherapy, as needed. Transjugular intrahepatic portosystemic shunt should be considered for variceal bleeding refractory to medical and endoscopic therapy. Secondary prophylaxis to reduce recurrence of bleeding uses nonselective β blockade and obliteration of varices through serial treatment via ligation or sclerotherapy. The only randomized controlled pediatric study has shown superiority of ligation over sclerotherapy in reducing the risk for rebleeding and complications.

Bibliography is available at Expert Consult.
Bibliography
Ingestions

327.1 Foreign Bodies in the Esophagus

Seema Khan and Susan R. Orenstein

The majority (80%) of foreign-body ingestions occur in children, most of whom are between 6 mo and 3 yr of age. Older children and adolescents with developmental delays and those with psychiatric disorders are also at increased risk. The presentation of a foreign body lodged in the esophagus constitutes an emergency and is associated with significant morbidity and mortality because of the potential for perforation and sepsis. Coins and small toy items are the most commonly ingested foreign bodies. Food impactions are less common in children than in adults, and usually occur in children in association with eosinophilic esophagitis, repair of esophageal atresia, and Nissen fundoplication. Most esophageal foreign bodies lodge at the level of the cricopharyngeus (upper esophageal sphincter), the aortic arch, or just superior to the diaphragm at the gastroesophageal junction (lower esophageal sphincter).

At least 30% of children with esophageal foreign bodies may be totally asymptomatic, so any history of foreign body ingestion should be taken seriously and investigated. An initial bout of choking, gagging, and coughing may be followed by excessive salivation, dysphagia, food refusal, emesis, or pain in the neck, throat, or sternal notch regions. Respiratory symptoms such as stridor, wheezing, cyanosis, or dyspnea may be encountered if the esophageal foreign body impinges on the larynx or membranous posterior tracheal wall. Cervical swelling, erythema, or subcutaneous crepitations suggest perforation of the oropharynx or proximal esophagus.

Evaluation of the child with a history of foreign body ingestion starts with plain anteroposterior radiographs of the neck, chest, and abdomen, along with lateral views of the neck and chest. The flat surface of a coin in the esophagus is seen on the anteroposterior view and the edge on the lateral view (Fig. 327-1). The reverse is true for coins lodged in the trachea; here, the edge is seen anteroposteriorly and the flat side is seen.
The Digestive System

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In anticipation of passage into the stomach. If there are no problems in handling secretions, meat impactions can be observed for up to 12 hr. In patients without prior esophageal surgeries, glucagon (0.05 mg/kg IV) can sometimes be useful in facilitating passage of distal esophageal food boluses by decreasing the lower esophageal sphincter pressure. The use of meat tenderizers or gas-forming agents can lead to perforation and are not recommended. An alternative technique for removing esophageal coins impacted for <24 hr, performed most safely by experienced radiology personnel, consists of passage of a Foley catheter beyond the coin at fluoroscopy, inflating the balloon, and then pulling the catheter and coin back simultaneously with the patient in a prone oblique position. Concerns about the lack of direct mucosal visualization and, when tracheal intubation is not used, the lack of airway protection prompt caution in the use of this technique. Bougienage of esophageal coins toward the stomach in selected uncomplicated pediatric cases has been suggested to be an effective, safe, and economical modality where endoscopy might not be routinely available.

Bibliography is available at Expert Consult.

327.2 Caustic Ingestions
Seema Khan and Susan R. Orenstein

Ingestion of caustic substances is a worldwide public health problem accounting for a significant burden on healthcare resources. According to an inpatient database of U.S. pediatric hospital discharges in 2009, the estimated number of caustic ingestions was 807 (95% CI, 731-882) cases, amounting to $22,900,000 in total hospital charges. The medical sequelae of caustic ingestions are esophagitis, necrosis, perforation, and stricture formation (see Chapter 63). Most cases (70%) are accidental ingestions of liquid alkali substances that produce severe, deep liquefaction necrosis; drain decloggers are most common, and because they are tasteless, more is ingested (Table 327-1).

Acidic agents (20% of cases) are bitter, so less may be consumed; they produce coagulation necrosis and a somewhat protective thick eschar. They can produce severe gastritis, and volatile acids can result in respiratory symptoms. Children younger than 5 yr of age account for half of the cases of caustic ingestions, and boys are far more often involved than girls. Caustic ingestions produce signs and symptoms such as vomiting, drooling, refusal to drink, oral burns, dysphagia, dyspnea, abdominal pain, hematemesis, and stridor. Twenty percent of patients develop esophageal strictures. Absence of oropharyngeal lesions does not exclude the possibility of significant esophagogastric injury, which can
Bibliography
lead to perforation or stricture. The absence of symptoms is usually associated with no or minimal lesions; hematemesis, respiratory distress, or presence of at least 3 symptoms predicts severe lesions. An upper endoscopy is recommended as the most efficient means of rapid identification of tissue damage and must be undertaken in all symptomatic children.

Dilution by water or milk is recommended as acute treatment, but neutralization, induced emesis, and gastric lavage are contraindicated. Treatment depends on the severity and extent of damage (Table 327-2).

Stricture risk is increased by circumferential ulcerations, white plaques, and sloughing of the mucosa. Strictures can require treatment with dilation, and in some severe cases, surgical resection and colon or small bowel interposition are needed. Silicone stents (self-expanding) placed endoscopically after a dilation procedure can be an alternative and conservative approach to the management of strictures. Rare late cases of superimposed esophageal carcinoma are reported. The role of corticosteroids is controversial; they are not recommended in 1st-degree burns, but they can reduce the risk of strictures in more-advanced
caustic esophagitis. Some centers also use antibiotics in the initial treat-
ment of caustic esophagitis on the premise that reducing superinfe-
tion in the necrotic tissue bed will, in turn, lower the risk of stricture
formation. However, multiple studies examining the role of antibiotics
in caustic esophagitis have not reported a clinically significant benefit
even in those with grade 2 or greater severity of esophagitis.

_Bibliography is available at Expert Consult._
Bibliography
Stomach and Intestines

Chapter 328
Normal Development, Structure, and Function
Chris A. Liacouras

DEVELOPMENT
The primitive gut is recognizable by the 4th wk of gestation and is composed of the foregut, midgut, and hindgut. The foregut gives rise to the upper gastrointestinal tract, which includes the esophagus, stomach, and duodenum to the level of the insertion of the common bile duct. The midgut gives rise to the rest of the small bowel and the large bowel to the level of the midtransverse colon. The hindgut forms the remainder of the colon and upper anal canal. The rapid growth of the midgut causes it to protrude out of the abdominal cavity through the umbilical ring during fetal development. The midgut subsequently returns to the peritoneal cavity and rotates counterclockwise until the cecum lies in the right lower quadrant. The process is normally complete by the 8th wk of gestation.

The liver derives from the hepatic diverticulum that evolves into parenchymal cells, bile ducts, vascular structures, and hematopoietic and Kupffer cells. The extrahepatic bile ducts and gallbladder develop first as solid cords that canalize by the 3rd mo of gestation. The dorsal and ventral pancreatic buds grow from the foregut by the 4th wk of gestation. The 2 buds fuse by the 6th wk. Exocrine secretory capacity is present by the 5th mo.

Cis-regulatory genomic sequences govern gene expression during development. Modules of cis sequences are linked and allow a cascade of gene regulation that controls functional development. Extrinsic factors have the capacity to influence gene expression. In the gut, several growth factors, including growth factor-β, insulin-like growth factor, and growth factors found in human colostrum (human growth factor and epidermal growth factor), influence gene expression. Propulsion of food down the gastrointestinal tract relies on the coordinated action of muscles in the bowel wall. The contractions are regulated by the enteric nervous system under the influence of a variety of peptides and hormones. The enteric nervous system is derived from neural crest cells that migrate in a cranial to caudal fashion. Migration of the neural crest tissue is complete by the 24th wk of gestation. Interruption of the migration results in Hirschsprung disease. Newborn bowel motor patterns are different from adults. Normal fasting upper gastrointestinal motility is characterized by a triphasic pattern known as the migrating motor complex. Migrating motor complexes occur less often in neonates and they have more nonmigrating phasic activity. This leads to ineffective propulsion, particularly in premature infants. Motility in the fed state consists of a series of ring contractions that spread caudal over variable distances.

DIGESTION AND ABSORPTION
The wall of the stomach, small bowel, and colon consists of 4 layers: the mucosa, submucosa, muscularis, and serosa. Eighty-five percent of the gastric mucosa is lined by oxyntic glands containing cells that secrete hydrochloric acid, pepsinogen, and intrinsic factor, and mucous and endocrine cells that secrete peptides having paracrine and endocrine effects. Pepsinogen is a precursor of the proteolytic enzyme pepsin, and intrinsic factor is required for the absorption of vitamin B₁₂. Pyloric glands are located in the antrum and contain gastrin-secreting cells. Acid production and gastrin levels are inversely related to each other except in pathologic secretory states. Acid secretion is low at birth but increases dramatically by 24 hr. Acid and pepsin secretion peak in the 1st 10 days and decrease from 10-30 days after birth. Intrinsic factor secretion rises slowly in the 1st 2 wk of life.

The small bowel is approximately 270 cm long at birth in a term neonate and grows to an adult length of 450-550 cm by 4 yr of age. The mucosa of the small intestine is composed of villi, which are finger-like projections of the mucosa into the bowel lumen that significantly expand the absorptive surface area. The mucosal surface is further expanded by a brush border containing digestive enzymes and transport mechanisms for monosaccharides, amino acids, dipeptides and tripeptides, and fats. The cells of the villi originate in adjacent crypts and become functional as they migrate from the crypt up the villus. The small bowel mucosa is completely renewed in 4-5 days, providing a mechanism for rapid repair after injury, but in young infants or malnourished children, the process may be delayed. Crypt cells also secrete fluid and electrolytes. The villi are present by 8 wk of gestation in the duodenum and by 11 wk in the ileum.

Disaccharidase activities are measurable at 12 wk, but lactase activity does not reach maximal levels until 36 wk. Even premature infants usually tolerate lactose-containing formulas because of carbohydrate salvage by colonic bacteria. In children of African and Asian ethnicity, lactase levels may begin to fall at 4 yr of age, leading to intolerance to mammalian milk. Mechanisms to digest and absorb protein, including pancreatic enzymes and mucosal mechanisms to transport amino acids, dipeptides, and tripeptides, are in place by the 20th wk of gestation.

Carbohydrates, protein, and fat are normally absorbed by the upper half of the small intestine; the distal segments represent a vast reserve of absorptive capacity. Most of the sodium, potassium, chloride, and water are absorbed in the small bowel. Bile salts and vitamin B₁₂ are selectively absorbed in the distal ileum, and iron is absorbed in the duodenum and proximal jejunum. Intraluminal digestion depends on the exocrine pancreas. Secretin and cholecystokinin stimulate synthesis and secretion of bicarbonate and digestive enzymes, which are released by the upper intestinal mucosa in response to various intraluminal stimuli, among them components of the diet.

Carbohydrate digestion is normally an efficient process that is completed in the distal duodenum. Starches are broken down to glucose, oligosaccharides, and disaccharides by pancreatic amylase. Residual glucose polymers are broken down at the mucosal level by glucoamylase. Lactose is broken down at the brush border by lactase, forming glucose and galactose; sucrose is broken down by sucrase-isomaltase to fructose and glucose. Galactose and glucose are primarily transported into the cell by a sodium- and energy-dependent process, whereas fructose is transported by facilitated diffusion.

Proteins are hydrolyzed by pancreatic enzymes, including trypsin, chymotrypsin, elastase, and carboxypeptidases, into individual amino acids and oligopeptides. The pancreatic enzymes are secreted as proenzymes, which are activated by release of the mucosal enzyme enterokinase. Oligopeptides are further broken down at the brush border by peptidases into dipeptides, tripeptides, and amino acids. Protein can enter the cell by separate noncompetitive carriers that can transport individual amino acids or dipeptides and tripeptides similar to those in the renal tubule. The human gut is capable of absorbing antigenic
intact proteins in the 1st few wk of life because of “leaky” junctions between enterocytes. Entry of potential protein antigens through the mucosal barrier might have a role in later food- and microbe-induced symptoms.

Fat absorption occurs in 2 phases. Dietary triglycerides are broken down into monoglycerides and free fatty acids by pancreatic lipase and colipase. The free fatty acids are subsequently emulsified by bile acids, forming micelles with phospholipids and other fat-soluble substances, and are transported to the cell membrane, where they are absorbed. The fats are re-esterified in the enterocyte, forming chylomicrons that are transported through the intestinal lymphatics to the thoracic duct. Medium-chain fats are absorbed more efficiently and can directly enter the cell. They are subsequently transported to the liver via the portal system. Fat absorption can be affected at any stage of the digestion and absorption process. Decreased pancreatic enzymes occur in cystic fibrosis, cholestatic liver disease leads to poor bile salt production and micelle formation, celiac disease affects mucosal surface area, abnormal chylomicron formation occurs in abetalipoproteinemia, and intestinal lymphangiectasia affects transport of the chylomicrons.

Fat absorption is less efficient in the neonate compared with adults. Premature infants can lose up to 20% of their fat calories compared with up to 6% in the adult. Decreased synthesis of bile acids and pancreatic lipase and decreased efficiency of ileal absorption are contributing factors. Fat digestion in the neonate is facilitated by lingual and gastric lipases. Bile salt–stimulated lipase in human milk augments the action of pancreatic lipase. Infants with malabsorption of fat are usually fed with formulas that have a greater percentage of medium-chain triglycerides, which are absorbed independently of bile salts.

The colon is a 75-100 cm sacculated tube formed by 3 strips of longitudinal muscle called taenia coli that traverse its length and fold the mucosa into haustra. Haustra and taenia appear by the 12th wk of gestation. The most common motor activity in the colon is nonpropulsive rhythmic segmentation that acts to mix the chyme and expose the contents to the colonic mucosa. Mass movement within the colon typically occurs after a meal. The colon extracts additional water and electrolytes from the luminal contents to render the stools partially or completely solid. The colon also acts to scavenge by-products of bacterial degradation of carbohydrates. Stool is stored in the rectum until distention triggers a defecation reflex that, when assisted by voluntary relaxation of the external sphincter, permits evacuation.
in approximately 20% of the male and 10% of the female descendants of a mother who had pyloric stenosis. The incidence of pyloric stenosis is increased in infants with B and O blood groups. Pyloric stenosis is occasionally associated with other congenital defects, including tracheoesophageal fistula and hypoplasia or agenesis of the inferior labial frenulum.

ETIOLOGY
The cause of pyloric stenosis is unknown, but many factors have been implicated. Pyloric stenosis is usually not present at birth and is more concordant in monozygotic than dizygotic twins. It is unusual in stillbirths and probably develops after birth. Pyloric stenosis has been associated with eosinophilic gastroenteritis, Apert syndrome, Zellweger syndrome, trisomy 18, Smith-Lemli-Opitz syndrome, and Cornelia de Lange syndrome. An association has been found with the use of erythromycin in neonates with highest risk if the medication is given within the 1st 2 wk of life. There have also been reports of higher incidence of pyloric stenosis among mostly female infants of mothers treated with macrolide antibiotics during pregnancy and breastfeeding. Abnormal muscle innervation, elevated serum levels of prostaglandins, and infant hypergastrinemia has been implicated. Reduced levels of neuronal nitric oxide synthase have been found with altered expression of the neuronal nitric oxide synthase exon 1c regulatory region, which influences the expression of the neuronal nitric oxide synthase gene. Reduced nitric oxide might contribute to the pathogenesis of pyloric stenosis.

CLINICAL MANIFESTATIONS
Nonbilious vomiting is the initial symptom of pyloric stenosis. The vomiting may or may not be projectile initially but is usually progressive, occurring immediately after a feeding. Emesis might follow each feeding, or it may be intermittent. The vomiting usually starts after 3 wk of age, but symptoms can develop as early as the 1st wk of life and as late as the 5th mo. Approximately 20% have intermittent emesis from birth that then progresses to the classic picture. After vomiting, the infant is hungry and wants to feed again. As vomiting continues, a progressive loss of fluid, hydrogen ion, and chloride leads to hypochloremic metabolic alkalosis. Greater awareness of pyloric stenosis has led to earlier identification of patients with fewer instances of chronic malnutrition and severe dehydration and at times a subclinical self-resolving hypertrophy.

Hyperbilirubinemia is the most common clinical association of pyloric stenosis, also known as icteropyloric syndrome. Unconjugated hyperbilirubinemia is more common than conjugated and usually resolves with surgical correction. It may be associated with a decreased level of glucuronyl transferase as seen in approximately 5% of affected infants; mutations in the bilirubin uridine diphosphate glucuronosyltransferase gene (UGT1A1) have also been implicated. If conjugated hyperbilirubinemia is a part of the presentation, other etiologies need to be investigated. Other coexistent clinical diagnoses have been described, including eosinophilic gastroenteritis, hiatal hernia, peptic ulcer, congenital nephrotic syndrome, congenital heart disease, and congenital hypothyroidism.

The diagnosis has traditionally been established by palpating the pyloric mass. The mass is firm, movable, approximately 2 cm in length, olive shaped, hard, best palpated from the left side, and located above and to the right of the umbilicus in the midepigastrium beneath the liver’s edge. The olive is easiest palpated after an episode of vomiting. After feeding, there may be a visible gastric peristaltic wave that progresses across the abdomen (Fig. 329-1).

Two imaging studies are commonly used to establish the diagnosis. Ultrasound examination confirms the diagnosis in the majority of cases. Criteria for diagnosis include pyloric thickness 3-4 mm, an overall pyloric length 15-19 mm, and pyloric diameter of 10-14 mm (Fig. 329-2). Ultrasoundography has a sensitivity of approximately 95%. When contrast studies are performed, they demonstrate an elongated pyloric channel (string sign), a bulge of the pyloric muscle into the antrum (shoulder sign), and parallel streaks of barium seen in the narrowed channel, producing a “double tract sign” (Fig. 329-3).
TREATMENT
The preoperative treatment is directed toward correcting the fluid, acid–base, and electrolyte losses. Correction of the alkalosis is essential to prevent postoperative apnea, which may be associated with anesthesia. Most infants can be successfully rehydrated within 24 hr. Vomiting usually stops when the stomach is empty, and only an occasional infant requires nasogastric suction.

The surgical procedure of choice is pyloromyotomy. The traditional Ramstedt procedure is performed through a short transverse skin incision. The underlying pyloric mass is cut longitudinally to the layer of the submucosa, and the incision is closed. Laparoscopic technique is equally successful and in one study resulted in a shorter time to full feedings and discharge from the hospital as well as greater parental satisfaction. The success of laparoscopy depends on the skill of the

DIFFERENTIAL DIAGNOSIS
Gastric waves are occasionally visible in small, emaciated infants who do not have pyloric stenosis. Infrequently, gastroesophageal reflux, with or without a hiatal hernia, may be confused with pyloric stenosis. Gastroesophageal reflux disease can be differentiated from pyloric stenosis by radiographic studies. Adrenal insufficiency from the adrenogenital syndrome can simulate pyloric stenosis, but the absence of a metabolic acidosis and elevated serum potassium and urinary sodium concentrations of adrenal insufficiency aid in differentiation (see Chapter 576). Inborn errors of metabolism can produce recurrent emesis with alkalosis (urea cycle) or acidosis (organic acidemia) and lethargy, coma, or seizures. Vomiting with diarrhea suggests gastrointeritis, but patients with pyloric stenosis occasionally have diarrhea. Rarely, a pyloric membrane or pyloric duplication results in projectile vomiting, visible peristalsis, and, in the case of a duplication, a palpable mass. Duodenal stenosis proximal to the ampulla of Vater results in the clinical features of pyloric stenosis but can be differentiated by the presence of a pyloric mass on physical examination or ultrasonography.

Figure 329-1 Gastric peristaltic wave in an infant with pyloric stenosis.

Figure 329-2 A, Transverse sonogram demonstrating a pyloric muscle wall thickness of >4 mm (distance between crosses). B, Horizontal image demonstrating a pyloric channel length >14 mm (wall thickness outlined between crosses) in an infant with pyloric stenosis.

Figure 329-3 Barium in the stomach of an infant with projectile vomiting. The attenuated pyloric canal is typical of congenital hypertrophic pyloric stenosis.
Chapter 329  •  Pyloric Stenosis and Other Congenital Anomalies of the Stomach  1799

surgeon. Postoperative vomiting occurs in half the infants and is thought to be secondary to edema of the pylorus at the incision site. In most infants, however, feedings can be initiated within 12-24 hr after surgery and advanced to maintenance oral feedings within 36-48 hr after surgery. Persistent vomiting suggests an incomplete pyloromyotomy, gastritis, gastroesophageal reflux disease, or another cause of the obstruction. The surgical treatment of pyloric stenosis is curative, with an operative mortality of 0-0.5%. Endoscopic balloon dilation has been successful in infants with persistent vomiting secondary to incomplete pyloromyotomy.

Conservative management with nasoduodenal feedings is advisable in patients who are not good surgical candidates. Oral and intravenous atropine sulfate (pyloric muscle relaxant) has also been described when surgical treatment is not available with 80% success rate described in some studies. In conservative protocols atropine is administered intravenously at a dose of 0.01 mg/kg 6 times a day 5 min before feeding. During atropine infusion, the heart rate needs to be continuously monitored by electrocardiography. Oral feeding is started at a volume of 10 mL formula, 6 times a day. The volume is increased day by day until patients tolerate 150 mL/kg/day unless vomiting occurs more than twice a day. When patients are able to tolerate the full volume of formula without vomiting more than twice a day, 0.02 mg/kg atropine is administered orally 6 times a day before feeding. As the conservative management takes longer and oral feedings may not be tolerated at first, worsening of the nutrition status may occur and total parenteral nutrition may be required. It was also postulated that surgical management is more time and cost effective.

Bibliography is available at Expert Consult.

329.2 Congenital Gastric Outlet Obstruction
Anna K. Hunter and Chris A. Liacouras

Gastric outlet obstruction resulting from pyloric atresia and antral webs is uncommon and accounts for <1% of all the atresias and diaphragms of the alimentary tract. The cause of the defects is unknown. Pyloric atresia has been associated with epidermolysis bullosa and usually presents in early infancy. The gender distribution is equal.

CLINICAL MANIFESTATIONS
Infants with pyloric atresia present with nonbilious vomiting, feeding difficulties, and abdominal distention during the 1st day of life. Polyhydramnios occurs in the majority of cases, and low birth weight is common. The gastric aspirate at birth is large (>20 mL fluid) and should be removed to prevent aspiration. Rupture of the stomach may occur as early as the 1st 12 hr of life. Infants with antral web may present with less dramatic symptoms, depending on the degree of obstruction. Older children with antral webs present with nausea, vomiting, abdominal pain, and weight loss.

DIAGNOSIS
The diagnosis of congenital gastric outlet obstruction is suggested by the finding of a large, dilated stomach on abdominal plain radiographs or in utero ultrasonography. Upper gastrointestinal (GI) contrast series is usually diagnostic and demonstrates a pyloric dimple. When contrast studies are performed, care must be taken to avoid possible aspiration. An antral web may appear as a thin septum near the pyloric channel. In older children, endoscopy has been helpful in identifying antral webs.

TREATMENT
The treatment of all causes of gastric outlet obstruction in neonates starts with the correction of dehydration and hypochloremic alkalosis. Persistent vomiting should be relieved with nasogastric decompression. Surgical or endoscopic repair should be undertaken when a patient is stable.

329.3 Gastric Duplication
Anna K. Hunter and Chris A. Liacouras

Gastric duplications are uncommon cystic or tubular structures that usually occur within the wall of the stomach. They account for 2-7% of all GI duplications. They are most commonly located on the greater curvature. Most are <12 cm in diameter and do not usually communicate with the stomach lumen; however, they do have common blood supply. Associated anomalies occur in as many as 35% of patients. Several hypotheses for the etiology of the duplication cysts have been developed including the splitting notochord theory, diverticulation, canalization defects, and caudal twinning.

The most common clinical manifestations are associated with partial or complete gastric outlet obstruction. In 33% of patients, the cyst may be palpable. Communicating duplications can cause gastric ulceration and be associated with hematemesis or melena.

Radiographic studies usually show a paragastric mass displacing the stomach. Ultrasound can show the inner hyperechoic mucosal and outer hypoechoic muscle layers that are typical of GI duplications. Surgical excision is the treatment for symptomatic gastric duplications.

Bibliography is available at Expert Consult.

329.4 Gastric Volvulus
Anna K. Hunter and Chris A. Liacouras

The stomach is tethered longitudinally by the gastrohepatic, gastroplenic, and gastrocolic ligaments. In the transverse axis, it is tethered by the gastrophrenic ligament and the retroperitoneal attachment of the duodenum. A volvulus occurs when one of these attachments is absent or elongated, allowing the stomach to rotate around itself. In some children, other associated defects are present, including intestinal malrotation, diaphragmatic defects, hiatal hernia, or adjacent organ abnormalities such as asplenia. Volvulus can occur along the longitudinal axis, producing organoaxial volvulus, or along the transverse axis, producing mesenteroaxial volvulus. Combined volvulus occurs if the stomach rotates around both organoaxial and mesenteroaxial axes.

The clinical presentation of gastric volvulus is nonspecific and suggests high intestinal obstruction. Gastric volvulus in infancy is usually associated with nonbilious vomiting and epigastric distention. It has also been associated with episodes of dyspnea and apnea in this age group. Acute volvulus can advance rapidly to strangulation and perforation. Chronic gastric volvulus is more common in older children; the children present with a history of emesis, abdominal pain and distension, early satiety, and failure to thrive.

The diagnosis is suggested in plain abdominal radiographs by the presence of a dilated stomach. Erect abdominal films demonstrate a double fluid level with a characteristic “beak” near the lower esophageal junction in mesenteroaxial volvulus. The stomach tends to lie in a vertical plane. In organoaxial volvulus, a single air–fluid level is seen without the characteristic beak with stomach lying in a horizontal plane. Upper GI series has also been used to aid the diagnosis.

Treatment of acute gastric volvulus is emergent surgery once a patient is stabilized. Laparoscopic gastropexy is the most common surgical approach. In selected cases of chronic volvulus in older patients, endoscopic correction has been successful.

Bibliography is available at Expert Consult.

329.5 Hypertrophic Gastropathy
Anna K. Hunter and Chris A. Liacouras

Hypertrophic gastropathy in children is uncommon and, in contrast to that in adults (Ménétrier disease), is usually a transient, benign, and self-limited condition.
Bibliography
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PATHOGENESIS
The condition is most often secondary to cytomegalovirus (CMV) infection, but other agents, including herpes simplex virus, *Giardia*, and *Helicobacter pylori*, are also implicated. The pathophysiologic mechanisms underlying the clinical picture are not completely understood but might involve widening of gap junctions between gastric epithelial cells with resultant fluid and protein losses. There is an association with increased expression of transforming growth factor-α in gastric mucosal tissue shown in CMV induced gastropathy. *H. pylori* infection can cause the elevation of serum glucagon-like peptide-2 levels, a mucosal growth-inducing gut hormone.

CLINICAL MANIFESTATIONS
Clinical manifestations include vomiting, anorexia, upper abdominal pain, diarrhea, edema (hypoproteinemic protein-losing enteropathy), ascites, and, rarely, hematemesis if ulceration occurs.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS
The mean age at diagnosis is 5 yr (range: 2 days-17 yr); the illness usually lasts 2-14 wk, with complete resolution being the rule. Endoscopy with biopsy and tissue CMV polymerase chain reaction is diagnostic. Endoscopy shows characteristic enlarged gastric folds. The upper GI series might show thickened gastric folds. The differential diagnosis includes eosinophilic gastroenteritis, gastric lymphoma or carcinoma, Crohn disease, and inflammatory pseudotumor.

TREATMENT
Therapy is supportive and should include adequate hydration, antisecretory agents (H₂ receptor blockade, acid suppression with proton pump inhibitors), and albumin replacement if the hypoalbuminemia is symptomatic. When *H. pylori* are detected, appropriate treatment is recommended. Ganciclovir in CMV-positive gastropathy is indicated only in severe cases. There are no official guidelines as far as the length of treatment. In practice, IV therapy is initiated for the 1st 24-48 hr. Treatment in continued with oral valganciclovir for a total of 3 wk. Complete recovery is the rule. Hypertrophic gastropathy should be considered in a previously healthy child with new onset edema and no other causes of protein losses. This is not a chronic condition in children. Disease tends to have much more severe course in adult patients.

*Bibliography is available at Expert Consult.*
Bibliography
narrowing (stenosis) of the intestinal lumen. More than 90% of intestinal stenosis and atresia occurs in the duodenum, jejunum, and ileum. Rare cases occur in the colon, and these may be associated with more proximal atresias.

Extrinsic causes of congenital intestinal obstruction involve compression of the bowel by vessels (e.g., preduodenal portal vein), organs (e.g., annular pancreas), and cysts (e.g., duplication, mesenteric). Abnormalities in intestinal rotation during fetal development also represent a unique extrinsic cause of congenital intestinal obstruction. Malrotation is associated with inadequate mesenteric attachment of the intestine to the posterior abdominal wall, which leaves the bowel vulnerable to autoobstruction as a result of intestinal twisting or volvulus. Malrotation is commonly accompanied by congenital adhesions that can compress and obstruct the duodenum as they extend from the cecum to the right upper quadrant.

Obstruction is typically associated with bowel distention, which is caused by an accumulation of ingested food, gas, and intestinal secretions proximal to the point of obstruction. As the bowel dilates, absorption of intestinal fluid is decreased and secretion of fluid and electrolytes is increased. This shift results in isotonic intravascular depletion, which is usually associated with hypokalemia. Bowel distention also results in a decrease in blood flow to the obstructed bowel. As blood flow is shifted away from the intestinal mucosa, there is loss of mucosal integrity. Bacteria proliferate in the stagnant bowel, with a predominance of coliforms and anaerobes. This rapid proliferation of bacteria, coupled with the loss of mucosal integrity, allows bacterial to translocate across the bowel wall and potentially lead to endotoxemia, bacteremia, and sepsis.

The clinical presentation of intestinal obstruction varies with the cause, level of obstruction, and time between the obstructing event and the patient’s evaluation. Classic symptoms of obstruction in the neonate include vomiting, abdominal distention, and obstipation. Obstruction high in the intestinal tract results in large-volume, frequent, bilious emesis with little or no abdominal distention. Pain is intermittent and is usually relieved by vomiting. Obstruction in the distal small bowel leads to moderate or marked abdominal distention with emesis that is progressively feculent. Both proximal and distal obstructions are eventually associated with obstruction. However, meconium stools can be passed initially if the obstruction is in the upper part of the intestinal tract or if the obstruction developed late in intrauterine life.

The diagnosis of congenital bowel obstruction relies on a combination of history, physical examination, and radiologic findings. In certain cases, the diagnosis is suggested in the prenatal period. Routine prenatal ultrasound can detect polyhydramnios, which often accompanies high intestinal obstruction. The presence of polyhydramnios should prompt aspiration of the infant’s stomach immediately after birth. Aspiration of more than 15-20 mL of fluid, particularly if it is bile stained, is highly indicative of proximal intestinal obstruction.

In the postnatal period, a plain radiograph is the initial diagnostic study and can provide valuable information about potential associated complications. With completely obstructing lesions, plain radiographs reveal bowel distention proximal to the point of obstruction. Upright or crossable lateral views typically demonstrate a series of air–fluid levels in the distended loops. Caution must be exercised in using plain films to determine the location of intestinal obstruction. Because colonic haustra are not fully developed in the neonate, small and large bowel obstructions may be difficult to distinguish with plain films. In these cases, contrast studies of the bowel or computed tomography images may be indicated. Oral or nasogastric contrast medium may be used to identify obstructing lesions in the proximal bowel, and contrast enemas may be used to diagnose more-distal entities. Indeed, enemas may also play a therapeutic role in relieving distal obstruction caused by meconium ileus or meconium plug syndrome.

Initial treatment of infants and children with bowel obstruction must be directed at fluid resuscitation and stabilizing the patient. Nasogastric decompression usually relieves pain and vomiting. After appropriate cultures, broad-spectrum antibiotics are usually started in ill-appearing neonates with bowel obstruction and those with suspected strangulating infarction. Patients with strangulation must have...
Congenital duodenal obstruction occurs in 2.5-10 per 100,000 live births. In most cases, it is caused by atresia, an intrinsic defect of bowel formation. It can also result from extrinsic compression by abnormal neighboring structures (e.g., annular pancreas, preduodenal portal vein), duplication cysts, or congenital bands associated with malrotation. Although intrinsic and extrinsic causes of duodenal obstruction occur independently, they can also coexist. Thus, a high index of suspicion for more than one underlying etiology may be critical to avoiding unnecessary reoperations in these infants.

Duodenal atresia complicates 1 per 10,000 live births and accounts for 25-40% of all intestinal atresias. In contrast to more-distal atresias, which likely arise from prenatal vascular accidents, duodenal atresia results from failed recanalization of the intestinal lumen during gestation. Throughout the 4th and 5th wk of normal fetal development, the duodenal mucosa exhibits rapid proliferation of epithelial cells. Persistence of these cells, which should degenerate after the 7th wk of gestation, leads to occlusion of the lumen (atresia) in approximately two-thirds of cases and narrowing (stenosis) in the remaining one-third. Duodenal atresia can take several forms, including a thin membrane that occludes the lumen, a short fibrous cord that connects 2 blind duodenal pouches, or a gap that spans 2 nonconnecting ends of the duodenum. The membranous form is most common, and it almost invariably occurs near the ampulla of Vater. In rare cases, the membrane is distensible and is referred to as a windsock web. This unusual form of duodenal atresia causes obstruction several centimeters distal to the origin of the membrane.

Approximately 50% of infants with duodenal atresia are premature. Concomitant congenital anomalies are common and include congenital heart disease (30%), malrotation (20-30%), annular pancreas (30%), renal anomalies (5-15%), esophageal atresia with or without tracheoesophageal fistula (5-10%), skeletal malformations (5%), and anorectal anomalies (5%). Of these anomalies, only complex congenital heart disease is associated with increased mortality. Annular pancreas is associated with increased late complications, including gastroesophageal reflux disease, peptic ulcer disease, pancreatitis, gastric outlet and recurrent duodenal obstruction, and gastric cancer. Thus, long-term follow-up of these patients into adulthood is warranted. Nearly half of patients with duodenal atresia have chromosome abnormalities; trisomy 21 is identified in up to one-third of patients.

**CLINICAL MANIFESTATIONS AND DIAGNOSIS**

The hallmark of duodenal obstruction is bilious vomiting without abdominal distention, which is usually noted on the 1st day of life. Peristaltic waves may be visualized early in the disease process. A history of polyhydramnios is present in half the pregnancies and is caused by inadequate absorption of amniotic fluid in the distal intestine. This fluid may be bile stained because of intrauterine vomiting. Jaundice is present in one-third of the infants.

The diagnosis is suggested by the presence of a "double-bubble" sign on a plain abdominal radiograph (Fig. 330-1). The appearance is caused by a distended and gas-filled stomach and proximal duodenum, which are invariably connected. Contrast studies are occasionally needed to exclude malrotation and volvulus because intestinal infarction can occur within 6-12 hr if the volvulus is not relieved. Contrast studies are generally not necessary and may be associated with aspiration. Prenatal diagnosis of duodenal atresia is readily made by fetal ultrasonography, which reveals a sonographic double-bubble. Prenatal identification of duodenal atresia is associated with decreased morbidity and fewer hospitalization days.

**TREATMENT**

The initial treatment of infants with duodenal atresia includes nasogastric or orogastric decompression and intravenous fluid replacement. Echocardiography, renal ultrasound, and radiology of the chest and spine should be performed to evaluate for associated anomalies. Definitive correction of the atresia is usually postponed until life-threatening anomalies are evaluated and treated.

The typical surgical repair for duodenal atresia is duodenoduodenostomy. This procedure is also preferred in cases of concomitant or isolated annular pancreas. In these instances, the duodenoduodenostomy is performed without dividing the pancreas. The dilated proximal bowel might have to be tapered to improve peristalsis. Postoperatively, a gastrostomy tube can be placed to drain the stomach and protect the airway. Intravenous nutritional support or a transanastomotic jejunal tube is needed until an infant starts to feed orally. Long-term prognosis is excellent, approaching 90% survival in most series.

**Bibliography is available at Expert Consult.**

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**330.1 Duodenal Obstruction**

*Christina Bales and Chris A. Liacouras*

The primary etiologies of congenital small bowel obstruction involve intrinsic abnormalities in anatomic development (jejunoileal stenosis...
Bibliography
Bibliography
and atresia), mucus secretion (meconium ileus), and bowel wall inner-
vation (long-segment Hirschsprung disease).

**Jejunoileal atresias** are generally attributed to intrauterine vascular accidents, which result in segmental infarction and resorption of the fetal intestine. Underlying events that potentiate vascular compromise include intestinal volvulus, intussusception, meconium ileus, and strangulating herniation through an abdominal wall defect associated with gastrochisis or omphalocele. Maternal behaviors that promote vasoconstriction, such as cigarette smoking and cocaine use, might also have a role. Only a few cases of familial inheritance have been reported. In these families, multiple intestinal atresias have occurred in an autosomal recessive pattern. Jejunoileal atresias have been linked with multiple births, low birthweight, and prematurity. Unlike atresia in the duodenum, they are not commonly associated with extraintes-
tinal anomalies.

Five types of jejunal and ileal atresias are encountered (Fig. 330-2). In type I, a mucosal web occludes the lumen but continuity is main-
tained between the proximal and distal bowel. Type II involves a small-
diameter solid cord that connects the proximal and distal bowel. Type III is divided into 2 subtypes. Type IIIa occurs when both ends of the bowel end in blind loops, accompanied by a small mesenteric defect. Type IIIb is similar, but it is associated with an extensive mesenteric defect and a loss of the normal blood supply to the distal bowel. The distal ileum coils around the ileocolic artery, from which it derives its entire blood supply, producing an ‘apple-peel’ appearance. This anomaly is associated with prematurity, an unusually short distal ileum, and significant foreshortening of the bowel. Type IV involves multiple atresias. Types II and IIIa are the most common, each account-
ing for 30-35% of cases. Type I occurs in approximately 20% of patients. Types IIIb and IV account for the remaining 10-20% of cases, with IIIb being the least-common configuration.

**Meconium ileus** occurs primarily in newborn infants with cystic fibrosis, an exocrine gland defect of chloride transport that results in abnormally viscous secretions. Approximately 80-90% of infants with meconium ileus have cystic fibrosis, but only 10-15% of infants with cystic fibrosis present with meconium ileus. In simple cases, the distal bowel is collapsed and filled with pellets of pale stool. The proximal bowel is dilated and filled with thick meconium that resembles sticky syrup or glue. Peristalsis fails to propel this viscid material forward, and it becomes impacted in the ileum. In complicated cases, a volvulus of the dilated proximal bowel can occur, resulting in intesti-
nal ischemia, atresia, and/or perforation. Perforation in utero results in meconium peritonitis, which can lead to potentially obstructing adhesions and calcifications.

Both intestinal atresia and meconium ileus must be distinguished from **long-segment Hirschsprung disease**. This condition involves congenital absence of ganglion cells in the myenteric and submucosal plexuses of the bowel wall. In a small subset (5%) of patients, the aganglionic segment includes the terminal ileum in addition to the entire length of the colon. Infants with long-segment Hirschsprung disease present with a dilated small intestine that is gangionated but has hypertrophied walls, a funnel-shaped transitional hypoganglionic zone, and a collapsed distal aganglionic bowel.

**CLINICAL MANIFESTATION AND DIAGNOSIS**

Distal intestinal obstruction is less likely than proximal obstruction to be detected in utero. Polyhydramnios is identified in 20-35% of jejunoileal atresias, and it may be the first sign of intestinal obstruction. Abdominal distention is rarely present at birth, but it develops rapidly after initiation of feeds in the 1st 12-24 hr. Distention is often accom-
panied by vomiting, which is often bilious. Up to 80% of infants fail to pass meconium in the 1st 24 hr of life. Jaundice, associated with unconjugated hyperbilirubinemia, is reported in 20-30% of patients.

In patients with obstruction caused by jejunoileal atresia or long-
segment Hirschsprung disease, plain radiographs typically demon-
strate multiple air-fluid levels proximal to the obstruction in the upright or lateral decubitus positions (Fig. 330-3). These levels may be absent in patients with meconium ileus because the viscosity of the secretions in the proximal bowel prevents layering. Instead, a typical hazy or ground-glass appearance may be appreciated in the right lower quadrant. This haziness is caused by small bubbles of gas that become trapped in inspissated meconium in the terminal ileal region. If there is meconium peritonitis, patchy calcification may also be noted, partic-
ularly in the flanks. Plain films can reveal evidence of pneumoperi-
toneum due to intestinal perforation. Air may be seen in the subphrenic regions on the upright view and over the liver in the left lateral decu-
bitus position.

Because plain radiographs do not reliably distinguish between small and large bowel in neonates, contrast studies are often required to localize the obstruction. Water-soluble enemas (Gastrografin, Hypaque) are particularly useful in differentiating atresia from meco-

**Figure 330-2** A and B, Classification of intestinal atresia. Type I: Mucosal obstruction caused by an intraluminal membrane with intact bowel wall and mesentery. Type II: Blind ends are separated by a fibrous cord. Type IIIa: Blind ends are separated by a V-shaped mesen-

**Figure 330-3** A, Abdominal radiograph in a neonate with bilious vomiting shows a few loops of dilated intestine with air-fluid levels. B, At laparotomy, a type I (mucosal) jejunal atresia was observed. (From O’Neill JA Jr, Grosfeld JL, Fonkalsrud EW, et al, editors: Principles of pediatric surgery, ed 2, St. Louis, 2003, Mosby, p. 493.)
can distinguish meconium ileus from ileal atresia and also identify concomitant intestinal malrotation.

**TREATMENT**

Patients with small bowel obstruction should be stable and in adequate fluid and electrolyte balance before operation or radiographic attempts at disimpaction unless volvulus is suspected. Documented infections should be treated with appropriate antibiotics. Prophylactic antibiotics are usually given before surgery.

Ileal or jejunal atresia requires resection of the dilated proximal portion of the bowel followed by end-to-end anastomosis. If a simple mucosal diaphragm is present, jejunoplasty or ileoplasty with partial excision of the web is an acceptable alternative to resection. In uncomplicated meconium ileus, Gastrografin enemas diagnose the obstruction and wash out the inspissated material. Gastrografin is hypertonic, and care must be taken to avoid dehydration, shock, and bowel perforation. The enema may have to be repeated after 8-12 hr. Resection after reduction is not needed if there have been no ischemic complications.

Approximately 50% of patients with simple meconium ileus do not adequately respond to water-soluble enemas and need laparotomy. Operative management is indicated when the obstruction cannot be relieved by repeated attempts at nonoperative management and for infants with complicated meconium ileus. The extent of surgical intervention depends on the degree of pathology. In simple meconium ileus, the plug can be relieved by manipulation or direct enteral irrigation with N-acetylcysteine following an enterotomy. In complicated cases, bowel resection, peritoneal lavage, abdominal drainage, and stoma formation may be necessary. Total parenteral nutrition is generally required.

**Bibliography is available at Expert Consult.**

### 330.3 Malrotation

**Melissa Kennedy and Chris A. Liacouras**

Malrotation is incomplete rotation of the intestine during fetal development and involves the intestinal nonrotation or incomplete rotation around the superior mesenteric artery. The gut starts as a straight tube from stomach to rectum. Intestinal rotation and attachment begins in the 5th wk of gestation when the midbowel (distal duodenum to midtransverse colon) begins to elongate and progressively protrudes into the umbilical cord until it lies totally outside the confines of the abdominal cavity. As the developing bowel rotates in and out of the abdominal cavity, the superior mesenteric artery, which supplies blood to this section of gut, acts as an axis. The duodenum, on reentering the abdominal cavity, moves to the region of the ligament of Treitz, and the colon that follows is directed to the left upper quadrant. The cecum subsequently rotates counterclockwise within the abdominal cavity and comes to lie in the right lower quadrant. The duodenum becomes fixed to the posterior abdominal wall before the colon is completely rotated. After rotation, the right and left colon and the mesenteric root become fixed to the posterior abdomen. These attachments provide a broad base of support to the mesentery and the superior mesenteric artery, thus preventing twisting of the mesenteric root and kinking of the vascular supply. Abdominal rotation and attachment are completed by the 12th wk of gestation.

Nonrotation occurs when the bowel fails to rotate after it returns to the abdominal cavity. The 1st and 2nd portions of the duodenum are in their normal position, but the remainder of the duodenum, jejunum, and ileum occupy the right side of the abdomen and the colon is located on the left. The most common type of malrotation involves failure of the cecum to move into the right lower quadrant (Fig. 330-4). The usual location of the cecum is in the subhepatic area. Failure of the cecum to rotate properly is associated with failure to form the normal broad-based adherence to the posterior abdominal wall. The mesentery, including the superior mesenteric artery, is tethered by a narrow stalk, which can twist around itself and produce a midgut volvulus. Bands of tissue (Ladd bands) can extend from the cecum to the right upper quadrant, crossing, and possibly obstructing, the duodenum.

Malrotation and nonrotation are often associated with other anomalies of the abdominal wall such as diaphragmatic hernia, gastrochisis, and omphalocele. Malrotation is also associated with the heterotaxy syndrome, which is a complex of congenital anomalies including congenital heart malformations, malrotation, biliary atresia, and either asplenia or polysplenia (see Chapter 431.11).

**CLINICAL MANIFESTATIONS**

The reported incidence of malrotation is approximately 1 in 500 infant population. The majority, about 75-85% of patients, present in the 1st yr of life, and more than 50% present within the 1st mo of life, with symptoms of acute or chronic obstruction. Vomiting is the most common symptom in this age group. Infants often present in the 1st wk of life with bilious emesis and acute bowel obstruction. Older infants present with episodes of recurrent abdominal pain that can mimic colic and suggest intermittent volvulus. Malrotation in older children can manifest with recurrent episodes of vomiting and/or abdominal pain. Patients occasionally present with malabsorption or protein-losing enteropathy associated with bacterial overgrowth. Symptoms are caused by intermittent volvulus or duodenal compression by Ladd bands or other adhesive bands affecting the small and large bowel. Approximately 25-50% of adolescents with malrotation are asymptomatic. Adolescents who become symptomatic present with acute intestinal obstruction or history of recurrent episodes of abdominal pain or postprandial bloating and occasional vomiting. Patients of any age with a rotational anomaly can develop acute bowel-threatening volvulus without preexisting symptoms.

An acute presentation of small bowel obstruction in a patient without previous bowel surgery can be the result of volvulus associated with malrotation. This is a life-threatening complication of malrotation, which resembles an acute abdomen or sepsis and is the main reason that symptoms suggesting malrotation should always be investigated. Volvulus occurs when the small bowel twists around the

Figure 330-4 The mechanism of intestinal obstruction with incomplete rotation of the midgut (malrotation). The dotted lines show the course the cecum should have taken. Failure to rotate has left obstructing bands across the duodenum and a narrow pedicle for the midgut loop, making it susceptible to volvulus. (From Nixon HH, O'Donnell B: The essentials of pediatric surgery, Philadelphia, 1961, JB Lippincott.)
Bibliography
superior mesenteric artery leading to vascular compromise of the bowel. The diagnosis may be suggested by ultrasound but is confirmed by contrast radiographic studies. The abdominal plain film is usually nonspecific but might demonstrate a gasless abdomen or evidence of duodenal obstruction with a double-bubble sign. Upper gastrointestinal series is the imaging test of choice and the gold standard in the evaluation and diagnosis of malrotation and volvulus. Normal rotation is indicated by the duodenal C-loop crossing the midline and a duodenojejunal junction located to the left of the spine. Upper gastrointestinal series is the best exam to visualize the malposition of the ligament of Treitz and can also reveal a corkscrew appearance of the small bowel or a duodenal obstruction with a “bird’s beak” appearance of the duodenum. Barium enema usually demonstrates malposition of the cecum but is normal in up to 20% of patients. Ultrasonography can demonstrate the inversion of the superior mesenteric artery and vein. A superior mesenteric vein located to the left of the superior mesenteric artery suggests malrotation. Malrotation with volvulus is suggested by duodenal obstruction, thickened bowel loops to the right of the spine, the superior mesenteric vein coiling around the superior mesenteric artery, and free peritoneal fluid.

**TREATMENT**

Surgical intervention is recommended for any patient with a significant rotational abnormality, regardless of age. If a volvulus is present, surgery is done immediately as an acute emergency, the volvulus is reduced, and the duodenum and upper jejunum are freed of any bands and remain in the right abdominal cavity. The colon is freed of adhesions and placed in the right abdomen with the cecum in the left lower quadrant, usually accompanied by incidental appendectomy. The Ladd procedure may be done laparoscopically for malrotation without volvulus and if gut ischemia is not present, but it is generally done as an open procedure if volvulus is present. The purpose of surgical intervention is to minimize the risk of subsequent volvulus rather than to return the bowel to a normal anatomic configuration. Extensive intestinal ischemia from volvulus can result in short bowel syndrome (see Chapter 330.7).

*Bibliography is available at Expert Consult.*
Bibliography
Duplications of the intestinal tract are rare anomalies that consist of well-formed tubular or spherical structures firmly attached to the intestine with a common blood supply. The lining of the duplications resembles that of the gastrointestinal (GI) tract. Duplications are located on the mesenteric border and can communicate with the intestinal lumen. Duplications can be classified into 3 categories: localized duplications, duplications associated with spinal cord defects and vertebral malformations, and duplications of the colon. Occasionally (10-15% of cases), multiple duplications are found.

**Localized duplications** can occur in any area of the GI tract but are most common in the ileum and jejunum. They are usually cystic or tubular structures within the wall of the bowel. The cause is unknown, but their development has been attributed to defects in recanalization of the intestinal lumen after the solid stage of embryologic development. Duplication of the intestine occurring in association with **vertebral and spinal cord anomalies** (hemivertebra, anterior spina bifida, band connection between lesion and lesion of cervical or thoracic spine) is thought to arise from splitting of the notochord in the developing embryo. **Duplication of the colon** is usually associated with anomalies of the urinary tract and genitals. Duplication of the entire colon, rectum, anus, and terminal ileum can occur. The defects are thought to be secondary to caudal twinning, with duplication of the hindgut, genital, and lower urinary tracts.

**CLINICAL MANIFESTATIONS**
Symptoms depend on the size, location, and mucosal lining. Duplications can cause bowel obstruction by compressing the adjacent intestinal lumen, or they can act as the lead point of an intussusception or a site for a volvulus. If they are lined by acid-secreting mucosa, they can cause ulceration, perforation, and hemorrhage of or into the adjacent bowel. Patients can present with abdominal pain, vomiting, palpable mass, or acute GI hemorrhage. Intestinal duplications in the thorax (neuroenteric cysts) can manifest as respiratory distress. Duplications of the lower bowel can cause constipation or diarrhea or be associated with recurrent prolapse of the rectum.

The diagnosis is suspected on the basis of the history and physical examination. Radiologic studies such as barium studies, ultrasonography, CT, and MRI are helpful but usually nonspecific, demonstrating cystic structures or mass effects. Radioisotope technetium scanning can localize ectopic gastric mucosa. The treatment of duplications is surgical resection and management of associated defects.

**331.2 Meckel Diverticulum and Other Remnants of the Omphalomesenteric Duct**

Meckel diverticulum is the most common congenital anomaly of the GI tract and is caused by the incomplete obliteration of the omphalomesenteric duct during the 7th wk of gestation. The omphalomesenteric duct connects the yolk sac to the gut in a developing embryo and provides nutrition until the placenta is established. Between the 5th and 7th wk of gestation, the duct attenuates and separates from the intestine. Just before this involution, the epithelium of the yolk sac develops a lining similar to that of the stomach. Partial or complete failure of involution of the omphalomesenteric duct results in various residual structures. Meckel diverticulum is the most common of these structures and is the most common congenital GI anomaly, occurring in 2-3% of all infants. A typical Meckel diverticulum is a 3-6 cm outpouching of the ileum along the antimesenteric border 50-75 cm (approximately 2 feet) from the ileocecal valve (Fig. 331-1). The distance from the ileocecal valve depends on the age of the patient. Meckel diverticulum has been conveniently referred to by the “rule of 2s,” which explains the classic presentation of this congenital anomaly. Meckel diverticulum are found in approximately 2% of the general population, are usually located 2 feet proximal to the ileocecal valve and are approximately 2 inches in length, can contain 2 types of ectopic tissue (pancreatic or gastric), generally present before the age
of 2 yr, and are found twice as commonly in females. Although intraabdominal in location, a rare presentation of a Meckel diverticulum is entrapment in an inguinal, umbilical, or femoral hernia (Littre hernia). Other omphalomesenteric duct remnants occur infrequently, including a persistently patent duct, a solid cord, or a cord with a central cyst or a diverticulum associated with a persistent cord between the diverticulum and the umbilicus.

CLINICAL MANIFESTATIONS
Symptoms of a Meckel diverticulum usually arise in the 1st or 2nd yr of life (average: 2.5 yr), but initial symptoms can occur in the 1st decade. The majority of symptomatic Meckel diverticula are lined by an ectopic mucosa, including an acid-secreting mucosa that causes intermittent painless rectal bleeding by ulceration of the adjacent normal ileal mucosa. This ectopic mucosa is most commonly of gastric origin, but it can also be pancreatic, jejunal, or a combination of these tissues. Unlike the upper duodenal mucosa, the acid is not neutralized by pancreatic bicarbonate.

The stool is typically described as brick colored or currant jelly colored. Bleeding can cause significant anemia but is usually self-limited because of contraction of the splanchnic vessels, as patients become hypovolemic. Bleeding from a Meckel diverticulum can also be less dramatic, with melanotic stools.

Less often, a Meckel diverticulum is associated with partial or complete bowel obstruction. The most common mechanism of obstruction occurs when the diverticulum acts as the lead point of an intussusception. The mean age of onset of obstruction is younger than that for patients presenting with bleeding. Obstruction can also result from intraperitoneal bands connecting residual omphalomesenteric duct remnants to the ileum and umbilicus. These bands cause obstruction by internal herniation or volvulus of the small bowel around the band. A Meckel diverticulum occasionally becomes inflamed (diverticulitis) and manifests similarly to acute appendicitis. These children are older, with a mean of 8 yr of age. Diverticulitis can lead to perforation and peritonitis.

DIAGNOSIS
The diagnosis of omphalomesenteric duct remnants depends on the clinical presentation. If an infant or child presents with significant painless rectal bleeding, the presence of a Meckel diverticulum should be suspected because Meckel diverticulum accounts for 50% of all lower GI bleeds in children younger than 2 yr of age.

Confirmation of a Meckel diverticulum can be difficult. Plain abdominal radiographs are of no value, and routine barium studies rarely fill the diverticulum. The most sensitive study is a Meckel radionuclide scan, which is performed after intravenous infusion of technetium-99m pertechnetate. The mucus-secreting cells of the ectopic gastric mucosa take up pertechnetate, permitting visualization of the Meckel diverticulum (Fig. 331-2). The uptake can be enhanced with various agents, including cimetidine, ranitidine, glucagon, and pentagastrin. The sensitivity of the enhanced scan is approximately 85%, with a specificity of approximately 95%. A false-negative scan may be seen in anemic patients; although false-positive results are uncommon, they have been reported with intussusception, appendicitis, duplication cysts, arteriovenous malformations, and tumors. Other methods of detection include radiolabeled tagged red blood cell scan (the patient must be actively bleeding), abdominal ultrasound, superior mesenteric angiography, abdominal CT scan, or exploratory laparoscopy. In patients who present with intestinal obstruction or a picture of appendicitis with omphalomesenteric duct remnants, the diagnosis is rarely made before surgery.

The treatment of a symptomatic Meckel diverticulum is surgical excision. A diverticulectomy can be performed safely as either a laparoscopic or open procedure, although most continue to be performed as open procedures. There is significant debate regarding the proper management of an asymptomatic Meckel's diverticulum and whether excision vs observation is appropriate. However, the risk of serious complications does seem to exceed the operative risk in children younger than 8 yr old.

Bibliography is available at Expert Consult.
Bibliography
Chapter 332
Motility Disorders and Hirschsprung Disease

332.1 Chronic Intestinal Pseudoobstruction
Kristin N. Fiorino and Chris A. Liacouras

Chronic intestinal pseudoobstruction comprises a group of disorders characterized as a motility disorder with a primary defect of impaired peristalsis; symptoms are consistent with intestinal obstruction in the absence of mechanical obstruction. The natural history of pseudoobstruction is that of a primary progressive disorder, although there are occasional cases of secondary pseudoobstruction caused by conditions that can transiently or permanently alter bowel motility. The most common cause of acute pseudoobstruction is Ogilvie syndrome (acute pseudoobstruction of the colon). Pseudoobstruction represents a wide spectrum of pathologic disorders from abnormal myoelectric activity to abnormalities of the nerves (intestinal neuropathy) or musculature (intestinal myopathy) of the gut. The organs involved can include the entire gastrointestinal tract or be limited to certain components, although almost always include the small bowel. The distinctive pathologic abnormalities are considered together because of their clinical similarities.

Most congenital forms of pseudoobstruction occur sporadically, although autosomal dominant, autosomal recessive, X-linked, and familial patterns of inheritance have been identified. Patients with autosomal dominant forms of pseudoobstruction have variable expressions of the disease. Acquired pseudoobstruction can follow episodes of acute gastroenteritis, presumably resulting in injury to the myenteric plexus.

In congenital pseudoobstruction, abnormalities of the muscle or nerves can be demonstrated in the majority of cases. In myopathies, the smooth muscle is involved, in which the outer longitudinal muscle layer is replaced by fibrous material. The enteric nervous system is usually altered in neuropathies and may involve disorganized ganglia, hypoganglionosis, or hyperganglionosis. Abnormalities in the interstitial cells of Cajal, the intestinal pacemaker, are classified as mesenchymopathies. In others, mitochondrial defects have been identified. Genetic defects have been identified in the transcription factor SOX10 and the DNA polymerase gamma gene (POLG) in mitochondrialopathies.

CLINICAL MANIFESTATIONS
More than half the children with congenital pseudoobstruction experience symptoms in the 1st few mo of life. Two-thirds of the infants presenting in the 1st few days of life are born prematurely, and approximately 40% have malrotation of the intestine. In 75% of all affected children, symptoms occur in the 1st yr of life, while the remainder are usually symptomatic within the next several years. The most common symptoms are abdominal distention and vomiting, which are present in 75% of affected infants. Constipation, growth failure, and abdominal pain occur in approximately 60% of patients, and diarrhea in 30-40%. The symptoms wax and wane in the majority of the patients; poor nutrition, psychologic stress, and intercurrent illness tend to exacerbate symptoms. Urinary tract and bladder involvement occurs in 80% of children with myopathic pseudoobstruction and in 20% of those with neuropathic disease. Symptoms can manifest as recurrent urinary tract infection, megacystis, or obstructive symptoms.

TREATMENT
Nutritional support is the mainstay of treatment for pseudoobstruction. Thirty percent to 50% of patients require partial or complete parenteral nutrition. Some patients can be treated with intermittent enteral supplementation, whereas others can maintain themselves on selective oral diets. Prokinetic drugs are generally used although studies have not shown definitive evidence of their efficacy. Isolated gastroparesis can follow episodes of viral gastroenteritis and spontaneously resolves, usually in 6-24 mo. Erythromycin, a motilin receptor agonist, and cisapride, a serotonin 5-HT4 receptor agonist, can enhance...
Mitochondrial neurogastrointestinal encephalomyopathy (MNGIE) is a multisystem autosomal recessive disease that initially presents with severe gastrointestinal disturbances; the neurologic manifestations usually occur later in the illness and may initially be subtle or asymptomatic.

MNGIE is caused by a mutation in the nuclear DNA TTYMP gene encoding thymidine phosphorylase that results in abnormalities in intergenomic communication with resulting instability of mitochondrial DNA. There are at least 50 individual mutations with a poor genotype–phenotype correlation and varying manifestations within each family. Consanguinity is present in 30% of families.

MNGIE affects both males and females and is usually diagnosed in the 2nd and 3rd decade (average age: 18 yr; range: 5 mo–35 yr). Onset is usually around age 12 yr, but there is often a 5–10 yr delay in the diagnosis.

MNGIE initially presents with gastrointestinal symptoms. Severe intestinal dysmotility and gastroparesis is associated with early satiety, and neurologic symptoms, lactic acidosis, ragged red fibers, and cytochrome C oxidase deficient fibers seen in most patients on muscle biopsy.

Most often following the onset of gastrointestinal manifestations, ptosis, progressive external ophthalmoplegia, hearing loss and peripheral neuropathy may develop. The neuropathy is either demyelinating or a mixed axonal demyelinating type and manifests as weakness, decreased or absent deep tendon reflexes, and aresthesias. Leukoencephalopathy is initially asymptomatic and noted on MRI as patchy lesions predominantly in the cortex but also in the basal ganglia and brainstem. Eventually the central nervous system lesions become diffuse and confluent. A small number of patients develop cognitive impairment or dementia.

The diagnosis is suggested by the constellation of gastrointestinal and neurologic symptoms, lactic acidosis, ragged red fibers, and cytochrome C oxidase deficient fibers seen in most patients on muscle biopsy. Treatment is focused on providing sufficient nutritional support and avoidance of infectious complications and of nutritional deficiencies. Stem cell transplantation has been successful in a small number of patients.

Overall the prognosis is poor with few surviving into the 4th or 5th decade.

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underlying pathology include failure to thrive, weight loss, abdominal pain, vomiting, or persistent anal fissure or fistula.

In functional constipation, daytime encopresis is common. Encopresis is defined as voluntary or involuntary passage of feces into inappropriate places at least once a month for 3 consecutive months once a chronicologic or developmental age of 4 yr has been reached. Encopresis is not diagnosed when the behavior is exclusively the result of the direct effects of a substance (e.g., laxatives) or a general medical condition (except through a mechanism involving constipation). Subtypes include retentive encopresis (with constipation and overflow incontinence) representing 65-95% of cases, and nonretentive encopresis (without constipation and overflow incontinence). Nonretentive fecal incontinence is defined as no evidence of fecal retention (impaction), ≥1 episodes per week in the previous 2 mo in a child at a development-age >4 yr, defecation in places inappropriate to the social context and no evidence of anatomic, inflammatory, metabolic, endocrine, or neoplastic process that could explain the symptoms. Encopresis can persist from infancy onward (primary) or can appear after successful toilet training (secondary).

**DIAGNOSIS**

The physical examination often demonstrates a large volume of stool palpated in the suprapubic area; rectal examination demonstrates a dilated rectal vault filled with guaiac-negative stool. Children with encopresis often present with reports of underwear soiling, and many parents initially presume that diarrhea, rather than constipation, is the cause. In retentive encopresis, associated complaints of difficulty with defecation, abdominal or rectal pain, impaired appetite with poor growth, and urinary (day and/or night) incontinence are common. Children often have large bowel movements that obstruct the toilet. There may also be retentive posturing or recurrent urinary tract infections. Nonretentive encopresis is more likely to occur as a solitary symptom and have associated primary underlying psychological etiology. Children with encopresis can present with poor school performance and attendance that is triggered by the scorn and derision from schoolmates because of the child’s offensive odor.

The presence of a hair tuft over the spine or spinal dimple, or failure to elicit a cremasteric reflex or anal wink suggests spinal pathology. A tethered cord is suggested by decreased or absent lower leg reflexes. Spinal cord lesions can occur with overlying skin anomalies. Urinary tract symptoms include recurrent urinary tract infection and enuresis. Children with no evidence of abnormalities on physical examination rarely require radiologic evaluation.

In refractory patients (intractable constipation), specialized testing should be considered to rule out conditions such as hypothyroidism, hypocalcemia, lead toxicity, celiac disease, and allergy testing. Colonic transit studies using radio-opaque markers or scintigraphy techniques may be useful. Selected children can benefit from MRI of the spine to identify an intraspinal process, motility studies to identify underlying myopathic or neuropathic bowel abnormalities, or a contrast enema to identify structural abnormalities. In patients with severe functional constipation, water-soluble contrast enema reveals the presence of a megarectosigmoid (Fig. 332-1). Anorectal motility studies can demonstrate a pattern of paradoxical contraction of the external anal sphincter during defecation, which can be treated by behavior modification and biofeedback. Colonic motility can guide therapy in refractory cases, demonstrating segmental problems that might require surgical intervention.

Complications of retentive encopresis include day and night urinary incontinence, urinary retention, urinary tract infection, megacystis, and rarely toxic megacolon.

**TREATMENT**

Therapy for functional constipation and encopresis includes patient education, relief of impaction, and softening of the stool. Caregivers must understand that soiling associated with overflow incontinence is associated with loss of normal sensation and not a willful act. There needs to be a focus on adherence with regular postprandial toilet sitting and adoption of a balanced diet. In addition, caregivers should be instructed not to respond to soiling with retaliatory or punitive measures, because children are likely to become angry, ashamed, and resistant to intervention. From the outset, parents should be actively encouraged to reward the child for adherence to a healthy bowel regimen and to avoid power struggles.

If an impaction is present on the initial physical examination, an enema is usually required to clear the impaction while stool softeners are started as maintenance medications. Typical regimens include the use of polyethylene glycol preparations, lactulose, or mineral oil (Tables 332-3 and 332-4). Prolonged use of stimulants such as senna or bisacodyl should be avoided.

Compliance can wane, and failure of this standard treatment approach sometimes requires more intensive intervention. In cases where behavioral or psychiatric problems are evident, involvement of a psychologist or behavioral management (e.g., behavior programs and/or biofeedback). Maintenance therapy is generally continued until a regular bowel pattern has been established and the association of pain with the passage of stool is abolished.

For children with chronic diarrhea and/or irritable bowel syndrome where stress and anxiety play a major role, stress reduction and learning effective coping strategies can play an important role in responding to the encopresis. Relaxation training, stress inoculation, assertiveness training, and/or general stress management procedures can be helpful. Children with spinal problems can be successfully managed with low volumes of fluid through a cecostomy or sigmoid tube.

**Bibliography is available at Expert Consult.**
**Table 332-3** Suggested Medications and Dosages for Disimpaction

<table>
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<tr>
<th>MEDICATION</th>
<th>AGE</th>
<th>DOSAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RAPID RECTAL DISIMPACTION</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glycerin suppositories</td>
<td>Infants and toddlers</td>
<td>60 mL</td>
</tr>
<tr>
<td>Phosphate enema</td>
<td>&lt;1 yr</td>
<td>6 mL/kg bodyweight, up to 135 mL twice</td>
</tr>
<tr>
<td>Milk of molasses enema</td>
<td>&gt;1 yr</td>
<td>(1:1 milk: molasses) 200-600 mL</td>
</tr>
<tr>
<td></td>
<td>Older children</td>
<td></td>
</tr>
<tr>
<td><strong>SLOW ORAL DISIMPACTION IN OLDER CHILDREN</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Over 2-3 Days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Polyethylene glycol with electrolytes</td>
<td></td>
<td>25 mL/kg bodyweight/hr, up to 1000 mL/hr</td>
</tr>
<tr>
<td></td>
<td></td>
<td>until clear fluid comes from the anus</td>
</tr>
<tr>
<td>Over 5-7 Days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Polyethylene without electrolytes</td>
<td></td>
<td>1.5 g/kg bodyweight/day for 3 days</td>
</tr>
<tr>
<td>Milk of magnesia</td>
<td></td>
<td>2 mL/kg bodyweight twice/day for 7 days</td>
</tr>
<tr>
<td>Mineral oil</td>
<td></td>
<td>3 mL/kg bodyweight twice/day for 7 days</td>
</tr>
<tr>
<td>Lactulose or sorbitol</td>
<td></td>
<td>2 mL/kg bodyweight twice/day for 7 days</td>
</tr>
</tbody>
</table>


**Table 332-4** Suggested Medications and Dosages for Maintenance Therapy of Constipation

<table>
<thead>
<tr>
<th>MEDICATION</th>
<th>AGE</th>
<th>DOSE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FOR LONG-TERM TREATMENT (YEARS)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Milk of magnesia</td>
<td>&gt;1 mo</td>
<td>1-3 mL/kg bodyweight/day, divided into 1-2 doses</td>
</tr>
<tr>
<td>Mineral oil</td>
<td>&gt;12 mo</td>
<td>1-3 mL/kg bodyweight/day, divided into 1-2 doses</td>
</tr>
<tr>
<td>Lactulose or sorbitol</td>
<td>&gt;1 mo</td>
<td>1-3 mL/kg bodyweight/day, divided into 1-2 doses</td>
</tr>
<tr>
<td>Polyethylene glycol 3350 (MiraLAX)</td>
<td>&gt;1 mo</td>
<td>0.7 g/kg bodyweight/day, divided into 1-2 doses</td>
</tr>
<tr>
<td><strong>FOR SHORT-TERM TREATMENT (MONTHS)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Senna (Senokot) syrup, tablets</td>
<td>1-5 yr</td>
<td>5 mL (1 tablet) with breakfast, max 15 mL daily</td>
</tr>
<tr>
<td></td>
<td>5-15 yr</td>
<td>2 tablets with breakfast, maximum 3 tablets daily</td>
</tr>
<tr>
<td>Glycerin enemas</td>
<td>&gt;10 yr</td>
<td>20-30 mL/day (½ glycerin and ½ normal saline)</td>
</tr>
<tr>
<td>Bisacodyl suppositories</td>
<td>&gt;10 yr</td>
<td>10 mg daily</td>
</tr>
</tbody>
</table>


### 332.4 Congenital Aganglionic Megacolon (Hirschsprung Disease)

**Kristin N. Fiorino and Chris A. Liacouras**

Hirschsprung disease, or congenital aganglionic megacolon, is a developmental disorder (neurocrystopathy) of the enteric nervous system, characterized by the absence of ganglion cells in the submucosal and myenteric plexus. It is the most common cause of lower intestinal obstruction in neonates, with an overall incidence of 1 in 5,000 live births. The male: female ratio for Hirschsprung disease is 4:1 for short-segment disease, and approximately 2:1 with total colonic aganglionosis. Prematurity is uncommon.

There is an increased familial incidence in long-segment disease. Hirschsprung disease may be associated with other congenital defects, including trisomy 21, Joubert syndrome, Goldberg-Shprintzen syndrome, Smith-Lemli-Opitz syndrome, Shah-Waardenburg syndrome, cartilage-hair hypoplasia, multiple endocrine neoplasia 2 syndrome, neurofibromatosis, neuroblastoma, congenital hypoventilation (Ondine’s curse), and urogenital or cardiovascular abnormalities. Hirschsprung disease has been seen in association with microcephaly, mental retardation, abnormal facies, autism, cleft palate, hydrocephalus, and micrognathia.

**PATHOLOGY**

Hirschsprung disease is the result of an absence of ganglion cells in the bowel wall, extending proximally and continuously from the anus for a variable distance. The absence of neural innervation is a consequence of an arrest of neuroblast migration from the proximal to distal bowel. Without the myenteric and submucosal plexus, there is inadequate relaxation of the bowel wall and bowel wall hypertonicity, which can lead to intestinal obstruction.

Hirschsprung disease is usually sporadic, although dominant and recessive patterns of inheritance have been demonstrated in family groups. Genetic defects have been identified in multiple genes that encode proteins of the RET signaling pathway (RET, GDNF, and NTN) and involved in the endothelin (EDN) type B receptor pathway (EDNRB, EDN3, and EVE-1). Syndromic forms of Hirschsprung disease have been associated with the LINCAM, SOX10, and ZFHX1B (formerly SIP1) genes.

The aganglionic segment is limited to the rectosigmoid in 80% of patients. Approximately 10-15% of patients have long-segment disease, defined as disease proximal to the sigmoid colon. Total bowel aganglionosis is rare and accounts for approximately 5% of cases. Observed histologically is an absence of Meissner’s and Auerbach’splexuses and hypertrophied nerve bundles with high concentrations of acetylcholinesterase between the muscular layers and in the submucosa.

**CLINICAL MANIFESTATIONS**

Hirschsprung disease is usually diagnosed in the neonatal period secondary to a distended abdomen, failure to pass meconium, and/or bilious emesis or aspirates with feeding intolerance. In 99% of healthy full-term infants, meconium is passed within 48 hr of birth. Hirschsprung disease should be suspected in any full-term infant (the disease is unusual in preterm infants) with delayed passage of stool. Some neonates pass meconium normally but subsequently present with a history of chronic constipation. Failure to thrive with hypoproteinemina from protein-losing enteropathy is a less common presentation because Hirschsprung disease is usually recognized early in the course of the illness. Breastfed infants might not suffer disease as severe as formula-fed infants.

Failure to pass stool leads to dilation of the proximal bowel and abdominal distention. As the bowel dilates, intraluminal pressure
Distention initiates relaxation of the internal anal sphincter in response to rectal distention. In patients with Hirschsprung disease, the internal anal sphincter fails to relax in response to rectal distention. Although the sensitivity and specificity can vary widely, in experienced hands, the test can be quite sensitive. The test, however, can be technically difficult to perform in young infants. A normal response in the course of manometric evaluation precludes a diagnosis of Hirschsprung disease; an equivocal or paradoxical response requires a repeat motility or rectal biopsy.

Increases, resulting in decreased blood flow and deterioration of the mucosal barrier. Stasis allows proliferation of bacteria, which can lead to enteroocolitis (Clostridium difficile, Staphylococcus aureus, anaerobes, coliforms) with associated diarrhea, abdominal tenderness, sepsis and signs of bowel obstruction. Early recognition of Hirschsprung disease before the onset of enteroocolitis is essential in reducing morbidity and mortality.

Hirschsprung disease in older patients must be distinguished from other causes of abdominal distention and chronic constipation (Table 332-5 and Fig. 332-2). The history often reveals constipation starting in infancy that has responded poorly to medical management. Fecal incontinence, fecal urgency, and stool-withholding behaviors are usually not present. The abdomen is tympanic and distended, with a large fecal mass palpable in the left lower abdomen. Rectal examination demonstrates a normally placed anus that easily allows entry of the finger but feels snug. The rectum is usually empty of feces, and when the finger is removed, there may be an explosive discharge of foul-smelling feces and gas. The stools, when passed, can consist of small pellets, be ribbon-like, or have a fluid consistency, unlike the large stools seen in patients with functional constipation. Intermittent attacks of intestinal obstruction from retained feces may be associated with pain and fever. Urinary retention with enlarged balder or hydrenephrosis can occur secondary to urinary compression.

In neonates, Hirschsprung disease must be differentiated from meconium plug syndrome, meconium ileus, and intestinal atresia. In older patients, the Currarino triad must be considered, which includes anorectal malformations (ectopic anus, anal stenosis, imperforate anus), sacral bone anomalies (hypoplasia, poor segmentation), and presacral anomaly (anterior meningoceles, teratoma, cyst).

**DIAGNOSIS**

Rectal suction biopsy is the gold standard for diagnosing Hirschsprung disease. The biopsy material should contain an adequate amount of submucosa to evaluate for the presence of ganglion cells. To avoid obtaining biopsies in the normal area of hypoganglionosis, which ranges from 3-17 mm in length, the suction rectal biopsy should be obtained no closer than 2 cm above the dentate line. The biopsy specimen should be stained for acetylcholinesterase to facilitate interpretation. Patients with aganglionosis demonstrate a large number of hypertrophied nerve bundles that stain positively for acetylcholinesterase with an absence of ganglion cells. Calretinin staining may provide a diagnosis of Hirschsprung disease when acetylcholinesterase staining may not be sufficient.

Anorectal manometry evaluates the internal anal sphincter while a balloon is distended in the rectum. In healthy individuals, rectal distention initiates relaxation of the internal anal sphincter in response to rectal distention. In patients with Hirschsprung disease, the internal anal sphincter fails to relax in response to rectal distention. Although the sensitivity and specificity can vary widely, in experienced hands, the test can be quite sensitive. The test, however, can be technically difficult to perform in young infants. A normal response in the course of manometric evaluation precludes a diagnosis of Hirschsprung disease; an equivocal or paradoxical response requires a repeat motility or rectal biopsy.

**Table 332-5** Distinguishing Features of Hirschsprung Disease and Functional Constipation

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>FUNCTIONAL</th>
<th>HIRSCHSPRUNG DISEASE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HISTORY</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Onset of constipation</td>
<td>After 2 yr of age</td>
<td>At birth</td>
</tr>
<tr>
<td>Encopresis</td>
<td>Common</td>
<td>Very rare</td>
</tr>
<tr>
<td>Failure to thrive</td>
<td>Uncommon</td>
<td>Possible</td>
</tr>
<tr>
<td>Enterocolitis</td>
<td>None</td>
<td>Possible</td>
</tr>
<tr>
<td>Forced bowel training</td>
<td>Usual</td>
<td>None</td>
</tr>
<tr>
<td><strong>EXAMINATION</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal distention</td>
<td>Uncommon</td>
<td>Common</td>
</tr>
<tr>
<td>Poor weight gain</td>
<td>Rare</td>
<td>Common</td>
</tr>
<tr>
<td>Rectum</td>
<td>Filled with stool</td>
<td>Empty</td>
</tr>
<tr>
<td>Rectal examination</td>
<td>Stool in rectum</td>
<td>Explosive passage of stool</td>
</tr>
<tr>
<td>Malnutrition</td>
<td>None</td>
<td>Possible</td>
</tr>
<tr>
<td><strong>INVESTIGATIONS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anorectal manometry</td>
<td>Relaxation of internal anal sphincter</td>
<td>Failure of internal anal sphincter relaxation</td>
</tr>
<tr>
<td>Rectal biopsy</td>
<td>Normal</td>
<td>No ganglion cells, increased acetylcholinesterase staining</td>
</tr>
<tr>
<td>Barium enema</td>
<td>Massive amounts of stool, no transition zone</td>
<td>Transition zone, delayed evacuation (&gt;24 hr)</td>
</tr>
</tbody>
</table>

An unprepared contrast enema is most likely to aid in the diagnosis in children older than 1 mo of age because the proximal ganglionic segment might not be significantly dilated in the 1st few wk of life. Classic findings are based on the presence of an abrupt narrow transition zone between the normal dilated proximal colon and a smaller-caliber obstructed distal ganglionic segment. In the absence of this finding, it is imperative to compare the diameter of the rectum to that of the sigmoid colon, because a rectal diameter that is the same as or smaller than the sigmoid colon suggests Hirschsprung disease. Radiologic evaluation should be performed without preparation to prevent transient dilation of the ganglionic segment. As many as 10% of newborns with Hirschsprung disease have a normal contrast study. Twenty-four-hour delayed films are helpful in showing retained contrast (see Fig. 332.2). If significant barium is still present in the colon, it increases the suspicion of Hirschsprung disease even if a transition zone is not identified. Barium enema examination is useful in determining the extent of aganglionosis before surgery and in evaluating other diseases that manifest as lower bowel obstruction in a neonate. Full-thickness rectal biopsies can be performed at the time of surgery to confirm the diagnosis and level of involvement.

**TREATMENT**

Once the diagnosis is established, the definitive treatment is operative intervention. Previously, a temporary ostomy was placed and definitive surgery was delayed until the child was older. Currently, many infants undergo a primary pull-through procedure except if there is associated enterocolitis or other complications, when a decompressing ostomy is usually required.

There are 3 basic surgical options. The first successful surgical procedure, described by Swenson, was to excise the ganglionic segment and anastomose the normal proximal bowel to the rectum 1-2 cm above the dentate line. The operation is technically difficult and led to the development of 2 other procedures. Duhamel described a procedure to create a neorectum, bringing down normally innervated bowel behind the aganglionic rectum. The neorectum created in this procedure has an anterior aganglionic segment with normal sensation and a posterior ganglionic segment with normal propulsion. The endorectal pull-through procedure described by Soave involves stripping the mucosa from the aganglionic rectum and bringing normally innervated colon through the residual muscular cuff, thus bypassing the abnormal bowel from within. Advances in techniques have led to successful laparoscopic single-stage endorectal pull-through procedures, which are the treatment of choice.

In ultrashort-segment Hirschsprung disease, also known as anal achalasia, the aganglionic segment is limited to the internal sphincter. The clinical symptoms are similar to those of children with functional constipation. Ganglion cells are present on rectal suction biopsy, but the anorectal manometry is abnormal, with failure of relaxation of the internal anal sphincter in response to rectal distention. Current treatment, although controversial, includes anal botulism injection to relax the anal sphincter and anorectal myectomy if indicated.

Long-segment Hirschsprung disease involving the entire colon and, at times, part of the small bowel presents a difficult problem. Anorectal manometry and rectal suction biopsy demonstrate findings of Hirschsprung disease, but radiologic studies are difficult to interpret because a colonic transition zone cannot be identified. The extent of aganglionosis can be determined accurately by biopsy at the time of laparotomy. When the entire colon is aganglionic, often together with a length of terminal ileum, ileal-anal anastomosis is the treatment of choice, preserving part of the aganglionic colon to facilitate water absorption, which helps the stools to become firm.

The prognosis of surgically treated Hirschsprung disease is generally satisfactory; the great majority of patients achieve fecal continence. Long-term postoperative problems include constipation, recurrent enterocolitis, stricture, prolapse, perianal abscesses, and fecal soiling. Some children require myectomy or a redo pull-through procedure.

### 332.5 Intestinal Neuronal Dysplasia

**Kristin N. Fiorino and Chris A. Liacouras**

Intestinal neuronal dysplasia (IND) describes different quantitative (hypo- or hyperganglionosis) and qualitative (immature or heterotopic ganglion cells) abnormalities of the myenteric and/or submucosal plexus. The typical histology is that of hyperganglionosis and giant ganglia. Type A occurs very rarely and is characterized by congenital aplasia or hypoplasia of the sympathetic innervation. Patients present early in the neonatal period with episodes of intestinal obstruction, diarrhea, and bloody stools. Type B, which accounts for more than 95% of cases, is characterized by malformation of the parasympathetic submucous and myenteric plexus with giant ganglia and thickened nerve fibers, increased acetylcholinesterase staining, and isolated ganglion cells in the lamina propria. IND type B mimics Hirschsprung disease, and patients present with chronic constipation.

Clinical manifestations include abdominal distention, constipation, and enterocolitis. Various lengths of bowel may be affected from segmental to the entire intestinal tract. IND has been observed in an isolated form and proximal to an aganglionic segment. Other intra- and extraintestinal manifestations are present in patients with IND. It has been reported in all age groups, most commonly in infancy, but is also seen in adults who have had constipation not dating back to childhood.

Associated diseases and conditions include Hirschsprung disease, prematurity, small left colon syndrome, and meconium plug syndrome. Studies have identified a deficiency in substance P in patients with IND. No mutations in the coding regions of the RET, GDNF, EDNRB, or EDN3 genes have been identified.

Management includes that for functional constipation and, if unsuccessful, surgery is indicated.

*Bibliography is available at Expert Consult.*

### 332.6 Superior Mesenteric Artery Syndrome (Wilkie Syndrome, Cast Syndrome, Arteriomesenteric Duodenal Compression Syndrome)

**Andrew Chu and Chris A. Liacouras**

Superior mesenteric artery syndrome results from compression of the 3rd duodenal segment by the artery against the aorta. Malnutrititions or catabolic states may cause mesenteric fat depletion, which collapses the duodenum within a narrowed aortomesenteric angle. Other etiologies include extraabdominal compression (e.g., body cast) and mesenteric tension, as can occur from ileoanal pouch anastomosis.

Symptoms include intermittent epigastric pain, anorexia, nausea, and vomiting. Risk factors include thin body habitus, prolonged bed rest, abdominal surgery, and exaggerated lumbar lordosis. Onset can be within weeks of a trigger, but some patients have chronic symptoms that evade diagnosis. A classic example is an underweight adolescent who begins vomiting 1-2 wk following scoliosis surgery. Recognition may be delayed in the context of an eating disorder.

The diagnosis is established radiologically by demonstrating a duodenal cutoff just right of midline along with proximal duodenal dilation, with or without gastric dilation. Although the upper gastrointestinal series remains a mainstay, modalities including CT, MR angiography, or ultrasound may be more appropriate if there is concern for other etiologies like malignancy. Upper endoscopy should be considered to rule out intraluminal pathology.

Treatment focuses on obstructive relief, nutritional rehabilitation, and correction of associated fluid and electrolyte abnormalities. Lateral or prone positioning can shift the duodenum away from obstructing structures and allow resumption of oral intake. In such cases, prokinetic agents (e.g., erythromycin) may be helpful. If repositioning is
Bibliography
Bibliography


Bibliography

unsuccessful, patients require nasojejunal enteral nutrition past the obstruction or parenteral nutrition if this is not tolerated. Patients with refractory courses may require surgery to bypass the obstruction.

*Bibliography is available at Expert Consult.*
Bibliography
Ileus is the failure of intestinal peristalsis caused by loss of coordinated gut motility without evidence of mechanical obstruction. In children, it is most often associated with abdominal surgery or infection (gastroenteritis, pneumonia, peritonitis). Ileus also accompanies metabolic abnormalities (e.g., uremia, hypokalemia, hypercalcemia, hypermagnesemia, acidosis) or administration of certain drugs, such as opiates, vincristine, and antimotility agents such as loperamide when used during gastroenteritis.

Ileus manifests with nausea, vomiting, feeding intolerance, abdominal distention with associated pain, and delayed passage of stool and bowel gas. Bowel sounds are minimal or absent, in contrast to early mechanical obstruction, when they are hyperactive. Abdominal radiographs demonstrate multiple air–fluid levels throughout the abdomen. Serial radiographs usually do not show progressive distention as they do in mechanical obstruction. Contrast radiographs, if performed, demonstrate slow movement of barium through a patent lumen. Ileus after abdominal surgery generally resolves within 72 hr.

Treatment involves correcting the underlying abnormality, supportive care of comorbidities, and mitigation of iatrogenic contributions. Electrolyte abnormalities should be identified and corrected, and narcotic agents, when used, should be weaned as tolerated. Nasogastric decompression can relieve recurrent vomiting or abdominal distention associated with pain; resultant fluid losses should be corrected with isotonic crystalloid solution. Prokinetic agents such as erythromycin are not routinely recommended. Selective peripheral opioid antagonists such as methylnaltrexone hold promise in decreasing postoperative ileus, but pediatric data are lacking.

Bibliography is available at Expert Consult.

Adhesions are fibrous tissue bands that result from peritoneal injury. They can constrict hollow organs and are a major cause of postoperative small bowel obstruction. Most remain asymptomatic, but problems can arise anytime after the 2nd postoperative week to years after surgery, regardless of surgical extent. In one study, the 5-year readmission risk because of adhesions varied by operative region (2.1% for colon to 9.2% for ileum) and procedure (0.3% for appendectomy to 25% for ileostomy formation/closure). The overall risk was 5.3% excluding appendectomy and 1.1% when appendectomy was included.

The diagnosis is suspected in patients with abdominal pain, constipation, emesis, and a history of intraperitoneal surgery. Nausea and vomiting quickly follow onset of pain. Initially, bowel sounds are hyperactive, and the abdomen is flat. Subsequently, bowel sounds disappear, and bowel dilation can cause abdominal distention. Fever and leukocytosis suggest bowel necrosis and peritonitis. Plain radiographs demonstrate obstructive features, and a CT scan or contrast studies may be needed to define the etiology.

Management includes nasogastric decompression, intravenous fluid resuscitation, and broad-spectrum antibiotics in preparation for surgery. Nonoperative intervention is contraindicated unless a patient is stable with obvious clinical improvement. In children with repeated obstruction, fibrin-glued plication of adjacent small bowel loops can reduce the risk of recurrent problems. Long-term complications include female infertility, failure to thrive, and chronic abdominal and/or pelvic pain.

Bibliography is available at Expert Consult.

Intussusception occurs when a portion of the alimentary tract is telescoped into an adjacent segment. It is the most common cause of intestinal obstruction between 5 mo and 3 yr of age and the most common abdominal emergency in children younger than 2 yr. Sixty percent of patients are younger than 1 yr of age, and 80% of the cases occur before age 24 mo; it is rare in neonates. The incidence varies from 1 to 4 per 1,000 live births. The male:female ratio is 3:1. Many small bowel–small bowel and a few small bowel–colon intussusceptions reduce spontaneously; if left untreated, ileal–colonic intussusception may lead to intestinal infarction, perforation, peritonitis, and death.

**ETIOLOGY AND EPIDEMIOLOGY**

Approximately 90% of cases of intussusception in children are idiopathic. The seasonal incidence has peaks in fall and winter. Correlation with prior or concurrent respiratory adenovirus (type C) infection has been noted, and the condition can complicate otitis media, gastroenteritis, Henoch-Schönlein purpura, or other upper respiratory tract infections. The risk of intussusception was increased in infants 1 yr of age or younger after receiving a tetravalent rhesus-human reassortant rotavirus vaccine within 2 wk of immunization. The Advisory Committee on Immunization Practices no longer recommends this vaccine, and it is no longer available. Although rotavirus produces an enterotoxin, there is no association between wild-type human rotavirus and intussusception. The currently approved rotavirus vaccines are associated with a slightly increased risk of intussusception.

It is postulated that gastrointestinal infection or the introduction of new food proteins results in swollen Peyer patches in the terminal ileum. Lymphoid nodular hyperplasia is another related risk factor. Prominent mounds of lymph tissue lead to mucosal prolapse of the ileum into the colon, thus causing an intussusception. In 2-8% of patients, recognizable lead points for the intussusception are found, such as a Meckel diverticulum, intestinal polyp, neurofibroma, intestinal duplication cysts, inverted appendix stump, leiomyomas, ectopic pancreatic tissue, anastomotic suture line, enterostomy tube, posttransplant lymphoproliferative disease, hemangioma, or malignant conditions such as lymphoma, or Kaposi sarcoma. Lead points are more common in children older than 2 yr of age; the older the child, the higher the risk of a lead point. In adults, lead points are present in 90%. Intussusception can complicate mucosal hemorrhage, as in Henoch-Schönlein purpura, idiopathic thrombocytopenic purpura, or hemophilia. Cystic fibrosis, celiac disease, and Crohn disease are other risk factors. Postoperative intussusception is ileocolic and usually occurs within several days of an abdominal operation. Intrauterine intussusception may be associated with the development of intestinal atresia. Intussusception in premature infants is rare.
Bibliography
Bibliography
Ileal–ileal intussusception may be more common than previously believed, is often idiopathic or associated with Henoch-Schönlein purpura, and usually resolves spontaneously.

**PATHOLOGY**

Intussusceptions are most often ileocolic, less commonly cecocolic, and occasionally ileal. Very rarely, the appendix forms the apex of an intussusception. The upper portion of bowel, the intussuscipiens, invaginates into the lower, the intussusceptum, pulling its mesentery along with it into the enveloping loop. Constriction of the mesentery obstructs venous return; engorgement of the intussusceptum follows, with edema, and bleeding from the mucosa leads to a bloody stool, sometimes containing mucus. The apex of the intussusception can extend into the transverse, descending, or sigmoid colon, even to and through the anus in neglected cases. This presentation must be distinguished from rectal prolapse. Most intussusceptions do not strangulate the bowel within the 1st 24 hr but can eventuate in intestinal gangrene and shock.

**CLINICAL MANIFESTATIONS**

In typical cases, there is sudden onset, in a previously well child, of severe paroxysmal colicky pain that recurs at frequent intervals and is accompanied by straining efforts with legs and knees flexed and loud cries. The infant may initially be comfortable and play normally between the paroxysms of pain; but if the intussusception is not reduced, the infant becomes progressively weaker and lethargic. At times, the lethargy is disproportionate to the abdominal signs. Eventually, a shock-like state, with fever and peritonitis, can develop. The pulse becomes weak and thready; the respirations become shallow and grunting, and the pain may be manifested only by moaning sounds. Vomiting occurs in most cases and is usually more frequent in the early phase. In the later phase, the vomitus becomes bile stained. Stools of normal appearance may be evacuated in the 1st few hr of symptoms. After this time, fecal excretions are small or more often do not occur, and little or no flatus is passed. Blood is generally passed in the 1st 12 hr, but at times not for 1-2 days, and infrequently not at all; 60% of infants pass a stool containing red blood and mucus, the currant jelly stool. Some patients have only irritability and alternating or progressive lethargy. The classic triad of pain, a palpable sausage-shaped abdominal mass, and bloody or currant jelly stool is seen in <30% of patients with intussusception. The combination of paroxysmal pain, vomiting and a palpable abdominal mass has a positive predictive value of >90%; the presence of rectal bleeding increases this to approximately 100%.

Palpation of the abdomen usually reveals a slightly tender sausage-shaped mass, sometimes ill defined, which might increase in size and firmness during a paroxysm of pain and is most often in the right upper abdomen, with its long axis cephalocaudal. If it is felt in the epigastrium, the long axis is transverse. Approximately 30% of patients do not have a palpable mass. The presence of bloody mucus on rectal examination supports the diagnosis of intussusception. Abdominal distention and tenderness develop as intestinal obstruction becomes more acute. On rare occasions, the advancing intestine prolapses through the anus. This prolapse can be distinguished from prolapse of the rectum by the separation between the protruding intestine and the rectal wall, which does not exist in prolapse of the rectum.

Ileoleal intussusception in children younger than 2 yr can have a less-typical clinical picture, the symptoms and signs being chiefly those of small intestinal obstruction; these often resolve without treatment. **Recurrent intussusception** is noted in 5-8% and is more common after hydrostatic than surgical reduction. Chronic intussusception, in which the symptoms exist in milder form at recurrent intervals, is more likely to occur with or after acute enteritis and can arise in older children as well as in infants.

**DIAGNOSIS**

When the clinical history and physical findings suggest intussusception, an ultrasound is typically performed. A plain abdominal radiograph might show a density in the area of the intussusception. Screening ultrasounds for suspected intussusception increases the yield of diagnostic or therapeutic enemas and reduces unnecessary radiation exposure in children with negative ultrasound examinations. The diagnostic findings of intussusception on ultrasound include a tubular mass in longitudinal views and a doughnut or target appearance in transverse images (Fig. 333-1). Ultrasound has a sensitivity of approximately 98-100% and a specificity of approximately 98% in diagnosing intussusception. Air, hydrostatic (saline), and, less often, water-soluble contrast enemas have replaced barium examinations. Contrast enemas demonstrate a filling defect or cupping in the head of the contrast media where its advance is obstructed by the intussusceptum (Fig. 333-2). A central linear column of contrast media may be visible in the compressed lumen of the intussusceptum, and a thin rim of contrast may be seen trapping around the invaginating intestine in the folds of mucosa within the intussusciplens (coiled-spring sign), especially after evacuation. Retrogression of the intussusceptum under pressure and visualized on x-ray or ultrasound documents successful reduction. Air reduction is associated with fewer complications and lower radiation exposure than traditional contrast hydrostatic techniques.

**DIFFERENTIAL DIAGNOSIS**

It may be particularly difficult to diagnose intussusception in a child who already has gastroenteritis; a change in the pattern of illness, in the character of pain, or in the nature of vomiting or the onset of rectal bleeding should alert the physician. The bloody stools and abdominal cramps that accompany enterocolitis can usually be differentiated from intussusception because in enterocolitis the pain is less severe and less regular, there is diarrhea, and the infant is recognizable ill between pains. Bleeding from a Meckel diverticulum is usually painless. Joint symptoms, purpura, or hematuria usually but not invariably accompany the intestinal hemorrhage of Henoch-Schönlein purpura. Because intussusception can be a complication of this disorder, ultrasonography may be needed to distinguish the conditions.
Corticosteroids may reduce the frequency of recurrent intussusception. Repeated reducible episodes caused by lymphonodular hyperplasia may respond to treatment of identifiable food allergies if present. A single recurrence of intussusception can usually be reduced radiologically. In patients with multiple ileal–colonic recurrences, a lead point should be suspected and laparoscopic surgery considered. It is unlikely that an intussusception caused by a lesion such as lymphosarcoma, polypp, or Meckel diverticulum will be successfully reduced by radiologic intervention. With adequate surgical management, laparoscopic reduction carries a very low mortality.

Bibliography is available at Expert Consult.

333.4 Closed-Loop Obstructions

Andrew Chu and Chris A. Liacouras

Closed-loop obstructions (i.e., internal hernia) result from bowel loops that enter windows created by mesenteric defects or adhesions and become trapped. Vascular engorgement of the strangulated bowel results in intestinal ischemia and necrosis unless promptly relieved. Prior abdominal surgery is an important risk factor. Symptoms include abdominal pain, distention, and bilious emesis. Symptoms can be intermittent if the herniated bowel slides in and out of the defect. Peritoneal signs suggest ischemic bowel. Plain radiographs demonstrate signs of small bowel obstruction or free air if the bowel has perforated. CT scan can identify and delineate internal hernias. Supportive management includes intravenous fluids, antibiotics, and nasogastric decompression. Prompt surgical relief of the obstruction is indicated to prevent bowel necrosis.

Bibliography is available at Expert Consult.

It is important in patients with cystic fibrosis to distinguish intussusception from distal intestinal obstruction syndrome. Distal intestinal obstruction syndrome requires antegrade treatment, which would be harmful if there was an intussusception.

TREATMENT

Reduction of an acute intussusception is an emergency procedure and should be performed immediately after diagnosis in preparation for possible surgery. In patients with prolonged intussusception and signs of shock, peritoneal irritation, intestinal perforation, or pneumatisos intestinalis, hydrostatic reduction should not be attempted.

The success rate of radiologic hydrostatic reduction under fluoroscopic or ultrasonic guidance is approximately 80-95% in patients with ileocolic intussusception. Spontaneous reduction of intussusception occurs in approximately 4-10% of patients. Bowel perforations occur in 0.5-2.5% of attempted barium and hydrostatic (saline) reductions. The perforation rate with air reduction is 0.1-0.2%. Surgical reduction is indicated in the presence of refractory shock, suspected bowel necrosis or perforation, peritonitis, and multiple recurrences (suspected lead point).

An ileoileal intussusception is best demonstrated by abdominal ultrasonography. Reduction by instillation of contrast agents, saline, or air might not be possible. Such intussusceptions can develop insidiously after bowel surgery and require reoperation if they do not spontaneously reduce. Ileoileal disease is common with Henoch-Schönlein purpura and other unidentifiable disorders and usually resolves without the need for any specific treatment. If manual operative reduction is impossible or the bowel is not viable, resection of the intussusception is necessary, with end-to-end anastomosis.

PROGNOSIS

Untreated intussusception in infants is usually fatal; the chances of recovery are directly related to the duration of intussusception before reduction. Most infants recover if the intussusception is reduced in the 1st 24 hr, but the mortality rate rises rapidly after this time, especially after the 2nd day. Spontaneous reduction during preparation for operation is not uncommon.

The recurrence rate after reduction of intussusceptions is approximately 10%, and after surgical reduction it is 2-5%; none has recurred after surgical resection. Most recurrences occur within 72 hr of reduction.
Chapter 333  •  Ileus, Adhesions, Intussusception, and Closed-Loop Obstructions

Bibliography


Bibliography
Once in the stomach, 95% of all ingested objects pass without difficulty through the remainder of the gastrointestinal tract. Perforation after ingestion of a foreign body is estimated to be <1% of all objects ingested. Perforation tends to occur in areas of physiologic sphincters (pylorus, ileocecal valve), acute angulation (duodenal sweep), congenital gut malformations (webs, diaphragms, diverticula), or areas of previous bowel surgery.

Most patients who ingest foreign bodies are between the ages of 6 mo and 6 yr. Coins are the most commonly ingested foreign body in children, and meat or food impactions are the most common accidental foreign body in adolescents and adults. Patients with nonfood foreign bodies often describe a history of ingestion. Young children might have a witness to ingestion. Immediate concerns are what is the foreign body, location of the foreign body, what is the size of the foreign body, and the time that the ingestion occurred. Approximately 90% of foreign bodies are opaque. Radiologic examination is routinely performed to determine the type, number, and location of the suspected objects. Contrast radiographs may be necessary to demonstrate some objects, such as plastic parts or toys.
Conservative management is indicated for most foreign bodies that have passed through the esophagus and entered the stomach. Most objects pass through the intestine in 4–6 days, although some take as long as 3–4 wk. While waiting for the object to pass, parents are instructed to continue a regular diet and to observe the stools for the appearance of the ingested object. Cathartics should be avoided. Exceptionally long or sharp objects are usually monitored radiologically. Parents or patients should be instructed to report abdominal pain, vomiting, persistent fever, and hematemesis or melena immediately to their physicians. Failure of the object to progress within 3–4 wk seldom implies an impending perforation but may be associated with a congenital malformation or acquired bowel abnormality.

Certain objects pose more risk than others. In cases of sharp foreign bodies, such as straight pins, weekly assessments are required. Surgical removal is necessary if the patient develops symptoms or signs of obstruction or perforation or if the foreign body fails to progress for several weeks. Small magnets used to secure earrings or parts of toys are associated with bowel perforation. Whereas a single magnet in the stomach may not require intervention in a asymptomatic child, a magnet in the esophagus requires immediate removal. When the multiple magnets disperse after ingestion, they may be attracted to each other across bowel wall, leading to pressure necrosis and perforation (Fig. 334-1). Inexpensive toy medallions containing lead can lead to lead toxicity. Newer coins can also decompose when subjected to prolonged acid exposure. Unless multiple coins are ingested; however, the metals released are unlikely to pose a clinical risk.

Ingestion of batteries rarely leads to problems, but symptoms can arise from leakage of alkali or heavy metal (mercury) from battery degradation in the gastrointestinal tract. Batteries can also generate electrical current and thereby cause low-voltage electrical burns to the intestine. If patients experience symptoms such as vomiting or abdominal pain, if a large-diameter battery (>20 mm in diameter) remains in the stomach for longer than 48 hr, or if a lithium battery is ingested, the battery should be removed. Batteries larger than 15 mm that do not pass the pylorus within 48 hr are less likely to pass spontaneously and generally require removal. In children younger than 6 yr of age, batteries larger than 15 mm are not likely to pass spontaneously and should be removed endoscopically. If the patient develops peritoneal signs, surgical removal is required. Batteries beyond the duodenum pass per rectum in 85% within 72 hr. The battery should be identified by size and imprint code or by evaluation of a duplicate measurement of the battery compartment. The National Battery Ingestion Hotline (202-865-3333) can be called for help in identification. The Poison Control Center (800-222-1222) can be called as well for ingestion of batteries and caustic materials. Lithium batteries result in more rapid enlargement in the small intestine. Surgical removal is indicated. Early endoscopic removal is indicated of an object suspected to contain lead. A lead level should be obtained.

Water-absorbing polymer balls (beads) can expand to approximately 400 times its starting size and if ingested may produce intestinal obstruction. Initially of a small diameter, they pass the pylorus only to rapidly enlarge in the small intestine. Surgical removal is indicated.

Children occasionally place objects in their rectum. Small blunt objects usually pass spontaneously, but large or sharp objects typically need to be retrieved. Adequate sedation is essential to relax the anal sphincter before attempted endoscopic or speculum removal. If the object is proximal to the rectum, observation for 12-24 hr usually allows the object to descend into the rectum.

**Bibliography is available at Expert Consult.**

### 334.2 Bezoars

*Judith R. Kelsen and Chris A. Liacouras*

A bezoar is an accumulation of exogenous matter in the stomach or intestine. They are predominantly composed of food or fiber. Most bezoars have been found in females with underlying personality problems or in neurologically impaired persons. Patients who have undergone abdominal surgery are at higher risk for the development of bezoars. The peak age at onset of symptoms is the 2nd decade of life.

Bezoars are classified on the basis of their composition. **Trichobezoars** are composed of the patient’s own hair. It is most frequently it is a complication of the psychiatric disorders trichotillomania and the most severe form is known as Rapunzel syndrome. **Phytobezoars** are
Bibliography
composed of a combination of plant and animal material, and gastric phytobezoars are the most common in patients with poor motility. **Lactobezoars** were previously found most often in premature infants and can be attributed to the high casein or calcium content of some premature formulas. Swallowed chewing gum can occasionally lead to a bezoar.

Trichobezoars can become large and form casts of the stomach; they can enter into the proximal duodenum. They manifest as symptoms of gastric outlet or partial intestinal obstruction including vomiting, anorexia, and weight loss. Patients might complain of abdominal pain, distention, and severe halitosis. Physical examination can demonstrate patchy baldness and a firm mass in the left upper quadrant. Patients occasionally have iron-deficiency anemia, hypoproteinemia, or steatorrhea caused by an associated chronic gastritis. Phytobezoars manifest in a similar manner. Detached segments of the bezoar or trichobezoar can migrate to the small intestine as a “satellite masses” and result in small bowel obstruction.

An abdominal plain film can suggest the presence of a bezoar, which can be confirmed on ultrasound or CT examination. On CT a bezoar appears a nonhomogeneous, nonenhancing mass within the lumen of the stomach or intestine. Oral contrast circumscribes the mass.

Bezoars in the stomach can usually be removed endoscopically. If endoscopy is unsuccessful, surgical intervention may be needed. Lactobezoars usually resolve when feedings are withheld for 24-48 hr. Coca-Cola has been used as a dissolution therapy for gastric phytobezoar and has been shown to be effective when used with endoscopy.

Sunflower seed bezoars are reported to cause rectal pain and constipation as a result of the seed shells being associated with fecal impaction. Endoscopic removal is indicated, as these bezoars are refractory to enema or lavage management.

*Bibliography is available at Expert Consult.*
Bibliography
Peptic ulcer disease, the end result of inflammation caused by an imbalance between cytoprotective and cytotoxic factors in the stomach and duodenum, manifests with varying degrees of gastritis or frank ulceration. The pathogenesis of peptic ulcer disease is multifactorial, but the final common pathway for the development of ulcers is the action of acid and pepsin-laden contents of the stomach on the gastric and duodenal mucosa and the inability of mucosal defense mechanisms to allay those effects. Abnormalities in the gastric and duodenal mucosa can be visualized on endoscopy, with or without histologic changes. Deep mucosal lesions that disrupt the muscularis mucosa of the gastric or duodenal wall define peptic ulcers. Gastric ulcers are generally located on the lesser curvature of the stomach, and 90% of duodenal ulcers are found in the duodenal bulb. Despite the lack of large population-based pediatric studies, rates of peptic ulcer disease in childhood appear to be low. Large pediatric centers anecdotally report an incidence of 5-7 children with gastric or duodenal ulcers per 2,500 hospital admissions each year.

Ulcers in children can be classified as primary peptic ulcers, which are chronic and more often duodenal, or secondary, which are usually more acute in onset and are more often gastric (Table 335-1). Primary ulcers are most often associated with Helicobacter pylori infection; idiopathic primary peptic ulcers account for up to 20% of duodenal ulcers in children. Secondary peptic ulcers can result from stress caused by sepsis, shock, or an intracranial lesion (Cushing ulcer), or in response to a severe burn injury (Curling ulcer). Secondary ulcers are often the result of using aspirin or nonsteroidal antiinflammatory drugs (NSAIDs); hypersecretory states like Zollinger-Ellison syndrome (see Chapter 335.1), short bowel syndrome, and systemic mastocytosis are rare causes of peptic ulceration.

**PATHOGENESIS**

**Acid Secretion**

By 3–4 yr of age, gastric acid secretion approximates adult values. Acid initially secreted by the oxyntic cells of the stomach has a pH of approximately 0.8, whereas the pH of the stomach contents is 1-2. Excessive acid secretion is associated with a large parietal cell mass, hypersecretion by antral G cells, and increased vagal tone, resulting in increased or sustained acid secretion in response to meals and increased secretion during the night. The secretagogues that promote gastric acid production include acetylcholine released by the vagus nerve, histamine secreted by enterochromaffin cells, and gastrin released by the G cells of the antrum. Mediators that decrease gastric acid secretion and enhance protective mucin production include prostaglandins.

**Mucosal Defense**

A continuous layer of mucous gel that serves as a diffusion barrier to hydrogen ions and other chemicals covers the gastrointestinal (GI) mucosa. Mucus production and secretion are stimulated by prostaglandin E2. Underlying the mucous coat, the epithelium forms a second-line barrier, the characteristics of which are determined by the biology of the epithelial cells and their tight junctions. Another important function of epithelial cells is to secrete chemokines when threatened by microbial attack. Secretion of bicarbonate into the mucous coat, which is regulated by prostaglandins, is important for neutralization of hydrogen ions. If mucosal injury occurs, active proliferation and migration of mucosal cells occurs rapidly, driven by epithelial growth factor, transforming growth factor-α, insulin-like growth factor, gastrin, and bombesin, and covers the area of epithelial damage.

**CLINICAL MANIFESTATIONS**

The presenting symptoms of peptic ulcer disease vary with the age of the patient. Hematemesis or melena is reported in up to half of the patients with peptic ulcer disease. School-age children and adolescents more commonly present with epigastric pain and nausea, presentations generally seen in adults. Dyspepsia, epigastric abdominal pain or fullness, is seen in older children. Infants and younger children usually

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**Table 335-1 Etiologic Classification of Peptic Ulcers**

| Positive for *Helicobacter pylori* infection |
| Drug (NSAID)-induced |
| *H. pylori* and NSAID-positive |
| *H. pylori* and NSAID-negative* |
| Acid hypersecretory state (Zollinger-Ellison syndrome) |
| Anastomosis ulcer after subtotal gastric resection |
| Tumors (cancer, lymphoma) |
| Rare specific causes |
| Crohn disease of the stomach or duodenum |
| Eosinophilic gastroenteritis |
| Systemic mastocytosis |
| Radiation damage |
| Viral infections (cytomegalovirus or herpes simplex infection, particularly in immunocompromised patients) |
| Colonization of stomach with *Helicobacter heilmannii* |
| Severe systemic disease |
| Cameron ulcer (gastric ulcer where a hiatal hernia passes through the diaphragmatic hiatus) |
| True idiopathic ulcer |

*Requires search for other specific causes.

NSAID, nonsteroidal anti-inflammatory drug.

present with feeding difficulty, vomiting, crying episodes, hematemesis, or melena. In the neonatal period, gastric perforation can be the initial presentation.

The classic symptom of peptic ulceration, epigastric pain alleviated by the ingestion of food, is present only in a minority of children. Many pediatric patients present with poorly localized abdominal pain, which may be periumbilical. The vast majority of patients with periumbilical or epigastric pain or discomfort do not have a peptic ulcer, but rather a functional GI disorder, such as irritable bowel syndrome or nonulcer (functional) dyspepsia. Patients with peptic ulceration rarely present with acute abdominal pain from perforation or symptoms and signs of pancreatitis from a posterior penetrating ulcer. Occasionally, bright red blood per rectum may be seen if the rate of bleeding is brisk and the intestinal transit time is short. Vomiting can be a sign of gastric outlet obstruction.

The pain is often described as dull or aching, rather than sharp or burning, as in adults. It can last from minutes to hours; patients have frequent exacerbations and remissions lasting from weeks to months. Nocturnal pain waking the child is common in older children. A history of typical ulcer pain with prompt relief after taking antacids is found in <33% of children. Rarely, in patients with acute or chronic blood loss, penetration of the ulcer into the abdominal cavity or adjacent organs produces shock, anemia, peritonitis, or pancreatitis. If inflammation and edema are extensive, acute or chronic gastric outlet obstruction can occur.

**DIAGNOSIS**

Esophagogastroduodenoscopy is the method of choice to establish the diagnosis of peptic ulcer disease. It can be safely performed in all ages by experienced pediatric gastroenterologists. Endoscopy allows the direct visualization of esophagus, stomach, and duodenum, identifying the specific lesions. Biopsy specimens must be obtained from the esophagus, stomach, and duodenum for histologic assessment as well as to screen for the presence of *H. pylori* infection. Endoscopy also provides the opportunity for hemostatic therapy including injection and the use of a heater probe or electrocoagulation if necessary. Fecal enzyme immunoassay tests for *H. pylori* are available and have varying utility in children.

**PRIMARY ULCERS**

*Helicobacter pylori* Gastritis

*H. pylori* is among the most common bacterial infections in humans. *H. pylori* is a Gram-negative, S-shaped rod that produces urease, catalase, and oxidase, which might play a role in the pathogenesis of peptic ulcer disease. The mechanism of acquisition and transmission of *H. pylori* is unclear, although the most likely mode of transmission is fecal–oral or oral–oral. Viable *H. pylori* organisms can be cultured from the stool or vomitus of infected patients. Risk factors such as low socioeconomic status in childhood or affected family members also influence the prevalence. All children infected with *H. pylori* develop histologic chronic active gastritis but are often asymptomatic. In children, *H. pylori* infection can manifest with abdominal pain or vomiting and, less often, refractory iron deficiency anemia or growth retardation. *H. pylori* can be associated, though rarely, with chronic autoimmune thrombocytopenia. Chronic colonization with *H. pylori* can predispose children to a significantly increased risk of developing a duodenal ulcer, gastric cancer such as adenocarcinoma, or mucosa-associated lymphoid tissue lymphomas. The relative risk of gastric carcinoma is 2.3–8.7 times greater in infected adults as compared to uninfected subjects. *H. pylori* is classified by the World Health Organization as a group 1 carcinogen.

Anemia, idiopathic thrombocytopenic purpura, short stature, and sudden infant death syndrome (SIDS) have also been reported as extra-gastric manifestations of *H. pylori* infection. In one published study, *H. pylori* infection has been correlated with cases of SIDS, but there is no evidence to suggest that *H. pylori* plays a role in the pathogenesis of SIDS.

The diagnosis of *H. pylori* infection is made histologically by demonstrating the organism in the biopsy specimens (Fig. 335-1). Although serologic assays using validated immunoglobulin G antibody detection may be helpful for screening children for the presence of *H. pylori*, they do not help predict active infection or assess the success of antimicrobial eradication therapy. 13C-urea breath tests and stool antigen tests are also noninvasive methods of detecting *H. pylori* infection. Nonetheless, for children with suspected *H. pylori* infection, an initial upper endoscopy is recommended to evaluate and confirm *H. pylori* disease. The range of endoscopic findings in children with *H. pylori* infection varies from being grossly normal to the presence of nonspecific gastritis with prominent rugal folds, nodularity (Fig. 335-2), or ulcers. Because the antral mucosa appears to be endoscopically normal in a significant number of children with primary *H. pylori* gastritis, gastric biopsies should always be obtained from the body and antrum of the stomach regardless of the endoscopic appearance. If *H. pylori* is identified, even in a child with no symptoms, eradication therapy should be offered (Tables 335-2 and 335-3).

**Idiopathic Ulcers**

*H. pylori*-negative duodenal ulcers in children who have no history of taking NSAIDs represent 15–20% of pediatric duodenal ulcers. These patients do not have nodularity in the gastric antrum or histologic
prostaglandin production increases the risk of mucosal injury. The severe erosive gastropathy produced by NSAIDs can ultimately result in bleeding ulcers or gastric perforations. The location of these ulcers is more common in the stomach than in the duodenum, and usually in the antrum.

**“STRESS” ULCERATION**

Stress ulceration usually occurs within 24 hr of onset of a critical illness in which physiologic stress is present. In many cases, the patients bleed from gastric erosions, rather than ulcers. Approximately 25% of the critically ill children in a pediatric intensive care unit have macroscopic evidence of gastric bleeding. Preterm and term infants in the neonatal intensive care unit can also develop gastric mucosal lesions and can present with upper GI bleeding or perforated ulcers. Although prophylactic measures to prevent stress ulcers in children are not standardized, drugs that inhibit gastric acid production are often used in the evidence of gastritis. In idiopathic ulcers, acid suppression alone is the preferred effective treatment. Either proton pump inhibitors (PPIs) or \( \text{H}_2 \) receptor antagonists may be used. Idiopathic ulcers have a high recurrence rate after discontinuing antisecretory therapy. These children should be followed closely, and if symptoms recur, antisecretory therapy should be restarted. In such cases, if the child is older than 1 yr, PPIs are preferred for maintenance therapy, because they have been shown to be superior to \( \text{H}_2 \) receptor antagonists in preventing recurrent ulcers.

### TABLE 335-2

<table>
<thead>
<tr>
<th>MEDICATIONS</th>
<th>DOSE</th>
<th>DURATION OF TREATMENT</th>
</tr>
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<tbody>
<tr>
<td>Amoxicillin</td>
<td>50 mg/kg/day in 2 divided doses</td>
<td>14 days</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>15 mg/kg/day in 2 divided doses</td>
<td>14 days</td>
</tr>
<tr>
<td>Proton pump inhibitor</td>
<td>1 mg/kg/day in 2 divided doses</td>
<td>1 mo</td>
</tr>
<tr>
<td>or</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>50 mg/kg/day in 2 divided doses</td>
<td>14 days</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>20 mg/kg/day in 2 divided doses</td>
<td>14 days</td>
</tr>
<tr>
<td>Proton pump inhibitor</td>
<td>1 mg/kg/day in 2 divided doses</td>
<td>1 mo</td>
</tr>
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<td>or</td>
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</tr>
<tr>
<td>Clarithromycin</td>
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<td>14 days</td>
</tr>
<tr>
<td>Metronidazole</td>
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<td>14 days</td>
</tr>
<tr>
<td>Proton pump inhibitor</td>
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<td>1 mo</td>
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</tbody>
</table>


### TABLE 335-3

<table>
<thead>
<tr>
<th>MEDICATION</th>
<th>PEDIATRIC DOSE</th>
<th>HOW SUPPLIED</th>
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<tbody>
<tr>
<td>( \text{H}_2 ) RECEPTOR ANTAGONISTS</td>
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<td></td>
</tr>
<tr>
<td>Cimetidine</td>
<td>20-40 mg/kg/day</td>
<td></td>
</tr>
<tr>
<td>Divided 2-4 x a day</td>
<td></td>
<td>Syrup: 300 mg/mL</td>
</tr>
<tr>
<td>Ranitidine</td>
<td>4-10 mg/kg/day</td>
<td></td>
</tr>
<tr>
<td>Divided 2 or 3 x a day</td>
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<td>Syrup: 75 mg/5 mL</td>
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<tr>
<td>Famotidine</td>
<td>1-2 mg/kg/day</td>
<td></td>
</tr>
<tr>
<td>Divided twice a day</td>
<td></td>
<td>Syrup: 40 mg/5 mL</td>
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<tr>
<td>Nizatidine</td>
<td>5-10 mg/kg/day divided twice a day</td>
<td></td>
</tr>
<tr>
<td>Older than 12 yr: 150 mg twice a day</td>
<td></td>
<td>Solution: 15 mg/ml</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tablets: 75 mg</td>
</tr>
</tbody>
</table>

| PROTON PUMP INHIBITORS | | |
| Omeprazole | 1.0-3.3 mg/kg/day weigh <20 kg: 10 mg/day weigh >20 kg: 20 mg/day | | Capsules: 10, 20, 40 mg |
| Divided for use in those older than 2 yr | Approved for use in those older than 1 yr | | Tablets: 15, 30 mg |
| Lansoprazole | 0.8-4 mg/kg/day weigh <30 kg: 15 mg/day weigh >30 kg: 30 mg/day | | Powder packet: 15, 30 mg |
| Divided for use in those older than 1 yr | | SoluTab: 15, 30 mg |
| Delayed release capsule: 5, 10 mg | | Delayed release tablet: 20 mg |
| Delayed release tablet: 20, 40 mg | | |
| Rabeprazole | 1-11 yr(weigh <15 kg): 5 mg/day | | Tablet: 20, 40 mg |
| 1-11 yr (weigh >15 kg): 10 mg/day | | Powder pack: 40 mg |
| >12 yr: 20 mg tablet | | |
| Pantoprazole | 1.5 yr:0.3-1.2 mg/kg/day (limited data) | | |
| >5 yr of age | | |
| weight >15 kg to <40 kg: 20 mg/day | | |
| weight >40 kg: 40 mg/day | | |

| CYTOPROTECTIVE AGENTS | | |
| Sucralfate | 40-80 mg/kg/day | | Suspension: 1,000 mg/5 mL |
| Tablet: 1,000 mg | | |
pediatric intensive care unit to reduce the rate of gastric erosions or ulcers.

**TREATMENT**

The management of acute hemorrhage includes serial monitoring of pulse, blood pressure, and hematocrit to insure hemodynamic stability and avoid significant hypovolemia and anemia. Normal saline can be used to resuscitate a patient who has poor intravascular volume status. This can be followed by packed red blood cell transfusions for significant symptomatic anemia. The patient's blood should be typed and cross matched, and a large-bore catheter should be placed for fluid or blood replacement. A nasogastric tube should be placed to determine if the bleeding has stopped. Significant anemia can occur after fluid resuscitation as a consequence of equilibration or continued blood loss (which can also cause shock). In adults, a conservative threshold for transfusion (<7 g/dL vs 9 g hemoglobin) resulted in improved survival and fewer episodes of rebleeding. Fortunately, most acute peptic ulcer bleeding stops spontaneously.

Patients with suspected peptic ulcer hemorrhage should receive high-dose intravenous PPI therapy, which lowers the risk of rebleeding. Some centers also use octreotide, which lowers splanchnic blood flow and gastric acid production.

Once the patient is hemodynamically stable, endoscopy may be indicated to identify the source of bleeding and treat a potential bleeding site. Methods used for vessel hemostasis include pressure, laser, thermal or electric coagulation; clips; bands; and injections (epinephrine, saline).

Ulcerial therapy has 2 goals: ulcer healing and elimination of the primary cause. Other important considerations are relief of symptoms and prevention of complications. The first-line drugs for the treatment of gastritis and peptic ulcer disease in children are PPIs and H2 receptor antagonists (see Table 335-3). PPIs are more potent in ulcer healing. Cytoprotective agents can also be used as adjunct therapy if mucosal lesions are present. Antibiotics in combination with a PPI must be used for the treatment of *H. pylori*-associated ulcers (see Table 335-2).

H2-receptor antagonists (cimetidine, ranitidine, famotidine, nizatidine) competitively inhibit the binding of histamine at the H2 subtype receptor of the gastric parietal cell. PPIs block the gastric parietal cell H+/K+-adenosine triphosphatase pump in a dose-dependent fashion, reducing basal and stimulated gastric acid secretion. Currently, 7 PPIs are available in the United States: omeprazole, lansoprazole, pantoprazole, esomeprazole, rabeprazole, dexlansoprazole, and omeprazole/sodium bicarbonate. Apart from the last 2, they are all approved in children and adolescents. They are well tolerated with only minor adverse effects, such as diarrhea (1-4%), headache (1-3%), and nausea (1%). When one considers therapeutic efficacy, the evidence suggests that all PPIs have comparable efficacy in treatment of peptic ulcer disease using standard doses and are superior to H2-receptor antagonists. PPIs have their greatest effect when given before a meal. Pantoprazole and esomeprazole are the only PPI available in intravenous form in United States. Intravenous PPI should be used in acute upper GI bleeding. In adults, intravenous PPI in acute upper GI bleeding setting decreases the bleeding and need of intervention during endoscopy.

**Treatment of Helicobacter pylori-Related Peptic Ulcer Disease**

In pediatrics, antibiotics and bismuth salts have been used in combination with PPIs to treat *H. pylori* infection (see Table 335-2). Eradication rates in children range from 68-92% when the dual or triple therapy is used for 4-6 wk. The ulcer healing rate ranges from 91-100%. Triple therapy yields a higher cure rate than dual therapy. The optimal regimen for the eradication of *H. pylori* infection in children has yet to be established, but the use of a PPI in combination with clarithromycin and amoxicillin or metronidazole for 2 wk is a well-tolerated and recommended triple therapy (see Table 335-2). Although children younger than 5 yr of age can become reinfected, the most common reason for treatment failure is poor compliance or antibiotic resistance. *H. pylori* has become more resistant to clarithromycin or metronida-
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Inflammatory Bowel Disease

Andrew B. Grossman and Robert N. Baldassano

The term *inflammatory bowel disease* (IBD) is used to represent 2 distinctive disorders of idiopathic chronic intestinal inflammation: Crohn disease and ulcerative colitis. Their respective etiologies are poorly understood, and both disorders are characterized by unpredictable exacerbations and remissions. The most common time of onset of IBD is during the preadolescent/adolescent era and young adulthood. A bimodal distribution has been shown with an early onset at 10-20 yr of age and a second, smaller peak at 50-80 yr of age. Approximately 25% of patients present before 20 yr of age. IBD may begin as early as the 1st yr of life, and an increased incidence among young children has
been observed since the turn of the century. Children with early-onset IBD are more likely to have colonic involvement. In developed countries, these disorders are the major causes of chronic intestinal inflammation in children beyond the 1st few yr of life. A third, less-common category, indeterminate colitis, represents approximately 10% of pediatric patients.

IBD may be classified according to age at onset: pediatric onset (<17 yr), early onset (<10 yr), very early onset (<6 yr), infant/toddler onset (0-2 yr), and neonatal onset IBD. Children with very early onset (representing ~1% of patients) and those <1 yr of age (0.2%), have a high incidence of monogenic causes of IBD (see Table 336-5) rather than idiopathic and probably polygenic-environmental causes of IBD.

Genetic and environmental influences are involved in the pathogenesis of IBD. The prevalence of Crohn disease in the United States is much lower for Hispanics and Asians than for whites and blacks. The risk of IBD in family members of an affected person has been reported in the range of 7-30%; a child whose parents both have IBD has a >35% chance of acquiring the disorder. Relatives of a patient with ulcerative colitis have a greater risk of acquiring ulcerative colitis than Crohn disease, whereas relatives of a patient with Crohn disease have a greater risk of acquiring this disorder; the 2 diseases can occur in the same family. The risk of occurrence of IBD among relatives of patients with Crohn disease is somewhat greater than for patients with ulcerative colitis.

The importance of genetic factors in the development of IBD is noted by a higher chance that both twins will be affected if they are monozygotic rather than dizygotic. The concordance rate in twins is higher in Crohn disease (36%) than in ulcerative colitis (16%). Genetic disorders that have been associated with IBD include Turner syndrome, the Hermansky-Pudlak syndrome, glycogen storage disease type Ib, and various immunodeficiency disorders. In 2001, the first IBD gene, NOD2, was identified through association mapping. A few months later, the IBD 5 risk haplotype was identified. These early successes were followed by a long period without notable risk factor discovery. Since 2006, the year of the first published genome wide array study on IBD, there has been an exponential growth in the set of validated genetic risk factors for IBD.

A perinuclear antineutrophil cytoplasmic antibody is found in approximately 70% of patients with ulcerative colitis compared with <20% of those with Crohn disease and is believed to represent a marker of genetically controlled immunoregulatory disturbance. Approximately 55% of those with Crohn disease are positive for anti-\textit{Sacharomyces cerevisiae} antibody. Since the importance of these were first described, multiple other serologic and immune markers of Crohn disease and ulcerative colitis have been recognized.

IBD is caused by dysregulated or inappropriate immune response to environmental factors in a genetically susceptible host. An abnormality in intestinal mucosal immunoregulation may be of primary importance in the pathogenesis of IBD, involving activation of cytokines, triggering a cascade of reactions that results in bowel inflammation. These cytokines are recognized as known or potential targets for IBD therapies.

Multiple environmental factors are recognized to be involved in the pathogenesis of IBD, none more critical than the gut microbiota. The increasing incidence of IBD over time is likely in part attributable to alterations in the microbiome. Evidence includes association between IBD and residence in or immigration to industrialized nations, with a “Western” diet, increased use of antibiotics at a younger age, high rates of vaccination, and less exposure to microbes at a young age. While gut microbes likely play an important role in the pathogenesis of IBD, the exact mechanism needs to be elucidated further. Some environmental factors are disease specific; for example, cigarette smoking is a risk factor for Crohn disease but paradoxically protects against ulcerative colitis.

It is usually possible to distinguish between ulcerative colitis and Crohn disease by the clinical presentation and radiologic, endoscopic, and histopathologic findings (Table 336-1). It is not possible to make a definitive diagnosis in approximately 10% of patients with chronic colitis; this disorder is called indeterminate colitis. Occasionally, a child initially believed to have ulcerative colitis on the basis of clinical findings is subsequently found to have Crohn colitis. This is particularly true for the youngest patients, because Crohn disease in this patient population can more often manifest as exclusively colonic inflammation, mimicking ulcerative colitis. The medical treatments of Crohn disease and ulcerative colitis overlap.

Extraintestinal manifestations occur slightly more commonly with Crohn disease than with ulcerative colitis (Table 336-2). Growth retardation is seen in 15-40% of children with Crohn disease at diagnosis. Decrease in height velocity occurs in nearly 90% of patients with Crohn disease diagnosed in childhood or adolescence. Of the extraintestinal manifestations that occur with IBD, joint, skin, eye, mouth, and hepatobiliary involvement tend to be associated with colitis, whether ulcerative or Crohn. The presence of some manifestations, such as peripheral arthritis, erythema nodosum, and anemia, correlates with activity of the bowel disease. Activity of pyoderma gangrenosum correlates less well with activity of the bowel disease, whereas sclerosing cholangitis, ankylosing spondylitis, and sacroiliitis do not correlate with intestinal disease. Arthritis occurs in 3 patterns: migratory peripheral arthritis involving primarily large joints, ankylosing
### Table 336-2 Extraintestinal Complications of Inflammatory Bowel Disease

<table>
<thead>
<tr>
<th>MUSCULOSKELETAL</th>
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<tr>
<td>Peripheral arthritis</td>
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<td>Granulomatous monoarthritis</td>
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<td>Granulomatous synovitis</td>
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<td>Rheumatoid arthritis</td>
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<td>Sacroiliitis</td>
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<td>Ankylosing spondylitis</td>
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<td>Digital clubbing and hypertrophic osteoarthropathy</td>
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<td>Periostitis</td>
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<td>Osteoporosis, osteomalacia</td>
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<tr>
<td>Rhabdomyolysis</td>
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<tr>
<td>Pelvic osteomyelitis</td>
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<tr>
<td>Recurrent multifocal osteomyelitis</td>
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<tr>
<td>Relapsing polyarthritis</td>
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<th>SKIN AND MUCOUS MEMBRANES</th>
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<tr>
<td>Oral lesions</td>
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<tr>
<td>Cheilitis</td>
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<td>Aphthous stomatitis, glossitis</td>
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<tr>
<td>Granulomatous oral Crohn disease</td>
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<tr>
<td>Inflammatory hyperplasia fissures and cobblestone mucosa</td>
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<tr>
<td>Periostomatitis vegetans</td>
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<th>DERMATOLOGIC</th>
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<tr>
<td>Erythema nodosum</td>
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<td>Pyoderma gangrenosum</td>
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<tr>
<td>Sweet syndrome</td>
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<td>Metastatic Crohn disease</td>
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<td>Psoriasis</td>
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<tr>
<td>Epidermolysis bullosa acquisita</td>
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<td>Perianal skin tags</td>
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<tr>
<td>Polyarteritis nodosa</td>
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<td>Conjunctivitis</td>
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<td>Uveitis, iritis</td>
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<td>Episcleritis</td>
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<td>Scleritis</td>
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<td>Retrolubular neuritis</td>
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<td>Chorioretinitis with retinal detachment</td>
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<td>Crohn keratopathy</td>
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<td>Posterior segment abnormalities</td>
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<td>Retinal vascular disease</td>
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<th>BRONCHOPULMONARY</th>
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<tr>
<td>Chronic bronchitis with bronchiectasis</td>
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<td>Chronic bronchitis with neutrophilic infiltrates</td>
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<tr>
<td>Fibrosing alveolitis</td>
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<td>Pulmonary vasculitis</td>
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<td>Small airway disease and bronchiolitis obliterans</td>
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<tr>
<td>Eosinophilic lung disease</td>
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<tr>
<td>Granulomatous lung disease</td>
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<tr>
<td>Tracheal obstruction</td>
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<tr>
<td>Cardiomyopathy</td>
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<tr>
<td>Endocarditis</td>
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<tr>
<td>Myocarditis</td>
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<tr>
<th>MALNUTRITION</th>
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<tr>
<td>Decreased intake of food</td>
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<tr>
<td>• Inflammatory bowel disease</td>
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<tr>
<td>• Dietary restriction</td>
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<td>Malabsorption</td>
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<tr>
<td>• Inflammatory bowel disease</td>
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<td>• Bowel resection</td>
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<tr>
<td>• Bile salt depletion</td>
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<tr>
<td>• Bacterial overgrowth</td>
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| Intestinal losses |  |
|• Electrolytes |  |
|• Minerals |  |
|• Nutrients |  |
|Increased caloric needs |  |
|• Inflammation |  |
|• Fever |  |

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<th>HEMATOLOGIC</th>
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<tbody>
<tr>
<td>Anemia: iron deficiency (blood loss)</td>
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<tr>
<td>Vitamin B₁₂ (ileal disease or resection, bacterial overgrowth, folate deficiency)</td>
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<tr>
<td>Anemia of chronic inflammation</td>
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<tr>
<td>Anaphylactoid purpura (Crohn disease)</td>
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<tr>
<td>Hyposplenism</td>
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<tr>
<td>Autoimmune hemolytic anemia</td>
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<tr>
<td>Coagulation abnormalities</td>
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<tr>
<td>Increased activation of coagulation factors</td>
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<tr>
<td>Activated fibrinolysis</td>
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<tr>
<td>Anticardiolipin antibody</td>
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<tr>
<td>Increased risk of arterial and venous thrombosis with cerebrovascular stroke, myocardial infarction, peripheral arterial, and venous occlusions</td>
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<thead>
<tr>
<th>RENAL AND GENITOURINARY</th>
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<tbody>
<tr>
<td>Metabolic</td>
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<tr>
<td>• Urinary crystal formation (nephrolithiasis, uric acid, oxylate)</td>
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<tr>
<td>Hypokalemic nephropathy</td>
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<tr>
<td>Inflammation</td>
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<tr>
<td>• Retroperitoneal abscess</td>
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<tr>
<td>• Fibrosis with ureteral obstruction</td>
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<td>• Fistula formation</td>
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<td>Glomerulitis</td>
<td></td>
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<tr>
<td>Membrane nephritis</td>
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<td>Renal amyloidosis, nephrotic syndrome</td>
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<tr>
<th>PANCREATITIS</th>
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<tr>
<td>Secondary to medications (sulfasalazine, 6-mercaptopurine, azathioprine, parenteral nutrition)</td>
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<tr>
<td>Ampullary Crohn disease</td>
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<tr>
<td>Granulomatous pancreatitis</td>
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<tr>
<td>Decreased pancreatic exocrine function</td>
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<tr>
<td>Sclerosing cholangitis with pancreatitis</td>
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<table>
<thead>
<tr>
<th>HEPATOBILIARY</th>
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<tbody>
<tr>
<td>Primary sclerosing cholangitis</td>
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<tr>
<td>Small duct primary sclerosing cholangitis (pericholangitis)</td>
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<tr>
<td>Carcinoma of the bile ducts</td>
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<td>Fatty infiltration of the liver</td>
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<td>Cholelithiasis</td>
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<td>Autoimmune hepatitis</td>
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<tr>
<th>ENDOCRINE AND METABOLIC</th>
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<tr>
<td>Growth failure, delayed sexual maturation</td>
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<tr>
<td>Thyroiditis</td>
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<tr>
<td>Osteoporosis, osteomalacia</td>
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<tr>
<th>NEUROLOGIC</th>
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<tr>
<td>Peripheral neuropathy</td>
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<tr>
<td>Meningitis</td>
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<tr>
<td>Vestibular dysfunction</td>
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<tr>
<td>Pseudotumor cerebri</td>
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<tr>
<td>Cerebral vasculitis</td>
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<tr>
<td>Migraine</td>
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spondylitis, and sacroiliitis. The peripheral arthritis of IBD tends to be nondestructive. Ankylosing spondylitis begins in the 3rd decade and occurs most commonly in patients with ulcerative colitis who have the human leukocyte antigen B27 phenotype. Symptoms include low back pain and morning stiffness; back, hips, shoulders, and sacroiliac joints are typically affected. Isolated sacroiliitis is usually asymptomatic but is common when a careful search is performed. Among the skin manifestations, erythema nodosum is most common. Patients with erythema nodosum or pyoderma gangrenosum have a high likelihood of having arthritis as well. Glomerulonephritis, uveitis, and a hypercoagulable state are other rare manifestations that occur in childhood. Cerebral thromboembolic disease has been described in children with IBD.

### 336.1 Chronic Ulcerative Colitis

*Andrew B. Grossman and Robert N. Baldassano*

Ulcerative colitis, an idiopathic chronic inflammatory disorder, is localized to the colon and spares the upper gastrointestinal (GI) tract. Disease usually begins in the rectum and extends proximally for a variable distance. When it is localized to the rectum, the disease is ulcerative proctitis, whereas disease involving the entire colon is pancolitis. Approximately 50-80% of pediatric patients have extensive colitis, and adults more commonly have distal disease. Ulcerative proctitis is less likely to be associated with systemic manifestations, although it may be less responsive to treatment than more-diffuse disease. Approximately 30% of children who present with ulcerative proctitis experience proximal spread of the disease. Ulcerative colitis has rarely been noted to present in infancy. Dietary protein intolerance (cow’s milk protein) is a transient disorder; symptoms are directly associated with the intake of the offending antigen.

The incidence of ulcerative colitis has remained relatively constant, in contrast to an increase in Crohn disease, but varies with country of origin. The age-specific incidence rates of pediatric ulcerative colitis in North America is 2 per 100,000 population. The prevalence of ulcerative colitis in northern European countries and the United States varies from 100-200 per 100,000 population. Men are slightly more likely to acquire ulcerative colitis than are women; the reverse is true for Crohn disease.

#### CLINICAL MANIFESTATIONS

Blood, mucus, and pus in the stool as well as diarrhea are the typical presentation of ulcerative colitis. Constipation may be observed in those with proctitis. Symptoms such as tenesmus, urgency, cramping abdominal pain (especially with bowel movements), and nocturnal bowel movements are common. The mode of onset ranges from insidious with gradual progression of symptoms to acute and fulminant (Table 336-3, Fig. 336-1). Fever, severe anemia, hypoalbuminemia, leukocytosis, and more than 5 bloody stools per day for 5 days define fulminant colitis. Chronicity is an important part of the diagnosis; it is difficult to know if a patient has a subacute, transient infectious colitis or ulcerative colitis when a child has had 1-2 wk of symptoms.

Symptoms beyond this duration often prove to be secondary to IBD. Anorexia, weight loss, and growth failure may be present, although these complications are more typical of Crohn disease.

**Extraintestinal manifestations** that tend to occur more commonly with ulcerative colitis than with Crohn disease include pyoderma gangrenosum, sclerosing cholangitis, chronic active hepatitis, and ankylosing spondylitis. Iron deficiency can result from chronic blood loss as well as decreased intake. Folate deficiency is unusual but may be accentuated in children treated with sulfasalazine, which interferes with folate absorption. Chronic inflammation and the elaboration of a variety of inflammatory cytokines can interfere with erythropoiesis and result in the anemia of chronic disease. Secondary amennorrhea is common during periods of active disease.

The clinical course of ulcerative colitis is marked by remission and relapse, often without apparent explanation. After treatment of initial symptoms, approximately 5% of children with ulcerative colitis have a prolonged remission (longer than 3 yr). Approximately 25% of children presenting with severe ulcerative colitis require colectomy within 5 yr of diagnosis, compared with only 5% of those presenting with mild disease. It is important to consider the possibility of enteric infection with recurrent symptoms; these infections can mimic a flare-up or actually provoke a recurrence. The use of nonsteroidal antiinflammatory drugs is considered by some to predispose to exacerbation.

It is generally believed that the risk of colon cancer begins to increase after 8-10 yr of disease and can then increase by 0.5–1% per year. The risk is delayed by approximately 10 yr in patients with colitis limited to the descending colon. Proctitis alone is associated with virtually no increase in risk over the general population. Because colon cancer is usually preceded by changes of mucosal dysplasia, it is recommended that patients who have had ulcerative colitis for longer than 10 yr be screened with colonoscopy and biopsies every 1-2 yr. Although this is the current standard of practice, it is not clear if morbidity and mortality are changed by this approach. Two competing concerns about this

<table>
<thead>
<tr>
<th>Score 1</th>
<th>Score 2</th>
<th>Score 3</th>
<th>Score 4</th>
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<tbody>
<tr>
<td>E1 (proctitis): inflammation limited to the rectum</td>
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<tr>
<td>E2 (left-sided; distal): inflammation limited to the splenic flexure</td>
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<td>E3 (pancolitis): inflammation extends to the proximal splenic flexure</td>
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<td>S0 (remission): no symptoms</td>
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<tr>
<td>S1 (mild): 4 or less stools per day (with or without blood), absence of systemic symptoms, normal inflammatory markers</td>
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<tr>
<td>S2 (moderate): 4 stools per day, minimum signs of systemic symptoms</td>
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<td>S3 (severe): 6 or more bloody stools per day, pulse rate of ≥90 beats per min, temperature ≥37.5°C (99.5°F), hemoglobin concentration &lt;105 g/L, erythrocyte sedimentation rate ≥30 mm/hr</td>
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**Table 336-3** Montreal classification of extent and severity of ulcerative colitis


**Figure 336-1** Mayo endoscopic score for ulcerative colitis. **A**, Score 0 = normal; endoscopic remission. **B**, Score 1 = mild; erythema, decreased vascular pattern, mild friability. **C**, Score 2 = moderate; marked erythema, absent vascular pattern, friability, erosions. **D**, Score 3 = severe; spontaneous bleeding, ulceration. (Images courtesy of Elena Ricart. From Ordás I, Eckmann L, Talamini M, et al: Ulcerative colitis, Lancet 380:1606–1616, 2012, Fig. 2, p. 1610.)
Infectious Agents Mimicking Inflammatory Bowel Disease

<table>
<thead>
<tr>
<th>AGENT</th>
<th>MANIFESTATIONS</th>
<th>DIAGNOSIS</th>
<th>COMMENTS</th>
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<tbody>
<tr>
<td><strong>BACTERIAL</strong></td>
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<tr>
<td>Campylobacter jejuni</td>
<td>Acute diarrhea, fever, fecal blood, and leukocytes</td>
<td>Culture</td>
<td>Common in adolescents, may relapse</td>
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<tr>
<td>Yersinia enterocolitica</td>
<td>Acute → chronic diarrhea, right lower quadrant pain, mesenteric adenitis–pseudoappendicitis, fecal blood, and leukocytes</td>
<td>Culture</td>
<td>Common in adolescents as fever of unknown origin, weight loss, abdominal pain</td>
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<tr>
<td>Clostridium difficile</td>
<td>Extraintestinal manifestations, mimics Crohn disease</td>
<td>Postantibiotic onset, watery → bloody diarrhea, pseudomembrane on sigmoidoscopy</td>
<td>Cytotoxin assay</td>
</tr>
<tr>
<td>Escherichia coli O157:H7</td>
<td>Colitis, fecal blood, abdominal pain</td>
<td>Culture and typing</td>
<td>Hemolytic uremic syndrome Usually acute</td>
</tr>
<tr>
<td>Salmonella</td>
<td>Watery → bloody diarrhea, foodborne, fecal leukocytes, fever, pain, cramps</td>
<td>Culture</td>
<td>Dysentery symptoms</td>
</tr>
<tr>
<td>Shigella</td>
<td>Watery → bloody diarrhea, fecal leukocytes, fever, pain, cramps</td>
<td>Culture</td>
<td>Ulceration on endoscopy May be chronic Contaminated drinking water Shellfish source</td>
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<tr>
<td>Edwardsiella tarda</td>
<td>Bloody diarrhea, cramps</td>
<td>Culture</td>
<td></td>
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<tr>
<td>Aeromonas hydrophila</td>
<td>Cramps, diarrhea, fecal blood</td>
<td>Culture</td>
<td></td>
</tr>
<tr>
<td>Plesiomonas shigelloides</td>
<td>Diarrhea, cramps</td>
<td>Culture</td>
<td></td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>Rarely bovine, now Mycobacterium</td>
<td>Culture, purified protein derivative, biopsy</td>
<td>Can mimic Crohn disease</td>
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<tr>
<td><strong>PARASITES</strong></td>
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<tr>
<td>Entamoeba histolytica</td>
<td>Acute bloody diarrhea and liver abscess, colic</td>
<td>Trophozoite in stool, colonic mucosal flask ulceration, serologic tests</td>
<td>Travel to endemic area</td>
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<td>Giardia lamblia</td>
<td>Foul-smelling, watery diarrhea, cramps, flatulence, weight loss; no colonic involvement</td>
<td><em>Owl</em>-like trophozoite and cysts in stool; rarely duodenal intubation</td>
<td>May be chronic</td>
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<td><strong>AIDS-ASSOCIATED ENTEROPATHY</strong></td>
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<tr>
<td>Cryptosporidium</td>
<td>Chronic diarrhea, weight loss</td>
<td>Stool microscopy</td>
<td>Mucosal findings not like inflammatory bowel disease</td>
</tr>
<tr>
<td>Isospora belli</td>
<td>As in Cryptosporidium</td>
<td>Stool microscopy</td>
<td>Tropical location More common when on immunosuppressive medications</td>
</tr>
</tbody>
</table>

**DIFFERENTIAL DIAGNOSIS**

The major conditions to exclude are infectious colitis, allergic colitis, and Crohn colitis. Every child with a new diagnosis of ulcerative colitis should have stool cultured for enteric pathogens, stool evaluation for Clostridium difficile, ova and parasites, and perhaps serologic studies for amebae (Table 336-4). Cytomegalovirus infection can mimic ulcerative colitis or be associated with an exacerbation of existing disease, usually in immunocompromised patients. The most difficult distinction is from Crohn disease because the colitis of Crohn disease can initially appear identical to that of ulcerative colitis, particularly in younger children. The gross appearance of the colitis or development of small bowel disease eventually leads to the correct diagnosis; this can occur years after the initial presentation.

At the onset, the colitis of hemolytic uremic syndrome may be identical to that of early ulcerative colitis. Ultimately, signs of microangiopathic hemolysis (the presence of schistocytes on blood smear), thrombocytopenia, and subsequent renal failure should confirm the diagnosis of hemolytic-uremic syndrome. Although Henoch-Schönlein purpura can manifest as abdominal pain and bloody stools, it is not usually associated with colitis. Behçet disease can be distinguished by its typical features (see Chapter 161). Other considerations are radiation proctitis, viral colitis in immunocompromised patients, and ischemic colitis (Table 336-5). In infancy, dietary protein intolerance can be confused with ulcerative colitis, although the former is a transient problem that resolves on removal of the offending protein, and ulcerative colitis is extremely rare in this age group. Hirschsprung disease can produce an enterocolitis before or within months after surgical correction; this is unlikely to be confused with ulcerative colitis.

**DIAGNOSIS**

The diagnosis of ulcerative colitis or ulcerative proctitis requires a typical presentation in the absence of an identifiable specific cause (see Tables 336-4 and 336-5) and typical endoscopic and histologic findings (see Tables 336-1 and 336-2). One should be hesitant to make a diagnosis of ulcerative colitis in a child who has experienced symptoms for <2-3 wk until infection has been excluded. When the diagnosis is suspected in a child with subacute symptoms, the physician should make a firm diagnosis only when there is evidence of chronicity on colonoscopic biopsy. Laboratory studies can demonstrate evidence of anemia (either iron deficiency or the anemia of chronic disease) or hypoalbuminemia. Although the sedimentation rate and C-reactive protein are often elevated, they may be normal even with fulminant colitis. An elevated white blood cell count is usually seen only with more-severe colitis. Fecal calprotectin levels are usually elevated and are increasingly recognized to be a more sensitive and specific marker of GI inflammation than typical laboratory parameters. Barium enema is suggestive but not diagnostic of acute (Fig. 336-2) or chronic burned-out disease (Fig. 336-3). The diagnosis of ulcerative colitis must be confirmed by endoscopic and histologic examination of the colon (see Fig. 336-1). Classically, disease starts in the rectum with a gross appearance characterized by erythema, edema, loss of vascular pattern, granularity, and friability. There may be a “cutoff” demarcating the margin between inflammation and normal colon, or the entire colon may be involved. There may
Typical histologic findings are cryptitis, crypt abscesses, separation of crypts by inflammatory cells, foci of acute inflammatory cells, edema, mucus depletion, and branching of crypts. The last finding is not seen in infectious colitis. Granulomas, fissures, or full-thickness involvement of the bowel wall (usually on surgical rather than endoscopic biopsy) suggests Crohn disease.

Perianal disease, with the exception of mild local irritation or anal fissures associated with diarrhea, should make the clinician think of Crohn disease. Plain radiographs of the abdomen might demonstrate loss of haustral markings in an air-filled colon or marked dilatation with toxic megacolon. With severe colitis, the colon may become dilated; a diameter of >6 cm, determined radiographically, in an adult suggests toxic megacolon. If it is necessary to examine the colon radiologically in a child with severe colitis (to evaluate the extent of involvement or to try to rule out Crohn disease), it is sometimes helpful to perform an upper GI contrast series with small bowel follow-through and then look at delayed films of the colon. A barium enema is contraindicated in the setting of a potential toxic megacolon.

**TREATMENT**

**Medical**

A medical cure for ulcerative colitis is not available; treatment is aimed at controlling symptoms and reducing the risk of recurrence, with a secondary goal of minimizing steroid exposure. The intensity of treatment varies with the severity of the symptoms.

The first drug class to be used with mild or mild-to-moderate colitis is an aminosalicylate. Sulfasalazine is composed of a sulfur moiety linked to the active ingredient 5-aminosalicylate (5-ASA). This linkage prevents the premature absorption of the medication in the upper GI tract, allowing it to reach the colon, where the 2 components are separated by bacterial cleavage. The dose of sulfasalazine is 50–75 mg/kg/24 hr (divided into 2–4 doses). Generally, the dose is not more than 2–4 g/24 hr. Hypersensitivity to the sulfa component is the major side effect of sulfasalazine and occurs in 10–20% of patients. Because of poor tolerance, sulfasalazine is used less commonly than other, better tolerated 5-ASA preparations (mesalamine, 50–100 mg/kg/day; balsalazine 110–175 mg/kg/day). Sulfasalazine and the 5-ASA preparations effectively treat active ulcerative colitis and prevent recurrence. It is recommended that the medication be continued even when the disorder is in remission. These medications might also decrease the lifetime risk of colon cancer.

Approximately 5% of patients have an allergic reaction to 5-ASA, manifesting as rash, fever, and bloody diarrhea, which can be difficult to distinguish from symptoms of a flare of ulcerative colitis. 5-ASA can also be given in enema or suppository form and is especially useful for proctitis. Hydrocortisone enemas are used to treat proctitis as well, but they are probably not as effective. A combination of oral and rectal 5-ASA as well as monotherapy with rectal preparation has been shown to be more effective than just oral 5-ASA for distal colitis. Extended release budesonide may also induce remission in patients with mild to moderate ulcerative colitis.

Probiotics are effective in adults for maintenance of remission for ulcerative colitis, although they do not induce remission during an active flare. The most promising role for probiotics has been to prevent pouchitis, a common complication following colectomy and ileal–pouch anal anastomosis surgery. Children with moderate to severe pancolitis or colitis that is unresponsive to 5-ASA therapy should be treated with corticosteroids, most commonly, prednisone. The usual starting dose of prednisone is 1–2 mg/kg/24 hr (40–60 mg maximum dose). This medication can be given once daily. With severe colitis, the dose can be divided twice daily and can be given intravenously. Steroids are considered an effective medication for acute flares, but they are not appropriate maintenance medications because of loss of effect and side effects, including growth retardation, adrenal suppression, cataracts, osteopenia, anesthetic necrosis of the head of the femur, glucose intolerance, risk of infection, mood disturbance, and cosmetic effects.

For a hospitalized patient with persistence of symptoms despite intravenous steroid treatment for 3–5 days, escalation of therapy or

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**Table 336-5** Chronic Inflammatory-Like Intestinal Disorders Including Monogenetic Diseases

<table>
<thead>
<tr>
<th>INFECTION  (see Table 336-4)</th>
<th>Chronic Inflammatory-Like Intestinal Disorders Including Monogenetic Diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIDS-Associated</td>
<td><em>Toxin</em></td>
</tr>
<tr>
<td>Immune–Inflammatory</td>
<td>Severe combined immunodeficiency diseases</td>
</tr>
<tr>
<td></td>
<td>Agammaglobulinemia</td>
</tr>
<tr>
<td></td>
<td>Chronic granulomatous disease</td>
</tr>
<tr>
<td></td>
<td>Wiskott–Aldrich syndrome</td>
</tr>
<tr>
<td></td>
<td>Common variable immunodeficiency diseases</td>
</tr>
<tr>
<td></td>
<td>Acquired immunodeficiency states</td>
</tr>
<tr>
<td></td>
<td>Dietary protein enterocolitis</td>
</tr>
<tr>
<td></td>
<td>Autoimmune polyendocrine syndrome type 1</td>
</tr>
<tr>
<td></td>
<td>Behçet disease</td>
</tr>
<tr>
<td></td>
<td>Lymphoid nodular hyperplasia</td>
</tr>
<tr>
<td></td>
<td>Eosinophilic gastroenteritis</td>
</tr>
<tr>
<td></td>
<td>Omenn syndrome</td>
</tr>
<tr>
<td></td>
<td>Graft-versus-host disease</td>
</tr>
<tr>
<td></td>
<td>IPEX (immune dysfunction, polyendocrinopathy, enteropathy, X-linked syndromes</td>
</tr>
<tr>
<td></td>
<td>Interleukin-10 signaling defects</td>
</tr>
<tr>
<td></td>
<td>Autoimmune enteropathy*</td>
</tr>
<tr>
<td></td>
<td>Microscopic colitis</td>
</tr>
<tr>
<td></td>
<td>Hyperimmunoglobulin M syndrome</td>
</tr>
<tr>
<td></td>
<td>Hyperimmunoglobulin E syndromes</td>
</tr>
<tr>
<td></td>
<td>Mevalonate kinase deficiency</td>
</tr>
<tr>
<td></td>
<td>Familial Mediterranean fever</td>
</tr>
<tr>
<td></td>
<td>Phospholipase C, defects</td>
</tr>
<tr>
<td></td>
<td>Familial hemophagocytic lymphohistiocytosis type 5</td>
</tr>
<tr>
<td></td>
<td>X-linked lymphoproliferative syndromes types 1, 2</td>
</tr>
<tr>
<td></td>
<td>Congenital neutropenias</td>
</tr>
<tr>
<td></td>
<td>Leukocyte adhesion deficiency 1</td>
</tr>
<tr>
<td>VASCULAR–ISCHEMIC DISORDERS</td>
<td>Systemic vasculitis (systemic lupus erythematosus, dermatomyositis)</td>
</tr>
<tr>
<td></td>
<td>Henoch–Schönlein purpura</td>
</tr>
<tr>
<td></td>
<td>Hemolytic uremic syndrome</td>
</tr>
<tr>
<td></td>
<td>Granulomatosis with angitis</td>
</tr>
<tr>
<td>OTHER</td>
<td>Glycogen storage disease type 1b</td>
</tr>
<tr>
<td></td>
<td>Dystrophic epidermolysis bullosa</td>
</tr>
<tr>
<td></td>
<td>X-linked ectodermal dysplasia and immunodeficiency</td>
</tr>
<tr>
<td></td>
<td>Dyseratosisis congenita</td>
</tr>
<tr>
<td></td>
<td>ADAM-17 deficiency</td>
</tr>
<tr>
<td></td>
<td>Prestenotic colitis</td>
</tr>
<tr>
<td></td>
<td>Diversion colitis</td>
</tr>
<tr>
<td></td>
<td>Radiation colitis</td>
</tr>
<tr>
<td></td>
<td>Neonatal necrotizing enterocolitis</td>
</tr>
<tr>
<td></td>
<td>Typhlitis</td>
</tr>
<tr>
<td></td>
<td>Sarcoidosis</td>
</tr>
<tr>
<td></td>
<td>Hirschsprung colitis</td>
</tr>
<tr>
<td></td>
<td>Intestinal lymphoma</td>
</tr>
<tr>
<td></td>
<td>Laxative abuse</td>
</tr>
<tr>
<td></td>
<td>Endometriosis</td>
</tr>
<tr>
<td></td>
<td>Hermansky–Pudlak syndrome</td>
</tr>
<tr>
<td></td>
<td>Trichohepatoenteric syndrome</td>
</tr>
<tr>
<td></td>
<td>PTEN hamartoma syndrome</td>
</tr>
</tbody>
</table>

*May be the same as IPEX.*

be some variability in the intensity of inflammation even in those areas involved. Flexible sigmoidoscopy can confirm the diagnosis; colonoscopy can evaluate the extent of disease and rule out Crohn colitis. A colonoscopy should not be performed when fulminant colitis is suspected because of the risk of provoking toxic megacolon or causing a perforation during the procedure. The degree of colitis can be evaluated by the gross appearance of the mucosa. One does not generally see discrete ulcers, which would be more suggestive of Crohn colitis. The endoscopic findings of ulcerative colitis result from microulcers, which give the appearance of a diffuse abnormality. With very severe chronic colitis, pseudopolyps may be seen. Biopsy of involved bowel demonstrates evidence of acute and chronic mucosal inflammation.
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Inflammatory Bowel Disease

Surgical options should be considered. The validated pediatric ulcerative colitis activity index can be utilized to help determine current disease severity based on clinical factors, and help determine who is more likely to respond to steroids and those who will likely require escalation of therapy (Table 336-6).

With medical management, most children are in remission within 3 mo; however, 5-10% continue to have symptoms unresponsive to treatment beyond 6 mo. Many children with disease requiring frequent corticosteroid therapy are started on immunomodulators such as azathioprine (2.0-2.5 mg/kg/day) or 6-mercaptopurine (1-1.5 mg/kg/day). Uncontrolled data suggest a corticosteroid-sparing effect in many treated patients. This is not an appropriate choice in a steroid nonresponsive patient with acute severe colitis because of longer onset of action. Lymphoproliferative disorders are associated with thiopurine use. Cyclosporine, which is associated with improvement in some children with severe or fulminant colitis, is rarely used owing to its high side-effect profile, its inability to change the natural history of disease, and the increasing use of infliximab, a chimeric monoclonal antibody to tumor necrosis factor (TNF)-α, which is also effective in cases of fulminant colitis. Infliximab is effective for induction and maintenance therapy in adults with moderate to severe disease. TNF blocking agents are associated with an increased risk of infection (particularly tuberculosis) and malignancies (lymphoma, leukemia). Adalimumab is also approved for treatment of moderate to severe ulcerative colitis in adults. Vedolizumab, a humanized monoclonal antibody that inhibits adhesion and migration of leukocytes into the gastrointestinal tract, is approved for the treatment of ulcerative colitis in adults. Tofacitinib, an oral Janus kinase inhibitor, is undergoing trials in adults with active moderate to severe ulcerative colitis.

Surgical

Colectomy is performed for intractable disease, complications of therapy, and fulminant disease that is unresponsive to medical management. No clear benefit of the use of total parenteral nutrition or a
continuous enteral elemental diet in the treatment of severe ulcerative colitis has been noted. Nevertheless, parenteral nutrition is used if oral intake is insufficient so that the patient will be nutritionally ready for surgery if medical management fails. With any medical treatment for ulcerative colitis, the clinician should always weigh the risk of the medication or therapy against the fact that colitis can be successfully treated surgically.

Surgical treatment for intractable or fulminant colitis is total colectomy. The optimal approach is to combine colectomy with an endorectal pull-through, where a segment of distal rectum is retained and the mucosa is stripped from this region. The distal ileum is pulled down and sutured at the internal anus with a J pouch created from ileum immediately above the rectal cuff. This procedure allows the child to maintain continence. Commonly, a temporary ileostomy is created to protect the delicate anastomosis between the sleeve of the pouch and the rectum. The ileostomy is usually closed within several months, restoring bowel continuity. At that time, stool frequency is often increased but may be improved with loperamide. The major complication of this operation is pouchitis, which is a chronic inflammatory reaction in the pouch, leading to bloody diarrhea, abdominal pain, and, occasionally, low-grade fever. The cause of this complication is unknown, although it is more common when the ileal pouch has been constructed for ulcerative colitis than for other indications (e.g., familial polyposis coli). Pouchitis is seen in 30–40% of patients who had ulcerative colitis. It commonly responds to treatment with oral metronidazole or ciprofloxacin. Probiotics have also been shown to decrease the rate of pouchitis as well as the recurrence of pouchitis following antibiotic therapy.

Support
Psychosocial support is an important part of therapy for this disorder. This may include adequate discussion of the disease manifestations and management between patient and physician, psychologic counseling for the child when necessary, and family support from a social worker or family counselor. Patient support groups have proved helpful for some families. Children with ulcerative colitis should be encouraged to participate fully in age-appropriate activities; however, activity may need to be reduced during periods of disease exacerbation.

### Table 336-6: Pediatric Ulcerative Colitis Activity Index

<table>
<thead>
<tr>
<th>ITEM</th>
<th>POINTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) Abdominal pain</td>
<td></td>
</tr>
<tr>
<td>No pain</td>
<td>0</td>
</tr>
<tr>
<td>Pain can be ignored</td>
<td>5</td>
</tr>
<tr>
<td>Pain cannot be ignored</td>
<td>10</td>
</tr>
<tr>
<td>(2) Rectal bleeding</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>0</td>
</tr>
<tr>
<td>Small amount only, in &lt;50% of stools</td>
<td>10</td>
</tr>
<tr>
<td>Small amount with most stools</td>
<td>20</td>
</tr>
<tr>
<td>Large amount (&gt;50% of the stool content)</td>
<td>30</td>
</tr>
<tr>
<td>(3) Stool consistency of most stools</td>
<td></td>
</tr>
<tr>
<td>Formed</td>
<td>0</td>
</tr>
<tr>
<td>Partially formed</td>
<td>5</td>
</tr>
<tr>
<td>Completely unformed</td>
<td>10</td>
</tr>
<tr>
<td>(4) Number of stools per 24 h</td>
<td></td>
</tr>
<tr>
<td>0-2</td>
<td>0</td>
</tr>
<tr>
<td>3-5</td>
<td>5</td>
</tr>
<tr>
<td>6-8</td>
<td>10</td>
</tr>
<tr>
<td>&gt;8</td>
<td>15</td>
</tr>
<tr>
<td>(5) Nocturnal stools (any episode causing wakening)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>0</td>
</tr>
<tr>
<td>Yes</td>
<td>10</td>
</tr>
<tr>
<td>(6) Activity level</td>
<td></td>
</tr>
<tr>
<td>No limitation of activity</td>
<td>0</td>
</tr>
<tr>
<td>Occasional limitation of activity</td>
<td>5</td>
</tr>
<tr>
<td>Severe restricted activity</td>
<td>10</td>
</tr>
<tr>
<td>Sum of Index (0-85)</td>
<td></td>
</tr>
</tbody>
</table>

### PROGNOSIS
The course of ulcerative colitis is marked by remissions and exacerbations. Most children with this disorder respond initially to medical management. Many children with mild manifestations continue to respond well to medical management and may stay in remission on a prophylactic 5-ASA preparation for long periods. An occasional child with mild onset, however, experiences intractable symptoms at a later time. Beyond the 1st decade of disease, the risk of development of colon cancer begins to increase rapidly. The risk of colon cancer may be diminished with surveillance colonoscopies beginning after 8-10 yr of disease. Detection of significant dysplasia on biopsy would prompt colectomy.

Bibliography is available at Expert Consult.

### 336.2 Crohn Disease (Regional Enteritis, Regional Ileitis, Granulomatous Colitis)

Andrew B. Grossman and Robert N. Baldassano

Crohn disease, an idiopathic, chronic inflammatory disorder of the bowel, involves any region of the alimentary tract from the mouth to the anus. Although there are many similarities between ulcerative colitis and Crohn disease, there are also major differences in the clinical course and distribution of the disease in the GI tract (see Table 336-1). The inflammatory process tends to be eccentric and segmental, often with skip areas (normal regions of bowel between inflamed areas). Although inflammation in ulcerative colitis is limited to the mucosa (except in toxic megacolon), GI involvement in Crohn disease is often transmural.

Compared to adult-onset disease, pediatric Crohn disease is more likely to have extensive anatomic involvement. At initial presentation, more than 50% of patients have disease that involves ileum and colon (ileocolitis), 20% have exclusively colonic disease, and upper GI involvement (esophagus, stomach, duodenum) is seen in up to 30% of children. Isolated small bowel disease is much less common in the pediatric population compared to adults. Isolated colonic disease is common in children younger than 8 yr of age and may be indistinguishable from ulcerative colitis. Anatomic location of disease tends to extend over time in children.

Crohn disease tends to have a bimodal age distribution, with the first peak beginning in the teenage years. The incidence of Crohn disease has been increasing, whereas that of ulcerative colitis has been stable. In the United States, the reported incidence of pediatric Crohn disease is 4.56 per 100,000 and the pediatric prevalence is 43 per 100,000 children.

### CLINICAL MANIFESTATIONS
Crohn disease can be characterized as inflammatory, stricturing, or penetrating. Patients with small bowel disease are more likely to have an obstructive pattern (most commonly with right lower quadrant pain) characterized by fibrostensis, and those with colonic disease are more likely to have symptoms resulting from inflammation (diarrhea, bleeding, cramping). Disease phenotypes often change as duration of disease lengthens (inflammatory becomes structuring and/or penetrating) (Fig. 336-4).

Systemic signs and symptoms are more common in Crohn disease than in ulcerative colitis. Fever, malaise, and easy fatigability are common. Growth failure with delayed bone maturation and delayed sexual development can precede other symptoms by 1 or 2 yr and is at least twice as likely to occur with Crohn disease as with ulcerative colitis. Children can present with growth failure as the only manifestation of Crohn disease. Decreased height velocity occurs in about 88% of prepubertal patients diagnosed with Crohn disease, and this often precedes GI symptoms. Causes of growth failure include inadequate caloric intake, suboptimal absorption or excessive loss of nutrients, the
include bile acid malabsorption with secondary diarrhea and vitamin Bi₂, malabsorption, with possible resultant deficiency. Chronic steatorrhea can lead to oxaluria with secondary renal stones. Increasing calcium intake can actually decrease the risk renal stones secondary to ileal inflammation. The risk of cholelithiasis is also increased secondarily to bile acid depletion.

A disorder with this diversity of manifestations can have a major impact on an affected child's lifestyle. Fortunately, the majority of children with Crohn disease are able to continue with their normal activities, having to limit activity only during periods of increased symptoms.

Figure 336-4 The Lémann Score. Exemplary visualization of the Lémann score, a new technique to score and study intestinal damage in Crohn disease. CDAI, Crohn disease activity index; CDEIS, Crohn disease of endoscopic severity; CRP, C-reactive protein. (From Baumgart DC, Sandborn WJ: Crohn's disease. Lancet 380:1590–1602, 2012, Fig. 5, p. 1596.)

Figure 336-5 Stenotic Crohn disease. Severe stenosis of the terminal ileum is present in this 16 yr old boy. Inflammatory effacement of the mucosal folds and small ulcerations characterize the proximal nonstenotic segment. (From The child with diarrhea. In Hoffman AD, Hilton SW, Edwards DK, editors: Practical pediatric radiology, ed 2, Philadelphia, 1994, WB Saunders, p. 267.)
more likely to be mistaken for ulcerative colitis than for Crohn disease. Celiac disease and *Giardia* infection have been noted to produce a Crohn-like presentation including diarrhea, weight loss, and protein-losing enteropathy. GI tuberculosis is rare but can mimic Crohn disease. Foreign-body perforation of the bowel (toothpick) can mimic a localized region with Crohn disease. Small bowel lymphoma can mimic Crohn disease but tends to be associated with nodular filling defects of the bowel without ulceration or narrowing of the lumen. Bowel lymphoma is much less common in children than is Crohn disease. Recurrent functional abdominal pain can mimic the pain of small bowel Crohn disease. Lymphoid nodular hyperplasia of the terminal ileum (a normal finding) may be mistaken for Crohn ileitis. Right lower quadrant pain or mass with fever can be the result of periappendiceal abscess. This entity is occasionally associated with diarrhea as well.

Growth failure may be the only manifestation of Crohn disease; other disorders such as growth hormone deficiency, gluten-sensitive enteropathy (celiac disease), Turner syndrome, or anorexia nervosa must be considered. If arthritis precedes the bowel manifestations, an initial diagnosis of juvenile idiopathic arthritis may be made. Refractory anemia may be the presenting feature and may be mistaken for a primary hematologic disorder. Chronic granulomatous disease of childhood can cause inflammatory changes in the bowel as well as perianal disease. Antral narrowing in this disorder may be mistaken for a stricture secondary to Crohn disease. Other immunodeficiencies or autoinflammatory conditions and monogenetic disorders may present with GI symptoms suggestive of IBD, particularly in very early or infant/toddler onset of disease (see Table 336-5).

**DIAGNOSIS**

Crohn disease can manifest as a variety of symptom combinations. At the onset, symptoms may be subtle (growth retardation, abdominal pain alone); this explains why the diagnosis might not be made until 1 or 2 yr after the start of symptoms. The diagnosis of Crohn disease depends on finding typical clinical features of the disorder (history, physical examination, laboratory studies, and endoscopic or radiologic findings), ruling out specific entities that mimic Crohn disease, and demonstrating chronicity. The history can include any combination of abdominal pain (especially right lower quadrant), diarrhea, vomiting, anorexia, weight loss, growth retardation, and extraintestinal manifestations. Only 25% initially have the triad of diarrhea, weight loss, and abdominal pain. Most do not have diarrhea, and only 25% have GI bleeding.

Children with Crohn disease often appear chronically ill. They commonly have weight loss and growth failure, and they are often

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**Figure 336-6** Stenosis in Crohn disease. A, MR enterography of Crohn disease restricted to the terminal ileum (Montreal category L1) with inflammatory stenosis. B, Ultrasound image of an intestinal stenosis in Crohn disease. *(From Baumgart DC, Sandborn WJ: Crohn’s disease. Lancet 380:1590–1602, 2012, Fig. 4, p. 1596.)*

**Figure 336-7** Crohn disease: sinuses and fistula. Severe ileocolitis has resulted in an ileocecal fistula (single arrows, lower) and sinus formation in the ascending colon (a) (arrows on platform). c, Cecum (arrowhead); ti, terminal ileum (paired arrows). *(From The child with diarrhea. In Hoffman AD, Hilton SW, Edwards DK, editors: Practical pediatric radiology, ed 2, Philadelphia, 1994, WB Saunders, p 268.)*

**DIFFERENTIAL DIAGNOSIS**

The most common diagnoses to be distinguished from Crohn disease are the infectious enteropathies (in the case of Crohn disease: acute terminal ileitis, infectious colitis, enteric parasites, and periappendiceal abscess) (see Tables 336-4, 336-5, and 336-7). *Vesivirus* can cause many of the radiologic and endoscopic findings in the distal small bowel that are seen in Crohn disease. The symptoms of bacterial dysentery are
Differential Diagnosis of Presenting Symptoms of Crohn Disease

<table>
<thead>
<tr>
<th>PRIMARY PRESENTING SYMPTOM</th>
<th>DIAGNOSTIC CONSIDERATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right lower quadrant abdominal pain, with or without mass</td>
<td>Appendicitis, infection (e.g., Campylobacter, Yersinia spp.), lymphoma, intussusception, mesenteric adenitis, Meckel diverticulum, ovarian cyst</td>
</tr>
<tr>
<td>Chronic periumbilical or epigastric abdominal pain</td>
<td>Irritable bowel syndrome, constipation, lactose intolerance, peptic ulcer disease</td>
</tr>
<tr>
<td>Rectal bleeding, no diarrhea</td>
<td>Fissure, polyp, Meckel diverticulum, rectal ulcer syndrome</td>
</tr>
<tr>
<td>Bloody diarrhea</td>
<td>Infection, hemolytic-uremic syndrome, Henoch-Schönlein purpura, ischemic bowel, radiation colitis</td>
</tr>
<tr>
<td>Watery diarrhea</td>
<td>Irritable bowel syndrome, lactose intolerance, giardiasis, Cryptosporidium infection, sorbitol, laxatives</td>
</tr>
<tr>
<td>Perirectal disease</td>
<td>Fissure, hemorrhoid (rare), streptococcal infection, condyloma (rare)</td>
</tr>
<tr>
<td>Growth delay</td>
<td>Endocrinopathy</td>
</tr>
<tr>
<td>Anorexia, weight loss</td>
<td>Anorexia nervosa</td>
</tr>
<tr>
<td>Arthritis</td>
<td>Collagen vascular disease, infection</td>
</tr>
<tr>
<td>Liver abnormalities</td>
<td>Chronic hepatitis</td>
</tr>
</tbody>
</table>


Malnourished. The earliest sign of growth failure is decreased height velocity, which can be present in up to 88% of prepubertal patients with Crohn disease and typically precedes symptoms. Children with Crohn disease often appear pale, with decreased energy level and poor appetite; the latter finding sometimes results from an association between meals and abdominal pain or diarrhea. There may be abdominal tenderness that is either diffuse or localized to the right lower quadrant. A tender mass or fullness may be palpable in the right lower quadrant. Perianal disease, when present, may be characteristic. Large anal skin tags (1-3 cm diameter) or perianal fistulas with purulent drainage suggest Crohn disease. Digital clubbing, findings of arthritis, and skin manifestations may be present.

A complete blood cell count commonly demonstrates anemia, often with a component of iron deficiency, as well as thrombocytosis. Although the erythrocyte sedimentation rate and C-reactive protein are often elevated, they may be unremarkable. The serum albumin level may be low, indicating small bowel inflammation or protein-losing enteropathy. Fecal calprotectin and lactoferrin are increasingly being measured, but top down treatment is being increasingly utilized.

The specific therapeutic modalities used depend on geographic localization of disease, severity of inflammation, age of the patient, and the presence of complications (abscess). Traditionally, a “step-up” treatment paradigm has been utilized in the treatment of pediatric Crohn disease, whereby early disease is treated with steroids and less immunosuppressive medications. Escalation of therapy would occur if disease severity increased, the patient was refractory to current medication, or for steroid dependence. More recently, a “top-down” approach has been espoused, particularly in adults after multiple studies demonstrated superior efficacy. With this approach, patients with moderate to severe Crohn disease are treated initially with stronger, disease modulating agents, with the goal of achieving mucosal healing, or deep remission, early in the disease course. This is thought to increase the likelihood of long-term remission while decreasing corticosteroid exposure. The role for this approach in pediatrics is still being determined, but top down treatment is being increasingly utilized.

TREATMENT

Crohn disease cannot be cured by medical or surgical therapy. The aim of treatment is to relieve symptoms and prevent complications of chronic inflammation (anemia, growth failure), prevent relapse, minimize corticosteroid exposure, and, if possible, effect mucosal healing.

Medical

The specific therapeutic modalities used depend on geographic localization of disease, severity of inflammation, age of the patient, and the presence of complications (abscess). Traditionally, a “step-up” treatment paradigm has been utilized in the treatment of pediatric Crohn disease, whereby early disease is treated with steroids and less immunosuppressive medications. Escalation of therapy would occur if disease severity increased, the patient was refractory to current medication, or for steroid dependence. More recently, a “top-down” approach has been espoused, particularly in adults after multiple studies demonstrated superior efficacy. With this approach, patients with moderate to severe Crohn disease are treated initially with stronger, disease modifying agents, with the goal of achieving mucosal healing, or deep remission, early in the disease course. This is thought to increase the likelihood of long-term remission while decreasing corticosteroid exposure. The role for this approach in pediatrics is still being determined, but top down treatment is being increasingly utilized.

5-Aminosalicylates

For mild terminal ileal disease or mild Crohn disease of the colon, an initial trial of mesalamine (50-100 mg/kg/day; maximum 3-4 g) may be attempted. Specific pharmaceutical preparations have been formulated to release the active 5-ASA compound throughout the small bowel, in the ileum and colon, or exclusively in the colon. Rectal preparations are used for distal colonic inflammation.
Antibiotics/Probiotics

Antibiotics such as metronidazole (10-20 mg/kg/day) are used for infectious complications, are first-line therapy for perianal disease (although perianal disease usually recurs when antibiotic is discontinued), and they may be effective for treatment of mild to moderate Crohn disease. To date, probiotics have not been shown to be effective in induction or maintenance of remission for pediatric Crohn disease.

Corticosteroids

Corticosteroids are utilized for acute exacerbations of pediatric Crohn disease because they effectively suppress acute inflammation, rapidly relieving symptoms (prednisone, 1-2 mg/kg/day, maximum 40-60 mg). The goal is to taper dosing as soon as the disease becomes quiescent. Clinicians vary in their tapering schedules, and the disease can flare during this process. There is no role for continuing corticosteroids as maintenance therapy because, in addition to their side effects, tolerance develops and steroids do not change disease course or promote healing of mucosa. A special controlled ileal-release formulation of budesonide, a corticosteroid with local antiinflammatory activity on the bowel mucosa and high hepatic first-pass metabolism, is also used for mild to moderate ileal or ileocecal disease (adult dose: 9 mg daily). Ileal-release budesonide appears to be more effective than mesalamine in the treatment of active ileocolonic disease but is less effective than prednisone. Although less effective than traditional corticosteroids, budesonide does cause less steroid-related side effects.

Immunomodulators

Approximately 70% of patients require escalation of medical therapy within the 1st yr of pediatric Crohn disease diagnosis. Immunomodulators such as azathioprine (2.0-2.5 mg/kg/day) or 6-mercaptopurine (1.0-1.5 mg/kg/day) may be effective in some children who have a poor response to prednisone or who are steroid dependent. Because a beneficial effect of these drugs can be delayed for 3-4 mo after starting therapy, they are not helpful acutely. The early use of these agents can decrease cumulative prednisone dosages over the 1st 1-2 yr of therapy. Genetic variations in an enzyme system responsible for metabolism of these agents (thiopurine S-methyltransferase) can affect response rates and potential toxicity. Lymphoproliferative disorders have developed from thiopurine use in patients with IBD. Other common toxicities include hepatitis, pancreatitis, increased risk of skin cancer, increased risk of infection, and slightly increased risk of lymphoma.

Methotrexate is another immunomodulator that is effective in the treatment of active Crohn disease and has been shown to improve height velocity in the 1st yr of administration. The advantages of this medication include once-weekly dosing by either subcutaneous or oral route (10-15 mg/m², adult dose 25 mg weekly) and a more-rapid onset of action (6-8 wk) than azathioprine or 6-mercaptopurine. Folic acid is usually administered concomitantly to decrease medication side effects. Administration of ondansetron prior to methotrexate has been shown to diminish the risk of the most common side effect of nausea. The most common toxicity is hepatitis. The immunomodulators are effective for the treatment of perianal fistulas.

Biologic Therapy

Therapy with antibodies directed against mediators of inflammation is used for patients with Crohn disease. Infliximab, a chimeric monoclonal antibody to TNF-α, is effective for the induction and maintenance of remission and mucosal healing in chronically active moderate to severe Crohn disease, healing of perianal fistulas, steroid sparing, and preventing postoperative recurrence. Pediatric data additionally support improved growth with the administration of this medication. The onset of action of infliximab is quite rapid and it is initially given as 3 infusions over a 6 wk period (0, 2, and 6 wk), followed by maintenance dosing beginning every 8 wk. The durability of response to infliximab is variable and dose escalation (higher dose and/or decreased interval) is often necessary. Measurement of serum trough infliximab level prior to an infusion can help guide dosing decisions. Side effects include infusion reactions, increased incidence of infections (especially reactivation of latent tuberculosis), increased risk of lymphoma, and the development of autoantibodies. The development of antibodies to infliximab is associated with an increased incidence of infusion reactions and decreased durability of response. Regularly scheduled dosing of infliximab, as opposed to episodic dosing on an as-needed basis, is associated with decreased levels of antibodies to infliximab. A purified protein derivative test for tuberculosis should be done before starting infliximab.

Adalimumab, a subcutaneously administered, fully humanized monoclonal antibody against TNF-α, is effective for the treatment of chronically active moderate to severe Crohn disease in adults and children. After a loading dose, this is typically administered once every 2 wk, although dose escalation is sometimes required with this medication. Vedolizumab, a humanized monoclonal antibody that inhibits adhesion and migration of leukocytes into the gastrointestinal tract, was recently approved for the treatment of Crohn disease in adults. Antibodies against interleukins 12 and 23 antiselective adhesion molecules (ustekinumab), chemokine antagonists, and antagonist to Janus kinase 3 are currently being tested.

Enteral Nutritional Therapy

Exclusive enteral nutritional therapy, whereby all of a patient’s calories are delivered via formula, is an effective primary as well as adjunctive treatment. The enteral nutritional approach is as rapid in onset of response and as effective as the other treatments. Pediatric studies have suggested similar efficacy to prednisone for improvement in clinical symptoms, but enteral nutritional therapy is superior to steroids for actual healing of mucosa. Because affected patients have poor appetite and these formulas are relatively unpalatable, they are often administered via a nasogastric or gastrostomy infusion, usually overnight. The advantages are that it is relatively free of side effects, avoids the problems associated with corticosteroid therapy, and simultaneously addresses the nutritional rehabilitation. Children can participate in normal daytime activities. A major disadvantage of this approach is that patients are not able to eat a regular diet because they are receiving all of their calories from formula. A novel approach where 80-90% of caloric needs are provided by formula, allowing children to have some food intake, has been successful. For children with growth failure, this approach may be ideal, however.

High-calorie oral supplements, although effective, are often not tolerated because of early satiety or exacerbation of symptoms (abdominal pain, vomiting, or diarrhea). Nonetheless, they should be offered to children whose weight gain is suboptimal even if they are not candidates for exclusive enteral nutritional therapy. The continuous administration of nocturnal nasogastric feedings for chronic malnutrition and growth failure has been effective with a much lower risk of complications than parenteral hyperalimentation.

Surgery

Surgical therapy should be reserved for very specific indications. Recurrence rate after bowel resection is high (>50% by 5 yr); the risk of requiring additional surgery increases with each operation. Potential complications of surgery include development of fistula or stricture, anastomotic leak, postoperative partial small bowel obstruction secondary to adhesions, and short bowel syndrome. Surgery is the treatment of choice for localized disease of small bowel or colon that is unresponsive to medical treatment, bowel perforation, fibrosed stricture with symptomatic partial small bowel obstruction, and intractable bleeding. Intraabdominal or liver abscess sometimes is successfully treated by ultrasonographic or CT-guided catheter drainage and concomitant intravenous antibiotic treatment. Open surgical drainage is necessary if this approach is not successful. Growth retardation was once considered an indication for resection; without other indications, trial of medical and/or nutritional therapy is currently preferred.

Perianal abscess often requires drainage unless it drains spontaneously. In general, perianal fistulas should be managed by a combined medical and surgical approach. Often, the surgeon places a seton through the fistula to keep the tract open and actively draining while
medical therapy is administered, to help prevent the formation of a perianal abscess. A severely symptomatic perianal fistula can require fistulotomy, but this procedure should be considered only if the location allows the sphincter to remain undamaged.

The surgical approach for Crohn disease is to remove as limited a length of bowel as possible. There is no evidence that removing bowel up to margins that are free of histologic disease has a better outcome than removing only grossly involved areas. The latter approach reduces the risk of short bowel syndrome. Laparoscopic approach is increasingly being used, with decreased postoperative recovery time. One approach to symptomatic small bowel stricture has been to perform a strictureplasty rather than resection. The surgeon makes a longitudinal incision across the stricture but then closes the incision with sutures in a transverse fashion. This is ideal for short strictures without active disease. The reoperation rate is no higher with this approach than with resection, whereas bowel length is preserved. Postoperative medical therapy with agents such as mesalamine, metronidazole, azathioprine, and, more recently, infliximab, is often given to decrease the likelihood of postoperative recurrence.

Severe perianal disease can be incapacitating and difficult to treat if unresponsive to medical management. Diversion of fecal stream can allow the area to be less active, but on reconnection of the colon, disease activity usually recurs.

**Support**

Psychosocial issues for the child with Crohn disease include a sense of being different, concerns about body image, difficulty in not participating fully in age-appropriate activities, and family conflict brought on by the added stress of this disease. Social support is an important component of the management of Crohn disease. Parents are often interested in learning about other children with similar problems, but children may be hesitant to participate. Social support and individual psychologic counseling are important in the adjustment to a difficult problem at an age that by itself often has difficult adjustment issues. Patients who are socially “connected” fare better. Ongoing education about the disease is an important aspect of management because children generally fare better if they understand and anticipate problems. The Crohn and Colitis Foundation of America has local chapters throughout the United States and supports several regional 1-wk camps for children with Crohn disease.

**PROGNOSIS**

Crohn disease is a chronic disorder that is associated with high morbidity but low mortality. Symptoms tend to recur despite treatment and often without apparent explanation. Weight loss and growth failure can usually be improved with treatment and attention to nutritional needs. Up to 15% of patients with early growth retardation secondary to Crohn disease have a permanent decrease in linear growth. Osteopenia is particularly common in those with chronic poor nutrition and frequent exposure to high doses of corticosteroids. Some of the extraintestinal manifestations can, in themselves, be major causes of morbidity, including sclerosing cholangitis, chronic active hepatitis, pyoderma gangrenosum, and ankylosing spondylitis.

The region of bowel involved and complications of the inflammatory process tend to increase with time and include bowel strictures, fistulas, perianal disease, and intra-abdominal or retroperitoneal abscess. A majority of patients with Crohn disease eventually require surgery for one of its many complications; the rate of reoperation is high. Surgery is unlikely to be curative and should be avoided except for the specific indications noted previously. An earlier, most aggressive medical treatment approach, with the goal of exacting mucosal healing may improve long-term prognosis, and this is an active area of investigation. The risk of colon cancer in patients with long-standing Crohn colitis approaches that associated with ulcerative colitis, and screening colonoscopy after 10 yr of colonic disease is indicated.

Despite these complications, most children with Crohn disease lead active, full lives with intermittent flare-up in symptoms.

*Bibliography is available at Expert Consult.*
Bibliography


Eosinophilic gastroenteritis consists of a group of rare and poorly understood disorders that have in common gastric and small intestine infiltration with eosinophils and peripheral eosinophilia. The esophagus and large intestine may also be involved. Tissue eosinophilic infiltration can be seen in mucosa, muscularis, or serosa. The mucosal form is most common and is diagnosed by identifying large numbers of eosinophils in biopsy specimens of gastric antrum or small bowel. This condition clinically overlaps the dietary protein hypersensitivity disorders of the small bowel and colon. The differential diagnosis also includes celiac disease, chronic granulomatous disease, connective tissue disorders and vasculitides, multiple infections (particularly parasites), hypereosinophilic syndrome, early inflammatory bowel disease, and rarely malignancy. Many patients have allergies to multiple foods, seasonal allergies, atopy, eczema, and asthma. Serum immunoglobulin E is commonly elevated. Peripheral eosinophilia is present in approximately 5-70% of patients with this disorder. Other laboratory abnormalities can include hypoalbuminemia, iron deficiency anemia, and elevated liver enzymes.

The presentation of eosinophilic gastroenteritis is nonspecific. Clinical symptoms often correlate with which layers of the gastrointestinal tract are affected. Mucosal involvement can produce nausea, vomiting, diarrhea, abdominal pain, gastrointestinal bleeding, protein-losing enteropathy, or malabsorption. Involvement of the muscularis can produce obstruction (especially of the pylorus) or intussusception, whereas serosal activity produces abdominal distention and eosinophilic ascites. Presentation in infants can be similar to pyloric stenosis. Laboratory testing often reveals peripheral eosinophilia, elevated serum immunoglobulin E levels, hypoalbuminemia, and anemia.

The disease usually runs a chronic, debilitating course with sporadic severe exacerbations. Although almost always effective for the treatment of isolated eosinophilic esophagitis, elemental diets are not always successful for the treatment of eosinophilic gastroenteritis. Orally administered cromolyn sodium and montelukast are sometimes successful. A majority of patients require treatment with systemic corticosteroids, which are often effective.

Bibliography is available at Expert Consult.
Bibliography
Chapter 338
Disorders of Malabsorption

David Branski

All disorders of malabsorption are associated with diminished intestinal absorption of one or more dietary nutrients. Malabsorption can result from a defect in the nutrient digestion in the intestinal lumen or from defective mucosal absorption. Malabsorption disorders can be categorized into generalized mucosal abnormalities usually
resulting in malabsorption of multiple nutrients (Table 338-1) or malabsorption of specific nutrients (carbohydrate, fat, protein, vitamins, minerals, and trace elements) (Table 338-2). Almost all the malabsorption disorders are accompanied by chronic diarrhea which further worsens the malabsorption. (see Chapter 341).

### CLINICAL APPROACH

The clinical features depend on the extent and type of the malabsorbed nutrient. The common presenting features, especially in toddlers with malabsorption, are diarrhea, abdominal distention, and failure to gain weight, with a fall in growth chart percentiles. Physical findings include abdominal distention, muscle wasting, and the disappearance of the subcutaneous fat, with subsequent loose skinfolds (Fig. 338-1). The nutritional consequences of malabsorption are more dramatic in toddlers because the limited energy reserves and higher proportion of ingested protein and energy do not lead to malnutrition, as long as they are compensated by an increased appetite. In conditions associated with protein and energy losses. In exocrine pancreatic insufficiency, fecal losses of up to 40% of ingested protein and energy do not lead to malnutrition, as long as they are compensated by an increased appetite. In conditions associated

### Table 338-1
<table>
<thead>
<tr>
<th>Malabsorption Disorders and Chronic Diarrhea Associated with Generalized Mucosal Defect</th>
</tr>
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<tbody>
<tr>
<td>Mucosal disorders</td>
</tr>
<tr>
<td>Gluten-sensitive enteropathy (celiac disease)</td>
</tr>
<tr>
<td>Cow’s milk and other protein-sensitive enteropathies</td>
</tr>
<tr>
<td>Eosinophilic enteropathy</td>
</tr>
<tr>
<td>Protein-losing enteropathy</td>
</tr>
<tr>
<td>Lymphangiecstasy (congenital and acquired)</td>
</tr>
<tr>
<td>Disorders causing bowel mucosal inflammation, Crohn disease</td>
</tr>
<tr>
<td>Congenital bowel mucosal defects</td>
</tr>
<tr>
<td>Microvillous inclusion disease</td>
</tr>
<tr>
<td>Tufting enteropathy</td>
</tr>
<tr>
<td>Carbohydrate-deficient glycoprotein syndrome</td>
</tr>
<tr>
<td>Enterocyte heparan sulfate deficiency</td>
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<tr>
<td>Enteric anendocrinosis (NUEOOG 2 mutation)</td>
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<tr>
<td>Trichotrophic enteric syndrome</td>
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<tr>
<td>Immunodeficiency disorders</td>
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<tr>
<td>Congenital immunodeficiency disorders</td>
</tr>
<tr>
<td>Selective immunoglobulin A deficiency (can be associated with celiac disease)</td>
</tr>
<tr>
<td>Severe combined immunodeficiency</td>
</tr>
<tr>
<td>Agammaglobulinemia</td>
</tr>
<tr>
<td>X-linked hypogammaglobulinemia</td>
</tr>
<tr>
<td>Wiskott-Aldrich syndrome</td>
</tr>
<tr>
<td>Common variable immunodeficiency disease</td>
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<tr>
<td>Chronic granulomatous disease</td>
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<tr>
<td>Acquired immune deficiency</td>
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<tr>
<td>HIV infection</td>
</tr>
<tr>
<td>Immunosuppressive therapy and post-bone marrow transplantation</td>
</tr>
<tr>
<td>Autoimmune enteropathy</td>
</tr>
<tr>
<td>IPEX (immune dysregulation, polyendocrinopathy, enteropathy, X-linked inheritance)</td>
</tr>
<tr>
<td>IPEX-like syndromes</td>
</tr>
<tr>
<td>Autoimmune polyglandular syndrome type 1</td>
</tr>
<tr>
<td>Miscellaneous</td>
</tr>
<tr>
<td>Immuno proliferative small intestinal disease</td>
</tr>
<tr>
<td>Short bowel syndrome</td>
</tr>
<tr>
<td>Blind loop syndrome</td>
</tr>
<tr>
<td>Radiation enteritis</td>
</tr>
<tr>
<td>Protein–calorie malnutrition</td>
</tr>
<tr>
<td>Crohn disease</td>
</tr>
<tr>
<td>Pseudointestinal primary hyperparathyroidism</td>
</tr>
</tbody>
</table>

### Table 338-2
<table>
<thead>
<tr>
<th>Classification of Malabsorption Disorders and Chronic Diarrhea Based on the Predominant Nutrient Malabsorbed</th>
</tr>
</thead>
<tbody>
<tr>
<td>CARBOHYDRATE MALABSORPTION</td>
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<tr>
<td>Lactose malabsorption</td>
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<tr>
<td>Congenital lactase deficiency</td>
</tr>
<tr>
<td>Hypolactasia (adult type)</td>
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<tr>
<td>Secondary lactase deficiency</td>
</tr>
<tr>
<td>Congenital sucrase–isomaltase deficiency</td>
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<tr>
<td>Glucose galactose malabsorption</td>
</tr>
<tr>
<td>FAT MALABSORPTION</td>
</tr>
<tr>
<td>Abetalipoproteinemia</td>
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<tr>
<td>Lymphangiecstasy</td>
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<tr>
<td>Homozygous hypobetalipoproteinemia</td>
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<tr>
<td>Chylomicron retention disease (Anderson disease)</td>
</tr>
<tr>
<td>Cystic fibrosis</td>
</tr>
<tr>
<td>Shwachman-Diamond syndrome</td>
</tr>
<tr>
<td>Johansson-Blizzard syndrome</td>
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<tr>
<td>Pearson syndrome</td>
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<tr>
<td>Secondary exocrine pancreatic insufficiency</td>
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<tr>
<td>Isolated enzyme deficiency</td>
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<tr>
<td>Enterokinase deficiency</td>
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<tr>
<td>Trypsinogen deficiency</td>
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<tr>
<td>Lipase/collipase deficiency</td>
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<tr>
<td>Chronic pancreatitis</td>
</tr>
<tr>
<td>Protein–calorie malnutrition</td>
</tr>
<tr>
<td>Decreased pancreatic secretion</td>
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<tr>
<td>Disrupted enteric enterohepatic circulation of bile salts</td>
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<tr>
<td>Cholestatic liver disease</td>
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<td>Bile acid synthetic defects</td>
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<tr>
<td>Bile acid malabsorption (terminal ileal disease)</td>
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<tr>
<td>PROTEIN/AMINO ACID MALABSORPTION</td>
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<tr>
<td>Lysinuric protein intolerance (defect in dibasic amino acid transport)</td>
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<td>Hartnup disease (defect in free neutral amino acids)</td>
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<td>Blue dipeptide syndrome (isolated tryptophan malabsorption)</td>
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<td>Oatmeal urine disease (defect in methionine absorption)</td>
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<td>Lowe syndrome (lysine and arginine malabsorption)</td>
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<td>Enterokinase deficiency</td>
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<tr>
<td>MINERAL AND VITAMIN MALABSORPTION</td>
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<td>Congenital chloride diarrhea</td>
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<td>Congenital sodium absorption defect</td>
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<td>Acrodermatitis enteropathica (zinc malabsorption)</td>
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<td>Menkes disease (copper malabsorption)</td>
</tr>
<tr>
<td>Vitamin D-dependent rickets</td>
</tr>
<tr>
<td>Folate malabsorption</td>
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<td>Congenital secondary to mucosal damage (celiac disease)</td>
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<tr>
<td>Vitamin B12 malabsorption</td>
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<tr>
<td>Autoimmune pernicious anemia</td>
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<td>Decreased gastric acid (H₂ blockers or proton pump inhibitors)</td>
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<td>Terminal ileal disease (e.g., Crohn disease) or resection</td>
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<tr>
<td>Inborn errors of vitamin B₁₂ transport and metabolism</td>
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<tr>
<td>Primary hypomagnesemia</td>
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<td>DRUG INDUCED</td>
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<tr>
<td>Sulfasalazine: folic acid malabsorption</td>
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<td>Cholestyramine: calcium and fat malabsorption</td>
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<td>Anticonvulsant drugs such as phenytoin (causing vitamin D deficiency and folic acid and calcium malabsorption)</td>
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<tr>
<td>Gastric acid suppression: vitamin B₁₂</td>
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<td>Methotrexate: mucosal injury</td>
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Diarrheal Diseases Appearing in the Neonatal Period

<table>
<thead>
<tr>
<th>CONDITION</th>
<th>CLINICAL FEATURES</th>
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<tbody>
<tr>
<td>Microvillus inclusion disease</td>
<td>Secretory watery diarrhea</td>
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<td>Tufting enteropathy</td>
<td>Secretory watery diarrhea</td>
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<td>Congenital glucose-galactose malabsorption</td>
<td>Acidic diarrhea</td>
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<td>Congenital lactase deficiency</td>
<td>Acidic diarrhea</td>
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<td>Congenital chloride diarrhea</td>
<td>Hydrarnion, secretory watery diarrhea</td>
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<td>Metabolic alkalosis</td>
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<td>Congenital defective jejunal Na⁺⁻H⁺ exchange</td>
<td>Hydrarnion, secretory watery diarrhea</td>
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<td>Congenital bile acid malabsorption</td>
<td>Steatorrhea</td>
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<td>Congenital enterokinase deficiency</td>
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<td>Congenital trypsinogen deficiency</td>
<td>Failure to thrive, edema</td>
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<tr>
<td>Congenital lipase and/or colipase deficiency</td>
<td>Failure to thrive, oily stool</td>
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<td>Enteric anendocrinosis (NEUROG 3 mutation)</td>
<td>Hyperchloremic acidosis, failure to thrive</td>
</tr>
<tr>
<td>Immunodeficiency and autoinflammatory diseases (see Table 336-5)</td>
<td>Failure to thrive, opportunistic infections, eczema</td>
</tr>
</tbody>
</table>


### 338.1 Evaluation of Children with Suspected Intestinal Malabsorption

*Michael J. Lentze and David Branski*

The investigation is guided by the history and physical examination. In a child presenting with chronic or recurrent diarrhea, the initial work-up should include stool cultures and antibody tests for parasites, stool microscopy for ova and parasites such as *Giardia*, and stool occult blood and leukocytes to exclude inflammatory disorders. Stool pH and reducing substances for carbohydrate malabsorption, and quantitative stool fat examination and α₁-antitrypsin to demonstrate fat and protein malabsorption, respectively, should also be determined. Fecal stool elastase-1 can determine exocrine pancreatic insufficiency.

A complete blood count including peripheral smear for microcytic anemia, lymphopenia (lymphangiectasia), neutropenia (Shwachman syndrome), and acanthocytosis (abetalipoproteinemia) is useful. If celiac disease is suspected, serum immunoglobulin (Ig) A and tissue transglutaminase (TG2) antibody levels should be determined. Depending on the initial test results, more-specific investigations can be planned.

**INVESTIGATIONS FOR CARBOHYDRATE MALABSORPTION**

Measurement of carbohydrate in the stool, using a Clinistest reagent that identifies reducing substances, is a simple screening test. An acidic stool with >2+ reducing substance suggests carbohydrate malabsorption. Sucrose or starch in the stool is not recognized as a reducing sugar until after hydrolysis with hydrochloric acid, which converts them to reducing sugars.

**Breath hydrogen test** is used to identify the specific carbohydrate that is malabsorbed. After an overnight fast, the suspected sugar (lactose, sucrose, fructose, or glucose) is administered as an oral solution (carbohydrate load 1-2 g/kg, maximum 50 g). In malabsorption,
the sugar is not digested or absorbed in the small bowel, passes on to the colon, and is metabolized by the normal bacteria flora. One of the products of this process is hydrogen gas, which is absorbed through the colon mucosa and excreted in the breath. Increased hydrogen concentration in the breath samples suggests carbohydrate malabsorption. A rise in breath hydrogen of 20 ppm above the baseline is considered a positive test. The child should not be on antibiotics at the time of the test, because colonic flora is essential for fermenting the sugar.

**Small bowel mucosal biopsies** can measure mucosal disaccharidase (lactase, sucrase, maltase, palatinase) concentrations directly. In primary enzyme deficiencies the mucosal enzyme levels are low and small bowel mucosal morphology is normal. Partial or total villous atrophy due to disorders such as celiac disease, or following rotavirus gastroenteritis can result in secondary disaccharidase deficiency and transient lactose intolerance. The disaccharidase levels revert to normal after mucosal healing.

**INVESTIGATIONS FOR FAT MALABSORPTION**

The presence of fat globules in the stool suggests fat malabsorption. The ability to assimilate fat varies with age; a premature infant can absorb only 65-75% of dietary fat, a full-term infant absorbs almost 90%, and an older child absorbs more than 95% of fat while on a regular diet. Quantitative determination of fat malabsorption requires a 3-day stool collection for evaluation of fat excretion and determination of the coefficient of fat absorption:

\[
\text{Coefficient of fat absorption}\% = \left( \frac{\text{fat intake} - \text{fecal fat losses}}{\text{fat intake}} \right) \times 100
\]

where fat intake and fat losses are in grams. Because fecal fat balance studies are cumbersome, expensive, and unpleasant to perform, simpler tests are often preferred. Among these stool tests, the acid steatocrit test is the most reliable. When bile acid deficiency is suspected of being the cause of fat malabsorption, the evaluation of bile acid levels in duodenal fluid aspirate may be useful.

Fat malabsorption and exocrine pancreatic insufficiency are usually associated with deficiencies of fat-soluble vitamins A, D, E, and K. Serum concentrations of vitamins A, D, and E can be measured. A prolonged prothrombin time is an indirect test to assess vitamin K deficiency.

**INVESTIGATIONS FOR PROTEIN-LOSING ENTEROPATHY**

Dietary and endogenous proteins secreted into the bowel are almost completely absorbed; <1 g of protein from these sources passes into the colon. The majority of the stool nitrogen is derived from gut bacterial proteins. Excessive bowel protein loss usually manifests as hypoalbuminemia. Because the most common cause of hypoalbuminemia in children is a renal disorder, urinary protein excretion must be determined. Other potential causes of hypoalbuminemia include liver disease (reduced production) and inadequate protein intake. Very rarely hypoalbuminemia can result from an extensive skin disorder causing protein loss via the skin. Measurement of stool \(\alpha_1\)-antitrypsin is a useful screening test for protein-losing enteropathy. This serum protein has a molecular weight similar to albumin; however, unlike albumin it is resistant to digestion in the gastrointestinal (GI) tract. Excessive \(\alpha_1\)-antitrypsin excretion in the stool should prompt further investigations to identify the specific cause of gut or stomach (Menetrier disease) protein loss.

**INVESTIGATIONS FOR EXOCRINE PANCREATIC FUNCTION** (Fig. 338-2)

Cystic fibrosis is the most common cause of exocrine pancreatic insufficiency in children; therefore, a sweat chloride test must be performed before embarking on invasive tests to investigate possible exocrine pancreatic insufficiency. Many cases of cystic fibrosis are detected by neonatal genetic screening programs; occasional rare mutations are undetected.

**Fecal elastase-1** estimation is a sensitive test to assess exocrine pancreatic function in chronic cystic fibrosis and pancreatitis. Elastase-1 is a stable endoprotease unaffected by exogenous pancreatic enzymes. One disadvantage of the fecal elastase-1 test is the lack of full differentiation between primary exocrine pancreatic insufficiency and exocrine pancreatic dysfunction secondary to intestinal villous atrophy. The proximal small bowel is the site for pancreozymin/cholecystokinin production; the latter is the hormone that stimulates enzyme secretion from the exocrine pancreas. Mucosal atrophy can lead to diminished pancreozymin/cholecystokinin secretion and subsequently to exocrine pancreatic insufficiency. Fecal elastase-1 can also give a false-positive result during acute episodes of diarrhea.

**Serum trypsinogen** concentration can also be used as a screening test for exocrine pancreatic insufficiency. In cystic fibrosis, the levels are greatly elevated early in life, and then they gradually fall, so that by 5-7 yr of age, most patients with cystic fibrosis with pancreatic insufficiency have subnormal levels. Patients with cystic fibrosis and adequate exocrine pancreatic function tend to have normal or elevated levels. In such patients, observing the trend in serial serum trypsinogen estimation may be useful in monitoring exocrine pancreatic function. In Shwachman syndrome, another condition associated with exocrine pancreatic insufficiency, the serum trypsinogen level is low.

Other tests for pancreatic insufficiency (nitroblue tetrazolium–paraaminobenzoic acid test and pancreolauryl test) measure urine or breath concentrations of substances released and absorbed across the mucosal surface following pancreatic digestion. These tests lack specificity and are rarely used in clinical practice.

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**Figure 338-2 Algorithm for assessment of exocrine pancreatic function.** *If not available, use other test. Perform appropriate imaging studies of the pancreas. **In case of borderline values, consider repeating the test with 3 independent samples. ***Consider differential diagnosis (especially consider mucosal villous atrophy and dilution effect of watery stool). GI, gastrointestinal. (Adapted from Walkowiak J, Nouis-Arvanitakis S, Henker J, et al: Indirect pancreatic function tests in children. J Pediatr Gastroenterol Nutr 40:107-114, 2005.)*
The gold standard test for exocrine pancreatic function is direct analysis of duodenal aspirate for volume, bicarbonate, trypsin, and lipase upon secretin, and pancreozymin/cholecystokinin stimulation. This involves duodenal intubation (see Chapter 348).

**INVESTIGATIONS FOR INTESTINAL MUCOSAL DISORDERS**

Establishing a specific diagnosis for malabsorption often requires histologic examination of small bowel mucosal biopsies. These are obtained during endoscopy, which allows multiple biopsies to be performed, because mucosal involvement can be patchy, especially in celiac disease. Periodic acid–Schiff (PAS) staining of mucosal biopsies and electron microscopy are necessary in congenital diarrhea to assess congenital microvillus atrophy. Bowel mucosal lesions can also be segmental in cases of intestinal lymphangiectasia. In these situations, radiographic small bowel series or repeated ultrasonographies can identify a region of thickened bowel responsible for protein loss. During endoscopy, mucosal biopsies can be obtained to measure mucosal disaccharidase activities. Duodenal aspirates can be performed to measure pancreatic enzyme concentration as well as quantitative bacterial cultures. Aspirates to demonstrate other infections and infestations such as Giardia may be useful.

**IMAGING PROCEDURES**

Plain radiographs and barium contrast studies might suggest a site and cause of intestinal motility disorders. Although flocculations of barium and dilated bowel with thickened mucosal folds have been attributed to diffuse malabsorptive lesions such as celiac disease, these abnormalities are nonspecific. Diffuse fluid-filled bowel loops during sonography also suggest malabsorption.

### 338.2 Celiac Disease (Gluten-Sensitive Enteropathy)

David Branski, Riccardo Troncone, and Alessio Fasano

**ETIOLOGY AND EPIDEMIOLOGY**

Celiac disease is an immune-mediated systemic disorder elicited by gluten and related prolamines in genetically susceptible individuals and characterized by the presence of a variable combination of gluten-dependent clinical manifestations, celiac disease–specific antibodies, HLA-DQ2 or DQ8 haplotypes, and enteropathy. Celiac disease–specific antibodies comprise autoantibodies against TG2, including endomysial antibodies (EMA), and antibodies against deamidated forms of gliadin peptides.

Celiac disease is triggered by the ingestion of wheat gluten and related prolamines from rye and barley. In most studies oats proved to be safe; however, a few celiac disease patients have oats prolamine–reactive mucosal T cells that can cause mucosal inflammation.

Celiac disease is a common disorder (1% prevalence of biopsy-proven disease). It is thought to be rare in Central Africa and East Asia. Environmental factors might affect the risk of developing celiac disease or the timing of its presentation. Neither the delayed introduction of gluten, or breastfeeding, or the introduction of small quantities of gluten prevents celiac disease in high-risk patients. Infectious agents have been hypothesized to play a role because frequent rotavirus infections are associated with an increased risk. It is plausible that the contact with gliadin at a time when there is ongoing intestinal inflammation, altered intestinal permeability, and enhanced antigen presentation can increase the risk of developing celiac disease, at least in a subset of persons (Fig. 338-3).

**GENETICS AND PATHOGENESIS**

A genetic predisposition is suggested by the family aggregation and the concordance in monzygotic twins, which approaches 100%. The strongest association is with human leukocyte antigen (HLA)-DQ2.5 (1 or 2 copies encoded by DQA1 *05 [for the chain] and DQB1*02 genes [for the chain]). Such a DQ molecule has been found to be present in more than 90% of celiac patients. The highly homologous DQ2.2 molecule confers a much lesser risk, while the data available on DQ2-negative celiac disease patients indicate that they almost invariably are HLA-DQ8–positive (DQA1*0301/DQB1*0302). A gene dosage effect has been suggested, and a molecular hypothesis for such a phenomenon has been proposed, based on the impact of the number and quality of the HLA-DQ2 molecules on gluten peptide presentation to T cells. Other non-HLA genes confer susceptibility to celiac disease. Genome-wide association studies have shown risk variants in genes controlling T-cell activation and recruitment, some being shared with type 1 diabetes and other autoimmune diseases. Interestingly, very few polymorphisms associated with celiac disease are in coding regions, as they often are in binding sites for transcription factors, then affecting gene expression.

Celiac disease is a T-cell–mediated chronic inflammatory disorder with an autoimmune component. Altered processing by intraluminal enzymes, changes in intestinal permeability and activation of innate immunity mechanisms precede the activation of the adaptive immune response. Immunodominant epitopes from gliadin are highly resistant to intraluminal and mucosal digestion; incomplete degradation favor immunity mechanisms preceding the activation of the adaptive immune response. Immunodominant epitopes from gliadin are highly resistant to intraluminal and mucosal digestion; incomplete degradation favor the immunostimulatory and toxic effects of these sequences. Some gliadin peptides (p31-43) are able to activate innate immunity, in particular they induce interleukin (IL)-15. The latter, but also type 1 interferons, may alter the tolerogenic phenotype of dendritic cells, resulting in lamina propria T-cell activation by other peptides presented in the context of HLA-DQ2 or HLA-DQ8 molecules. Gliadin-specific T-cell responses are enhanced by the action of TG2; the enzyme converts particular glutamine residues into glutamic acid, which results in higher affinity of these gliadin peptides for HLA-DQ2 or HLA-DQ8. The pattern of cytokines produced following gliadin activation is clearly dominated by interferon-γ (T-helper type 1 skewed); IL-21 is also upregulated. Downstream T-cell activation, a complex remodeling of the mucosa takes place, involving increased levels of metalloproteinases and growth factors, which leads to the classical flat mucosa. A severe impairment of intraepithelial lymphocytes (IELs) homeostasis is present in celiac disease. IL-15 is implicated in the expression of natural killer receptors CD94 and NKG2D, as well as in epithelial expression of stress molecules, thus enhancing cytotoxicity, cell apoptosis, and villous atrophy. The most evident expression of autoimmunity is the presence of serum antibodies to TG2. However, the

**Figure 338-3 Causative factors in celiac disease.** HLA, human leukocyte antigen. (From Di Sabatino A, Corassa GR: Celiac disease. Lancet 373:1480–1490, 2009.)

![Diagram showing causative factors in celiac disease](image-url)
mechanisms leading to autoimmunity are largely unknown, as well as their pathogenetic significance. “Potential” celiac disease, in which TG2 antibodies can be detected in situ without any histologic abnormality, shows that the production of antibodies does not necessarily lead to intestinal damage. The finding of IgA deposits on extracellular TG2 in the liver, lymph nodes, and muscles indicates that TG2 is accessible to the gut-derived autoantibodies.

**CLINICAL PRESENTATION AND ASSOCIATED DISORDERS**

Clinical features of celiac disease vary considerably (Table 338-4). Intestinal symptoms are common in children whose disease is diagnosed within the 1st 2 yr of life; failure to thrive, chronic diarrhea, vomiting, abdominal distention, muscle wasting, anorexia, and irritability are present in most cases (see Fig. 338-1). Occasionally there is constipation, rectal prolapse, or intussusception. As the age at presentation of the disease shifts to later in childhood, and with the more liberal use of serologic screening tests, extraintestinal manifestations and associated disorders, without any accompanying digestive symptoms, have increasingly become recognized, affecting almost all organs (Table 338-5).

The most common extraintestinal manifestation of celiac disease is iron-deficiency anemia, unresponsive to iron therapy. Osteoporosis may be present; in contrast to the situation in adults, it can be reversed by a gluten-free diet, with restoration of normal peak bone densitometric values. Other extraintestinal manifestations include short stature, arthritis and arthralgia, epilepsy with bilateral occipital calcifications, peripheral neuropathies, cardiomypathy, isolated hypertransaminasemia, dental enamel hypoplasia, aphthous stomatitis, and alopecia. The mechanisms responsible for the severity and the variety of clinical presentations remain obscure. Nutritional deficiencies or abnormal immune responses have been advocated.

Silent celiac disease is being increasingly recognized, mainly in asymptomatic 1st-degree relatives of celiac disease patients investigated during screening studies. However, small bowel biopsy in these people reveals severe mucosal damage consistent with celiac disease. Potential celiac disease is defined when patients have positive celiac disease–specific antibodies, but without documented small bowel damage. It is important to follow these patients because they can develop established celiac disease in the future (Table 338-6).

Some diseases, many with an autoimmune pathogenesis, are found with a higher-than-normal incidence in celiac disease patients. Among these are type 1 diabetes, autoimmune thyroid disease, Addison disease, Sjögren syndrome, autoimmune cholangitis, autoimmune hepatitis, primary biliary cirrhosis. Such associations have been interpreted as a consequence of the sharing of identical HLA haplotypes.

### Table 338-4 | Some Clinical Manifestations of Celiac Disease in Children and Adolescents

<table>
<thead>
<tr>
<th>SYSTEM</th>
<th>MANIFESTATION</th>
<th>(POSSIBLE) CAUSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal</td>
<td>Diarrhea</td>
<td>Atrophy of the small bowel mucosa</td>
</tr>
<tr>
<td></td>
<td>Distended abdomen</td>
<td>Malabsorption</td>
</tr>
<tr>
<td></td>
<td>Vomiting</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Anorexia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Weight loss</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Failure to thrive</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Rectal prolapse</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Aphthous stomatitis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Intussusception</td>
<td></td>
</tr>
<tr>
<td>Hematologic</td>
<td>Anemia</td>
<td>Iron malabsorption</td>
</tr>
<tr>
<td>Skeletal</td>
<td>Rickets</td>
<td>Calcium/vitamin D malabsorption</td>
</tr>
<tr>
<td></td>
<td>Osteoporosis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Enamel hypoplasia of the teeth</td>
<td></td>
</tr>
<tr>
<td>Muscular</td>
<td>Atrophy</td>
<td>Malnutrition</td>
</tr>
<tr>
<td>Neurologic</td>
<td>Peripheral neuropathy</td>
<td>Thiamine/vitamin B12 deficiency</td>
</tr>
<tr>
<td></td>
<td>Epilepsy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Irritability</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cerebral calcifications</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cerebellar ataxia</td>
<td></td>
</tr>
<tr>
<td>Endocrinologic</td>
<td>Short stature</td>
<td>Malnutrition</td>
</tr>
<tr>
<td></td>
<td>Pubertas tarda</td>
<td>Calcium/vitamin D malabsorption</td>
</tr>
<tr>
<td></td>
<td>Secondary hyperparathyroidism</td>
<td></td>
</tr>
<tr>
<td>Dermatologic</td>
<td>Dermatitis herpetiformis</td>
<td>Autoimmunity</td>
</tr>
<tr>
<td></td>
<td>Alopecia areata</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Erythema nodosum</td>
<td></td>
</tr>
<tr>
<td>Respiratory</td>
<td>Idiopathic pulmonary hemosiderosis</td>
<td></td>
</tr>
</tbody>
</table>


### Table 338-5 | Risk Groups for Celiac Disease

<table>
<thead>
<tr>
<th>Case-Finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>First-degree relatives</td>
</tr>
<tr>
<td>Dermatitis herpetiformis</td>
</tr>
<tr>
<td>Unexplained iron-deficiency anemia</td>
</tr>
<tr>
<td>Autoimmune thyroiditis</td>
</tr>
<tr>
<td>Type 1 diabetes</td>
</tr>
<tr>
<td>Unexplained infertility</td>
</tr>
<tr>
<td>Recurrent abortion</td>
</tr>
<tr>
<td>Dental enamel hypoplasia</td>
</tr>
<tr>
<td>Cryptic hypertransaminasemia</td>
</tr>
<tr>
<td>Autoimmune liver disease</td>
</tr>
<tr>
<td>Short stature</td>
</tr>
<tr>
<td>Delayed puberty</td>
</tr>
<tr>
<td>Down, Williams, and Turner syndromes</td>
</tr>
<tr>
<td>Irritable bowel syndrome</td>
</tr>
<tr>
<td>Unexplained osteoporosis</td>
</tr>
<tr>
<td>Sjögren syndrome</td>
</tr>
<tr>
<td>Epilepsy (poorly controlled) with occipital calcifications</td>
</tr>
<tr>
<td>Selective immunoglobulin A deficiency</td>
</tr>
<tr>
<td>Autoimmune endocrinopathies</td>
</tr>
<tr>
<td>Addison disease</td>
</tr>
<tr>
<td>Aphthous stomatitis</td>
</tr>
<tr>
<td>Ataxia</td>
</tr>
<tr>
<td>Alopecia</td>
</tr>
<tr>
<td>Polyneuropathy</td>
</tr>
<tr>
<td>Irritable bowel syndrome</td>
</tr>
</tbody>
</table>


### Table 338-6 | Clinical Spectrum of Celiac Disease

<table>
<thead>
<tr>
<th>SYMPTOMATIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frank malabsorption symptoms: chronic diarrhea, failure to thrive, weight loss</td>
</tr>
<tr>
<td>Extraintestinal manifestations: anemia, fatigue, hypertransaminasemia, neurologic disorders, short stature, dental enamel defects, arthralgia, aphthous stomatitis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SILENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>No apparent symptoms in spite of histologic evidence of villous atrophy</td>
</tr>
<tr>
<td>In most cases identified by serologic screening in at-risk groups (see Table 330-1)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>LATENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects who have a normal histology, but at some other time, before or after, have shown a gluten-dependent enteropathy</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>POTENTIAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects with positive celiac disease serology but without evidence of altered jejunal histology</td>
</tr>
<tr>
<td>It might or might not be symptomatic</td>
</tr>
</tbody>
</table>
The relation between celiac disease and other autoimmune diseases is poorly defined; once those diseases are established, they are not influenced by a gluten-free diet. Other associated conditions include selective IgA deficiency and Down, Turner, and Williams syndromes.

Patients with celiac disease show increased long-term mortality, the risk rising with delayed diagnosis and/or poor dietary compliance. Non-Hodgkin lymphoma is the main cause of death. Adult patients can develop complications such as refractory celiac disease, ulcerative jejunoileitis, or enteropathy-associated T-cell lymphoma.

**DIAGNOSIS**

The diagnosis of celiac disease is based on a combination of symptoms, antibodies, HLA, and duodenal histology (Table 338-7). The initial approach to symptomatic patients is to test for anti-TG2 IgA antibodies and in addition for total IgA in serum to exclude IgA deficiency. As an alternative for total IgA in serum direct testing for IgG anti–deamidated forms of gliadin peptides antibodies can be performed. If IgA anti-TG2 antibodies are negative and serum total IgA is normal for age (or IgG anti–deamidated forms of gliadin peptides antibodies are negative), celiac disease is unlikely to be the cause of the symptoms. If anti-TG2 antibody testing is positive the patients should be referred to a pediatric gastroenterologist for further diagnostic workup, which depends on the serum antibody levels. Patients with positive anti-TG2 antibody levels <10 × upper limits of normal should undergo upper endoscopy with multiple biopsies. In patients with positive anti-TG2 antibody levels at or >10 × upper limits of normal, blood should be drawn for HLA and EMA testing. If the patient is positive for EMA antibodies and positive for DQ2 or DQ8 HLA testing, the diagnosis of celiac disease is confirmed, a gluten-free diet is started and the patient is followed for improvement of symptoms and decline of antibodies. In the rare case of negative results for HLA and/or anti-EMA in a child with TG2 antibody titers ≥10 × upper limits of normal, the different possibilities for false-positive and false-negative test results need to be considered. In these circumstances, the diagnostic workup should be extended, including repeated testing and duodenal biopsies. In totally asymptomatic persons belonging to high-risk groups, celiac disease should always be diagnosed using duodenal biopsies. When biopsies are indicated at least 4 fragments should be obtained from the descending part of the duodenum and at least 1 from the duodenal bulb. The diagnosis is confirmed by an antibody decline and preferably a clinical response to a gluten-free diet. Gluten challenge and repetitive biopsies will only be necessary in selected cases in which diagnostic uncertainty remains.

**TREATMENT**

The only treatment for celiac disease is lifelong strict adherence to a gluten-free diet (Fig. 338-4). This requires a wheat-, barley-, and rye-free diet. Despite evidence that oats are safe for most patients with celiac disease, there is concern regarding the possibility of contamination of oats with gluten during harvesting, milling, and shipping. Nevertheless, it seems wise to add oats to the gluten-free diet only when the latter is well established, so that possible adverse reactions can be readily identified. There is a consensus that all celiac disease patients should be treated with a gluten-free diet regardless of the presence of symptoms. However, whereas it is relatively easy to assess the health improvement after treatment of celiac disease in patients with clinical symptoms of the disease, it proves difficult in persons with asymptomatic celiac disease. The nutritional risks, particularly osteopenia, are those mainly feared for subjects who have silent celiac disease and continue on a gluten-containing diet. Little is known about the health risks in untreated patients with minor enteropathy, which may be clinically silent. There are no guidelines concerning the need for a gluten-free diet in subjects with “potential” celiac disease (patients with positive celiac disease–associated serology but without enteropathy).

The Codex Alimentarius Guidelines define gluten-free as <20 ppm, but, although analytical methods for gluten detection have already reached a satisfactory degree of sensitivity, more information is needed on the daily gluten amount that may be tolerated by celiac disease patients. The data available so far seem to suggest that the threshold should be set to <50 mg/day, although individual variability makes it difficult to set a universal threshold.

It is important that an experienced dietician with specific expertise in celiac disease counseling educates the family and the child about dietary restriction. Compliance with a gluten-free diet can be difficult, especially in adolescents. It is recommended that children with celiac disease be monitored with periodic visits for assessment of symptoms, growth, physical examination, and adherence to the gluten-free diet. Periodic measurements of TG2 antibody levels to document reduction in celiac disease.
in antibody titers can be helpful as indirect evidence of adherence to a gluten-free diet, although they are inaccurate in detecting slight dietary transgressions.

**NONCELIAC GLUTEN SENSITIVITY**

Wheat-induced symptoms in patients who do not have celiac disease have been described in 2 groups. IgE-mediated wheat allergy may have overlapping symptoms with celiac disease but more often presents without an enteropathy but with symptoms of atopy (urticaria, angioedema, eczema, asthma, rhinitis) and is diagnosed by the presence of IgE antibodies to wheat (serum specific IgE or skin prick tests). In contrast to celiac disease and nonceliac gluten sensitivity, symptoms in IgE-mediated disease occur soon after ingestion of wheat products.

**Gluten sensitivity** has been defined as enteric (abdominal pain, bloating, diarrhea) and systemic (headache, fatigue, muscle aches, rash) after ingesting wheat in the absence of enteropathy or HLA risk factors and autoantibodies. Symptoms are often similar to patients with irritable bowel syndrome and some patients with irritable bowel syndrome respond positively to a gluten-free diet. This is an area of uncertainty in pediatrics because most studies have been performed in adults.

Bibliography is available at Expert Consult.

### 338.3 Other Malabsorptive Syndromes

**Philip M. Sherman, David Branski, and Olivier Goulet**

#### CONGENITAL INTESTINAL MUCOSAL DEFECTS

**Microvillus Inclusion Disease (Congenital Microvillus Atrophy)**

Microvillus inclusion disease (MVID) is an autosomal recessive disorder, which manifests at birth with profuse watery secretory diarrhea. It is the most severe cause of congenital diarrhea involving the development of intestinal mucosa. Light microscopy of the small bowel mucosa demonstrates diffuse thinning of the mucosa, with hypoplastatic villus atrophy and no inflammatory infiltrate. Diagnosis may be easily performed with light microscopy using PAS and CD10 staining, which shows a very thin or absent brush border, together with positive PAS and CD10 intracellular inclusions. Electron microscopy shows enterocytes with absent or sparse microvilli. The apical cytoplasm of the enterocytes contains electron-dense secretory granules; the hallmark is presence of microvilli within involutions of the apical membrane. Polyhydramnios is not a classic presentation of MVID but is increasingly observed according to the progresses in prenatal follow up. Neonates usually present very early onset of severe watery diarrhea up to 200–330 mL/kg/day) causing dehydration and failure to thrive. Despite parenteral nutrition, diarrhea continues and initial fluid management is difficult. The disease is fatal without long-term parenteral nutrition support. Most children die in infancy or early childhood. To date, no causal treatment exists for MVID. Trials with antiinflammatory drugs, including steroids and antisecretory medications (such as Sandostatin or loperamide), did not significantly change stool volumes over a prolonged period; colostrum and epidermal growth factor have failed as well, but octreotide has shown a partial improvement in 1 patient, other than water produces diarrhea. Villus-crypt architecture in small bowel biopsies is normal, but staining for neuroendocrine cells (e.g., somatostatin, glucagon) is usually positive. Tufting enteropathy is often associated with punctiform keratitis and conjunctival dysplasia resembling typical pictures in tufts. The genetic basis of tufting enteropathy supports this speculation, because mutations in the EPCAM gene, encoding an epithelial cell adhesion molecule protein, have been described. The phenotype associated with mutations of EPCAM is usually an isolated congenital diarrhea without associated extradigestive symptoms, except in some patients with late-onset arthritis. A founder effect at the EPCAM locus in congenital tufting enteropathy (CTE) has been shown in the Arabian Gulf population.

In the syndromic form of CTE, diarrhea is associated with one or more of these same anomalies: superficial punctate keratitis, choanal, esophageal or intestinal atresia, anal imperforation, hair dysplasia, skin hyperlaxity, bone abnormalities, hexadactyly, and facial dysmorphism. Anomalies appear isolated for most, except for superficial punctate keratitis and choanal atresia that are consistently found in the population of patients with mutated SPINT2 for conjunctival inflammation (100%) and in 50% of cases for choanal atresia; moreover, these anomalies are never found in the population of patients with EPCAM mutations.

**No treatment** has been effective, so management requires permanent parenteral nutrition with possible intestinal transplantation (see Chapter 339).

**Enteric Anendocrinosis**

Mutations of the NEUROG3 gene produce generalized mucosal malabsorption, vomiting, diarrhea, failure to thrive, dehydration, and a hyperchloremic metabolic acidosis. Oral alimentation with anything other than water produces diarrhea. Villus-crypt architecture in small bowel biopsies is normal, but staining for neuroendocrine cells (e.g., employing antichromogranin antibodies) demonstrates a complete absence of this secretory cell lineage with preservation of goblet cells and Paneth cells. **Treatment** is with total parenteral nutrition and small bowel transplantation.

**PROPROTEIN CONVERTASE 1/3 DEFICIENCY**

Chronic watery, neonatal onset diarrhea is described in infants with hyperinsulinism, hypoglycemia, hypoponadism, and hypoadrenalinism. Small bowel biopsy reveals a nonspecific enteropathy. A clue to the autosomal recessive condition is subsequent onset of marked obesity with hyperphagia in the toddler years in both affected probands and symptomatic siblings. Elevated serum levels of proinsulin are highly supportive of this underdiagnosed disorder, which is caused by loss-of-function mutations in the PCSK1 gene.

It is likely that in very rare cases a milder phenotype may allow slow weaning from parenteral nutrition, allowing the patient to reach young adulthood and enjoy partial oral feeding.

**Tufting Enteropathy (Congenital Tufting Enteropathy)**

Tufting enteropathy (intestinal epithelial dysplasia) manifests in the 1st few wk of life with persistent watery diarrhea and accounts for a small fraction of infants with intractable diarrhea of infancy. The distinctive feature on small intestinal mucosal biopsy is focal epithelial “tufts” (teardrop-shaped groups of closely packed enterocytes with apical rounding of the plasma membrane) involving 80–90% of the epithelial surface. However, the typical pathology does not appear immediately after birth, and in other known enteropathies, tufts are seen on ≤15% of the epithelial surface. One difficulty comes from the mononuclear T cell’s infiltration of the lamina propria, which can guide wrongly to a disimmune enteropathy, especially when initially lacking tufts. The increased intestinal permeability caused by cell adhesion defect could be responsible for the inflammatory reaction. Colonic epithelium shows abnormalities that are more difficult to identify. Electron microscopy does not help in establishing the diagnosis.

The pathogenesis of this severe digestive disease is from a disorder of cell–cell and cell–matrix interactions, because there is an abnormal distribution of α6β4-integrin along the crypt–villus axis, increased expression of desmoglein, and ultrastructural changes of desmosomes. Tufting enteropathy is often associated with punctiform keratitis and conjunctival dysplasia resembling typical pictures of tufts. The genetic basis of tufting enteropathy supports this speculation, because mutations in the EPCAM gene, encoding an epithelial cell adhesion molecule protein, have been described. The phenotype associated with mutations of EPCAM is usually an isolated congenital diarrhea without associated extradigestive symptoms, except in some patients with late-onset arthritis. A founder effect at the EPCAM locus in congenital tufting enteropathy (CTE) has been shown in the Arabian Gulf population.

In the syndromic form of CTE, diarrhea is associated with one or more of these same anomalies: superficial punctate keratitis, choanal, esophageal or intestinal atresia, anal imperforation, hair dysplasia, skin hyperlaxity, bone abnormalities, hexadactyly, and facial dysmorphism. Anomalies appear isolated for most, except for superficial punctate keratitis and choanal atresia that are consistently found in the population of patients with mutated SPINT2 for conjunctival inflammation (100%) and in 50% of cases for choanal atresia; moreover, these anomalies are never found in the population of patients with EPCAM mutations.

**No treatment** has been effective, so management requires permanent parenteral nutrition with possible intestinal transplantation (see Chapter 339).
Chapter 338 - Disorders of Malabsorption

Bibliography


CARBOHYDRATE-DEFICIENT GLYCOPROTEIN SYNDROME AND ENTEROCYTE HEPARAN SULFATE DEFICIENCY

Congenital disorders of glycosylation (also carbohydrate-deficient glycoprotein [CDG]) are genetic disorders of assembly of N-glycans in the cytosol and endoplasmic reticulum, resulting in a variety of manifestations (see Chapter 87.6). The subtypes of CDG I are all associated with protein-losing enteropathy. Diagnosis can be established by isoelectric focusing of serum transferrin, enzyme analysis, and DNA analysis. Oral mannose can provide effective therapy in CDG Ib, so early identification of children presenting with hypoglycemia, hypothyroidism, and/or thyroid binding globulin deficiency is beneficial.

Congenital enterocyte heparan deficiency is a rare cause of intractable diarrhea with protein-losing enteropathy, which may be an unusual presentation of the CDG syndrome type I (also known as Jaeken syndrome) (see Chapter 87.6). Heparan sulfate is a glycosaminoglycan with multiple roles in the intestine, including restriction of charged macromolecules, such as albumin, in the vascular lumen.

SYNDROMIC DIARRHEA

Syndromic diarrhea (SD), also known as phenotypic diarrhea or trichohaptoenteric syndrome is a congenital enteropathy manifesting with early onset of severe diarrhea requiring parenteral nutrition. The estimated prevalence is approximately 1 per 300,000–400,000 live births in Western Europe. Patients are born small for gestational age and present with diarrhea starting in the 1st 6 mo of life (<1 mo of age in most cases). They have an abnormal phenotype, including facial dysmorphism with prominent forehead, broad nose, and hypertelorism and a distinct abnormality of hair, trichorhesis nodosa. Hairs are soft, easily removed, and poorly pigmented. Abnormal cutaneous spots including café-au-lait on the lower limbs may be observed. Liver disease affects about half of the patients with extensive fibrosis or cirrhosis. Cardiac abnormalities and colitis have been reported sporadically, as well as 1 case involving polyhydramnios, placental abnormalities, and congenital hemochromatosis. The patients have defective antibody responses despite normal serum immunoglobulin levels and defective antigen-specific skin tests despite positive proliferative responses in vitro. Microscopic analysis shows twisted hair (pili torti), aniso- and polikliotrachosis, and trichorhesis nodosa. Histopathologic analysis shows nonspecific villus atrophy with or without mononuclear cell infiltration of the lamina propria, and without specific histologic abnormalities involving the epithelium. The common association of the disorder with parental consanguinity and/or affected siblings indicates a genetic origin with autosomal recessive transmission. Mutations in the TTC37 gene are the basis of the syndrome. TTC37 encodes a protein known as Thespin, which is in many tissues (vascular endothelium, lymph, pituitary stalk, lung, and intestine), but is not expressed in the liver. In patients with SD, with no mutation in TTC37, there are mutations in the SKIV2L gene. This gene encodes a protein of the Ski multiprotein complex that is involved in the control of RNA by the exosome, including the regulation of normal messenger RNA and the degradation of nonfunctional messenger RNA.

Prognosis of this type of intractable diarrhea of infancy is poor, with most patients having died between the ages of 2 and 5 yr, some of them with early-onset liver disease.

AUTOIMMUNE ENTEROPATHY

Symptoms of autoimmune enteropathy usually occur after the 1st 6 mo of life, presenting with chronic diarrhea, protein-losing enteropathy, malabsorption, and failure to thrive. The diagnosis is based on the endoscopic and histologic evaluation of the inflammation mainly of the small bowel but also of the colon. Histologic findings in the small bowel include partial or complete villous atrophy, crypt hyperplasia, and an increase in chronic inflammatory cells in the lamina propria. In contrast to gluten-sensitive enteropathy (celiac disease), there is no increased number in intraepithelial lymphocytes. Immunologic analyses indicate the presence of autoantibodies and, most importantly, of anti-enterocyte antibodies, as well as anti-autoimmune enteropathy-75 kDa. Specific serum antienterocyte antibodies can be identified in 50% or more of patients by indirect immunofluorescent staining of normal small bowel mucosa and kidney. In some patients anti-goblet cell antibodies also can be demonstrated.

Extraintestinal autoimmune disorders are usual and include arthritis, membranous glomerulonephritis, insulin-dependent diabetes, thrombocytopenia, autoimmune hepatitis, hypothyroidism, and hemolytic anemia. It is essential to exclude an underlying primary immune deficiency, particularly in boys with other autoimmune features (e.g., diabetes mellitus), because a proportion has underlying immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome (see Chapter 126.5). Different phenotypes of IPEX syndrome patients, as well as IPEX-like forms of autoimmune enteropathy that are FOXP3-independent are described involving girls as well with or without extraintestinal autoimmune disorders. Contrary to classical IPEX, the cause of IPEX-like or type 2 autoimmune enteropathy is only partially elucidated on a molecular basis. However, in patients who do not show genetic defects in FOXP3 or CD25, abnormal functions of CD4+CD25 high-regulatory T cells should be documented. Autoimmune enteropathy is reported in cases of Schimke immunooosseous dysplasia.

Treatment options are rather limited and based on T-cell–suppressivive immunomodulation. Upon initial stabilization using steroid pulse therapy and calcineurin-dependent immunosuppressive drugs, such as tacrolimus, most often patients are maintained on ramapycin with azathioprine, methotrexate or rituximab in few patients. A theoretic alternative treatment option could be in form of hematopoietic stem cell transplantation; this treatment option is preferable in patients with a molecular defect, such as previously shown for patients with classical IPEX syndrome.

BILE ACID MALABSORPTION

In primary bile acid malabsorption, mutation of the ileal sodium–bile acid cotransporter gene, SLC10A2, results in congenital diarrhea, steatorrhea, interruption of enterohepatic circulation of bile acids, and reduced plasma cholesterol levels. Bile acids are normally synthesized from cholesterol in the liver and secreted into the small intestine, where they facilitate absorption of fat, fat-soluble vitamins, and cholesterol. Bile acids are reabsorbed in the distal ileum, return to the liver via the portal venous circulation, and resecrete into bile. Normally, the enterohepatic circulation of bile acids is an extremely efficient process; only 10% of the intestinal bile acids escape reabsorption and are eliminated in feces. Bile acid secretion is largely autoregulated, but there is only a limited capacity to increase bile acid secretion. Reduction in the bile acid pool from bile acid malabsorption causes steatorrhea, which requires restriction of dietary fat. Unabsorbed bile acids stimulate chloride excretion in the colon, resulting in diarrhea, which responds to cholestyramine, an anion-binding resin. Secondary bile acid malabsorption can result from ileal disease, such as in Crohn disease, and following an ileal resection.

Chronic neonatal-onset diarrhea has also been described in autosomal recessive cerebrotendinous xanthomatosis, which is caused by an inborn error of bile acid synthesis resulting from 27-hydroxylase deficiency. These children also present with juvenile-onset cata­ racts and developmental delay. Neonatal cholestasis has also been described as a presenting feature. Tendon xanthomas develop in the second and third decades of life. The diagnosis is important to establish, because treatment is effective when employing oral chenodeoxycholic acid.

INTESTINAL LYPHANGIECTASIA

Obstruction of the lymphatic drainage of the intestine can be caused by either congenital defects in lymphatic duct formation or by secondary causes (Table 338-8). The congenital form is often associated with lymphatic abnormalities elsewhere in the body, as occur with Turner, Noonan, and Klippel-Trenauay-Weber syndromes. Causes of secondary lymphangectasia include constrictive pericarditis, heart failure, retroperitoneal fibrosis, abdominal tuberculosis, and retroperitoneal malignancies. Lymph rich in proteins, lipids, and lymphocytes leak
The diagnosis is suggested by the typical findings in association with an elevated fecal α₁-antitrypsin clearance. Radiologic findings of uniform, symmetric thickening of mucosal folds throughout the small intestine are characteristic but nonspecific. Small bowel mucosal biopsy can show dilated lacteals with distortion of villi and no inflammatory infiltrate. A patchy distribution and deeper mucosal involvement on occasion causes false-negative results on small bowel histology. Video capsule endoscopy may reveal similar lesions (Figs. 338-5 and 338-6). Treatment of lymphangiectasia includes restricting the amount of long-chain fat ingested and administering a formula containing protein and medium-chain triglycerides (MCTs). Supplementing a low-fat diet with MCT oil in cooking is used in the management of older children with lymphangiectasia. Rarely, parenteral nutrition is required. If only a portion of the intestine is involved, surgical resection may be considered.

ABETALIPOPROTEINEMIA
Abetalipoproteinemia is a rare autosomal recessive disorder of lipoprotein metabolism (Bassen-Kornzweig syndrome) (see Chapter 86). It is associated with severe fat malabsorption from birth. Children fail to thrive during the 1st yr of life, with stools that are pale, foul smelling, and bulky. The abdomen is distended and deep tendon reflexes are absent as a result of peripheral neuropathy, which is secondary to vitamin E (fat-soluble vitamin) deficiency. Intellectual development tends to be slow. After 10 yr of age, intestinal symptoms are less severe, ataxia develops, and there is a loss of position and vibration sensation into the bowel lumen, resulting in protein-losing enteropathy, steatorrhea, and lymphocyte depletion. Hypoalbuminemia, hypogammaglobulinemia, edema, lymphopenia, malabsorption of fat and fat-soluble vitamins, and chylous ascites often occur. Intestinal lymphangiectasia can also manifest with ascites, peripheral edema and a low serum albumin.

Table 338-8 Causes of Protein-Losing Enteropathy

<table>
<thead>
<tr>
<th>Causes of Protein-Losing Enteropathy</th>
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</thead>
<tbody>
<tr>
<td>Mucosal inflammation</td>
</tr>
<tr>
<td>Infection</td>
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<tr>
<td>Cytomegalovirus</td>
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<tr>
<td>Bacterial overgrowth</td>
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<tr>
<td>Invasive bacterial infection</td>
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<tr>
<td><em>Clostridium difficile</em></td>
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<tr>
<td><em>Helicobacter pylori</em></td>
</tr>
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<td>Giardiasis</td>
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<tr>
<td>Measles</td>
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<tr>
<td><em>Strongyloides stercoralis</em></td>
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<tr>
<td>Gastric inflammation</td>
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<tr>
<td>Menetrier disease</td>
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<tr>
<td>Eosinophilic gastroenteropathy</td>
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<tr>
<td>Intestinal inflammation</td>
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<tr>
<td>Celiac disease</td>
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<tr>
<td>Crohn disease</td>
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<tr>
<td>Eosinophilic gastroenteropathy</td>
</tr>
<tr>
<td>Tropical sprue</td>
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<tr>
<td>Radiation enteritis</td>
</tr>
<tr>
<td>Primary intestinal lymphangiectasia</td>
</tr>
<tr>
<td>Secondary intestinal lymphangiectasia</td>
</tr>
<tr>
<td>Constrictive pericarditis</td>
</tr>
<tr>
<td>Congestive heart failure</td>
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<tr>
<td>Post-Fontan procedure</td>
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<td>Malrotation</td>
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<td>Noonan syndrome</td>
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<td>Sarcoidosis</td>
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<td>Radiation therapy</td>
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<td>Arsenic poisoning</td>
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<td>Colonic inflammation</td>
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<tr>
<td>Inflammatory bowel diseases</td>
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<tr>
<td>Necrotizing enterocolitis</td>
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<tr>
<td>Congenital disorders of glycosylation</td>
</tr>
<tr>
<td>Enteroctye heparin sulfate deficiency</td>
</tr>
</tbody>
</table>

with the onset of intention tremors unless vitamin E levels are maintained in the normal range. These latter symptoms reflect involvement of the posterior columns, cerebellum, and basal ganglia. In adolescence, atypical retinitis pigmentosa develops without adequate supplemental of vitamin E; for instance, using a tocopheryl polyethylene glycol succinate (TPGS) formulation of the vitamin.

Diagnosis rests on the presence of acanthocytes in the peripheral blood smear and extremely low plasma levels of cholesterol (<50 mg/dL); triglycerides are also very low (<20 mg/dL). Chylomicrons and very-low-density lipoproteins are not detectable, and the low-density lipoprotein fraction is virtually absent from the circulation. Marked triglyceride accumulation in villus enterocytes occurs in the duodenal mucosa. Steatorrhea occurs in younger patients, but other processes of nutrient assimilation are intact. Rickets may be an unusual initial
manifestation of abetalipoproteinemia and hypobetalipoproteinemia. Rickets is caused by steatorrhea-induced calcium losses and vitamin D deficiency. Patients have mutations of the microsomal triglyceride transfer protein gene, resulting in absence of microsomal triglyceride transfer protein function in the small bowel. This protein is required for normal assembly and secretion of very low density lipoproteins and chylomicrons.

Specific treatment is not available. Large supplements of the fat-soluble vitamins A, D, E, and K should be given. Vitamin E (100-200 mg/kg/24 hr) appears to arrest neurologic and retinal degeneration.

Limiting long-chain fat intake can alleviate intestinal symptoms; MCTs can be used to supplement fat intake.

HOMOZYGOUS HYPOBETALIPOPROTEINEMIA

Homozygous hypobetalipoproteinemia (see Chapter 86) is transmitted as an autosomal dominant trait. The homozygous form is indistinguishable from abetalipoproteinemia. The parents of these patients, as heterozygotes, have reduced plasma low-density lipoprotein and apoprotein-β concentrations, whereas the parents of patients with abetalipoproteinemia have normal levels. On transmission electron microscopy of small bowel biopsies, the size of lipid vacuoles in enterocytes differentiates between abetalipoproteinemia and hypobetalipoproteinemia: many small vacuoles are present in hypobetalipoproteinemia, and larger vacuoles are seen in abetalipoproteinemia.

CHYLOCERON RETENTION DISEASE (ANDERSON DISEASE)

In chylomicron retention disease, a rare recessive disorder, there is a defect in chylomicron exocytosis from enterocytes. Sarl-guanosine triphosphate promotes the formation of endoplasmic reticulum to Golgi transport carriers, and Sar1b is defective in Anderson disease. These patients have severe intestinal symptoms with steatorrhea, chronic diarrhea, and failure to thrive. Acanthocytosis is rare and neurologic manifestations are less severe than those observed in abetalipoproteinemia. Plasma cholesterol levels are moderately reduced (<75 mg/dL) and fasting triglycerides are normal, but the fat-soluble vitamins, particularly A and E, are very low. Treatment is early aggressive therapy with fat-soluble vitamins and modification of dietary fat intake, as in the treatment of abetalipoproteinemia.

WOLMAN DISEASE

Wolman disease is a rare, lethal lipid storage disease that leads to lipid accumulation in multiple organs, including the small intestine. In addition to vomiting, severe diarrhea, and hepatosplenomegaly, patients have steatorrhea as a result of lymphatic obstruction. Deficiency of lysosomal acid lipase is the underlying cause of disease (see Chapter 80). Successful long-term bone marrow engraftment results in normalization of peripheral blood leukocyte lysosomal enzyme acid lipase activity, with subsequent resolution of diarrhea and the restoration of developmental milestones.

DGAT1 MUTATION

Two siblings in one family with severe protracted diarrhea starting at 3 days of age had loss-of-function homozygous splice mutations in the diacylglycerol acyltransferase (DGAT1) gene that catalyzes the final step in the synthesis of triglycerides.

Bibliography is available at Expert Consult.

338.4 Intestinal Infections and Infestations Associated with Malabsorption

Raanan Shamir and David Branski

Malabsorption is a rare consequence of primary intestinal infection and infestation in immunocompetent children. Malabsorption is mainly seen after infection with Campylobacter, Shigella, Salmonella, Giardia, cryptosporidium, coccidiodosis, and rotavirus. These infectious causes of malabsorption are more common in immunocompromised children.

POSTINFECTIOUS DIARRHEA

In infants and very young toddlers chronic diarrhea can appear following infectious enteritis, regardless of the nature of the pathogen. The pathogenesis of the diarrhea is not always clear and may be related to secondary lactase deficiency, food protein allergy, antibiotic-associated colitis (including pseudomembranous colitis caused by Clostridium difficile toxin), or a combination of these. Treatment is supportive and may include a lactose-free diet in the presence of secondary lactase deficiency; infants might require a semi-elemental diet. The beneficial effect of specific probiotic products should await well-controlled clinical trials.

BACTERIAL OVERGROWTH

Bacteria are normally present in large numbers in the colon (10^{11}-10^{13} colony-forming units [CFU]/g of feces) and have a symbiotic relationship with the host, providing nutrients and protecting the host from pathogenic organisms. Bacteria are usually present only in a small number in the stomach and small bowel and excessive numbers of bacteria in the stomach or small bowel are harmful. Gastric acid pH prevents the ingested organisms from colonizing the small bowel. Small bowel motility and the migrating motor complex cleanse the small bowel between meals and at night; the ileocecal valve prevents colonic bacteria from refluxing into the ileum. Mucosal defenses such as mucus and immunoglobulins prevent bacterial overgrowth in the small bowel. Bacterial overgrowth can result from clinical conditions that alter the gastric pH or small bowel motility, including disorders such as partial bowel obstruction, diverticula, intestinal failure, intestinal duplications, diabetes mellitus, idiopathic intestinal pseudoobstruction syndrome, and scleroderma. Prematurity, immunodeficiency, and malnutrition are other factors associated with bacterial overgrowth of the small bowel.

Diagnosis of bacterial overgrowth can be made by culturing small bowel aspirate (>10^5 CFU/mL) or by lactulose hydrogen breath test. Lactulose is a synthetic disaccharide, which is not digested by mucosal brush border enzymes but can be fermented by bacteria. High baseline hydrogen and a quick rise in hydrogen in expired breath samples support the diagnosis of bacterial overgrowth, but false-positive tests are common.

Bacterial overgrowth leads to inefficient intraluminal processing of dietary fat and to steatorrhea due to bacterial deconjugation of bile salts, vitamin B_{12} malabsorption, and microvillus brush border damage with malabsorption. Bacterial consumption of vitamin B_{12} and enhanced synthesis of folate result in decreased vitamin B_{12} and increased folate serum levels. Overproduction of α-lactate (the isomer of L-lactate) can cause stupor, neurologic dysfunction, and shock from α-lactacidosis. Lactic acidosis should be suspected in children at risk of bacterial overgrowth, who show signs of neurologic deterioration and a high anion gap metabolic acidosis not explained by measurable acids such as L-lactate. Measurement of α-lactate is required because standard lactate assay only measures the L-isomer.

Treatment of bacterial overgrowth focuses on correction of underlying causes such as partial obstruction. The oral administration of antibiotics is the mainstay of therapy. Initial treatment with 2-4 wk of metronidazole can provide relief for many months. Cycling of antibiotics including azithromycin, trimethoprim-sulfamethoxazole, ciprofloxacin, and metronidazole may be required. Other alternatives are oral nonabsorbable antibiotics such as aminoglycosides, nitazoxanide, or rifaximin. Occasionally, antifungal therapy is required to control fungal overgrowth of the bowel.

TROPICAL SPRUE

Natives and expatriates of certain tropical regions can present with a diffuse lesion of the small intestinal mucosa—tropical sprue, even long after emigration. The endemic regions include South India, the Philippines, and some islands in the Caribbean. It is uncommon in Africa, Jamaica, and Southeast Asia. The etiology of this disorder is unclear;
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Bibliography


because it follows outbreaks of acute diarrheal disease and improves with antibiotic therapy, an infectious etiology is suspected. The incidence is decreasing worldwide, possibly due to common use of antibiotics for gastroenteritis in developing countries. Yet, in 2011, tropical sprue was still the leading cause of malabsorption in a referral center in south India. Clinical symptoms include fever and malaise followed by watery diarrhea. After about a week the acute features subside, and anorexia, intermittent diarrhea, and chronic malabsorption result in severe malnutrition characterized by glossitis, stomatitis, cheilosis, night blindness, hyperpigmentation, and edema reflecting the various nutrient deficiencies. Muscle wasting is often marked, and the abdomen is often distended. Megaloblastic anemia results from folate and vitamin B12 deficiencies.

Diagnosis is made by small bowel biopsy, which shows villous flattening, crypt hyperplasia, and a chronic inflammatory cell infiltrate of the lamina propria with adjacent lipid accumulation in the surface epithelium.

**Treatment** requires nutritional supplementation, including supplementation of folate and vitamin B12. To prevent recurrence, 6 mo of therapy with oral folic acid (5 mg) and tetracycline or sulfonamides is recommended. Relapses occur in 10-20% of patients who continue to reside in an endemic tropical region; additional courses of antibiotics may be necessary.

**WHIPPLE DISEASE**

Whipple disease is a chronic systemic infectious disorder. It is a rare disease, especially in childhood. The disease is caused by an infectious agent, Tropheryma whipplei, which can be cultured from a lymph node in the involved tissue.

The most common symptoms in Whipple disease are diarrhea, abdominal pain, weight loss, and joint pains. Malabsorption, lymphadenopathy, skin hyperpigmentation, and neurologic changes are also common. Neurologic manifestations and malabsorption are also common.

Involvement of other organs such as eyes, heart, and kidneys has been reported.

Diagnosis requires a high index of suspicion and is made upon demonstration of PAS-positive macrophage inclusions in the biopsy material, usually a duodenal biopsy. Positive identification using polymerase chain reaction for T. whipplei confirms the diagnosis. It should not be done on stool specimens, because false-positive results were reported in healthy individuals.

**Treatment** requires antibiotics such as cotrimoxazole for 1-2 yr. A 2-wk course of intravenous ceftriaxone or meropenem, followed by cotrimoxazole for 1 yr, is recommended.

*Bibliography is available at Expert Consult.*

### 338.5 Immunodeficiency Disorders

*Ernest G. Seidman and David Branski*

Malabsorption can occur with congenital immunodeficiency disorders, and chronic diarrhea with failure to thrive is often the mode of presentation. Defects of humoral and or cellular immunity may be involved, including selective IgA deficiency, agammaglobulinemia, common variable immunodeficiency disease (CVID), severe combined immunodeficiency, Wiskott-Aldrich syndrome, or chronic granulomatous disease. Although most patients with selective IgA deficiency are asymptomatic, malabsorption caused by giardiasis or nonspecific enteropathy with bacterial overgrowth can occur. Malabsorption syndrome or chronic noninfectious diarrhea has been reported in 60% of children with CVID, most often in the subgroup with low memory B cell counts. Malabsorption has also been reported in approximately 10% of patients with late-onset CVID, often secondary to giardiasis. Celiac disease is more common in patients with IgA deficiency and CVID. Paradoxically, it is more difficult to exclude the diagnosis of celiac disease because of the lack of reliability of IgA- and IgG-based serologic tests. Malabsorption as a result of chronic rotavirus, giardiasis, bacterial overgrowth, and protein-losing enteropathy are well-recognized complications of X-linked agammaglobulinemia. Malabsorption associated with immunodeficiency is exacerbated by villus atrophy and secondary disaccharidase deficiency. In chronic granulomatous disease, phagocytic function is impaired and granulomas develop throughout the GI tract, mimicking Crohn disease. In addition to failure to thrive, it is important to consider that malabsorption associated with immunodeficiency is often complicated by micronutrient deficiencies, including vitamins A, E, and B12, and calcium, zinc, and iron.

Overall, immunodeficiencies such as hypogammaglobulinemia in the pediatric age group are more often secondary to other conditions such as cancer and chemotherapy, chronic infections, malabsorption, nephrotic syndrome, or cardiac disease. Malnutrition, diarrhea, and failure to thrive are common in untreated children with HIV infection. The risk of GI infection is related to the depression of the CD4 count. Opportunistic infections include Cryptosporidium parvum, cytomegalovirus, Mycobacterium avium-intracellulare, Isospora belli, Enterocytozoon bieneusi, Candida albicans, astrovirus, calicivirus, adenovirus, and the usual bacterial enteropathogens. In these patients, Cryptosporidium can cause a chronic secretory diarrhea.

**Cancer chemotherapy** can damage the bowel mucosa, leading to secondary malabsorption of disaccharides such as lactose. After bone marrow transplantation, mucosal damage from graft-versus-host disease can cause diarrhea and malabsorption. Small bowel biopsies show nonspecific villus atrophy, mixed inflammatory cell infiltrates, and increased apoptosis. Cancer chemotherapy and bone marrow transplantation are associated with pancreatic damage leading to exocrine pancreatic insufficiency.

*Bibliography is available at Expert Consult.*

### 338.6 Immunoproliferative Small Intestinal Disease

*Ernest G. Seidman and David Branski*

Malignant lymphomas of the small intestine are categorized into 3 subtypes: Burkitt lymphoma, non-Hodgkin lymphomas, and Mediterranean lymphoma. Burkitt lymphoma, the most common form in children, characteristically involves the terminal ileum with extensive abdominal involvement. The relatively uncommon “Western” type of non-Hodgkin lymphomas (usually large B-cell type), can involve various parts of the small intestine. Mediterranean lymphoma predominantly involves the proximal small intestine. The World Health Organization recommended the term immunoproliferative small intestinal disease (IPSID) for the syndrome associated with Mediterranean lymphoma, because in its early stages it does not appear to be a truly malignant lymphoma. Many of the patients with “secretory” IPSID syndrome have variable levels of abnormal immunoglobulin in serum or other body fluids, identified as truncated α heavy chain. The World Health Organization classification lists IPSID with heavy chain diseases as a special variant of extranodal marginal zone B-cell small intestinal mucosa-associated lymphoid tissue lymphoma.

IPSID occurs most often in the proximal small intestine in older children and young adults in the Mediterranean basin, Middle East, Asia, and Africa. Poverty and frequent episodes of gastroenteritis during infancy are antecedent risk factors. The initial clinical presentation is intermittent diarrhea and abdominal pain. Later, chronic diarrhea with malabsorption (60-80%), protein-losing enteropathy, weight loss, digital clubbing, and growth failure ensue. Intestinal obstruction, abdominal masses, and ascites are common in advanced stages.

In contrast to primary nonimmunoproliferative small intestinal lymphomas, in which the pathology in the intestine is usually focal, involving specific segments of the intestine and leaving the segments between the involved areas free of disease, the pathology in IPSID is diffuse, with a mucosal cellular infiltrate involving large segments of
Bibliography
Bibliography
the intestine and sometimes the entire length of the intestine, thus producing malabsorption. Molecular and immunohistochemical studies demonstrated an association with *Campylobacter jejuni* infection. The differential diagnosis includes chronic enteric infections (parasites, tropical sprue), celiac disease, and other lymphomas. Radiologic findings include multiple filling defects, ulcers, strictures, and enlarged mesenteric lymph nodes on CT scan.

The diagnosis is usually established by endoscopic biopsies and/or laparotomy. Upper endoscopy shows thickening, erythema, and nodularity of the mucosal folds in the duodenum and proximal jejunum. As the disease progresses, tumors usually appear in the proximal small intestine and rarely in the stomach. The diagnosis requires multiple duodenal and jejunal mucosal biopsies showing dense mucosal infiltrates, consisting of centrocyte-like and plasma cells. Progression to higher-grade large-cell lymphoplasmacytic and immunoblastic lymphoma is characterized by increased plasmacytic atypia with formation of aggregates and later sheets of dystrophic plasma cells and immunoblasts invading the submucosa and muscularis propria. A serum marker of IgA, a heavy-chain paraprotein, is present in most cases.

Treatment of early-stage IPSID with antibiotics results in complete remission in 30-70% of cases. However, the majority of untreated IPSID cases progress to lymphoplasmacytic and immunoblastic lymphoma invading the intestinal wall and mesenteric lymph nodes and can metastasize to distant organs, requiring chemotherapy.

*Bibliography is available at Expert Consult.*

### 338.7 Short Bowel Syndrome

*Jon A. Vanderhoof and David Branski*

Short bowel syndrome results from congenital malformations or resection of the small bowel. Table 338-9 lists the causes of short bowel syndrome. Loss of >50% of the small bowel, with or without a portion of the large intestine, can result in symptoms of generalized malabsorption disorder or in specific nutrient deficiencies, depending on the region of the bowel resected. At birth, the length of small bowel is 200-250 cm; by adulthood, it grows to 300-800 cm. Bowel resection in an infant has a better prognosis than in an adult because of the potential for intestinal growth. An infant with as little as 15 cm of bowel with an ileocecal valve, or 20 cm without, has the potential to survive and be eventually weaned from total parenteral nutrition.

In addition to the length of the bowel, the anatomic location of the resection is also important. The jejunum has more circular folds and longer villi. The proximal 100-200 cm of jejunum is the main site for carbohydrate, protein, iron, and water-soluble vitamin absorption, whereas fat absorption occurs over a longer length of the small bowel. Depending on the region of the bowel resected, specific nutrient malabsorption can result. Vitamin B<sub>12</sub> and bile salts are only absorbed in the distal ileum (Fig. 338-7). Jejunal resections are generally tolerated better than ileal resections because the ileum can adapt to absorb nutrients and fluids. Net sodium and water absorption is relatively much higher in the ileum. Ileal resection has a profound effect on fluid and electrolyte absorption due to malabsorption of sodium and water by the remaining ileum; ileal malabsorption of bile salts stimulates increased colonic secretion of fluid and electrolytes.

### Table 338-9 Causes of Short Bowel Syndrome

<table>
<thead>
<tr>
<th>CONGENITAL</th>
<th>Causes of Short Bowel Syndrome</th>
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<tr>
<td>Congenital short bowel syndrome</td>
<td>Multiple atresias</td>
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<tr>
<td>Gastroschisis</td>
<td>Necrotizing enterocolitis</td>
</tr>
<tr>
<td>BOWEL RESECTION</td>
<td>Volvulus with or without malrotation</td>
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<td>Long segment Hirschsprung disease</td>
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<td></td>
<td>Crohn disease</td>
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<tr>
<td></td>
<td>Trauma</td>
</tr>
</tbody>
</table>

**Figure 338-7** Absorption of nutrients in the small bowel varies with the region.

| Duodenum and Proximal jejunum |
|---|---|
| • Calcium |
| • Magnesium |
| • Phosphorus |
| • Iron |
| • Folic acid |

| Colonic absorption |
|---|---|
| • Water |
| • Electrolytes |

| Distal ileum |
|---|---|
| • Vitamin B<sub>12</sub> |
| • Bile acids |

| Throughout the small intestine |
|---|---|
| • Monoglycerides and fatty acids as micellar complexes |
| • Medium chain triglycerides directly into portal circulation |

| Proximal 100-200 cm of small intestine |
|---|---|
| • Carbohydrates |
| • Protein |
| • Water-soluble vitamins |
Bibliography


TREATMENT
After bowel resection, treatment of short bowel syndrome is initially focused on repletion of the massive fluid and electrolyte losses while the bowel initially accommodates to absorb these losses. Nutritional support is often provided via parenteral nutrition. A central venous catheter should be inserted to provide parenteral fluid and nutrition support. The ostomy or stool output should be measured and fluid and electrolyte losses adequately replaced. Measurement of urinary Na+ to assess body Na+ stores is useful to prevent Na+ depletion. Maintaining urinary Na+ higher than K+ ensures that Na+ intake is adequate. Use of oral glucose electrolyte solutions improves intestinal sodium absorption, particularly in patients without a colon.

After the initial few weeks following resection, fluid and electrolyte losses stabilize, and the focus of therapy shifts to bowel rehabilitation with the gradual reintroduction of enteral feeds. Continuous small-volume trophic enteral feeding should be initiated with a low-extensively hydrolyzed protein and MCT-enriched formula or mother’s milk to stimulate gut hormones and promote mucosal growth. Enteral feeding also increases pancreaticobiliary flow and reduces parenteral nutrition-induced hepatotoxicity. As soon as possible, the infant should be given a small amount of water and then formula or mother’s milk by mouth to maintain an interest in oral feeding and minimize or avoid the development of oral aversion. As intestinal adaptation occurs, enteral feeding increases and parenteral supplementation decreases. The bowel mucosa proliferates and bowel lengths with growth.

Approximately 50% of patients with short bowel syndrome achieve enteral autonomy within 5 yr of bowel resection. Many have initial successes but then require intermittent periods of parenteral nutrition. Enteral autonomy often requires years to achieve.

Patients may require repeat surgeries for obstruction or bowel lengthening procedures (longitudinal lengthening, serial transverse enteroplasties, or both).

After achieving the maximal increase in bowel absorptive capacity, management of specific micronutrient and vitamin deficiencies and treatment of transient problems such as postinfectious mucosal malabsorption are required. GI infections such as rotavirus or small bowel bacterial overgrowth can cause setbacks in the progression to full enteral feeding in patients with marginal absorptive function. A marked increase in stool output or evidence of carbohydrate malabsorption (stool pH <5.5 and positive test for reducing substances) contraindicate further increases in enteral feeds. Slow advancement of continuous enteral feeding rates continues until all nutrients are provided enterally. Then the feeds can be altered to include increased oral or bolus feeding volumes.

In patients with large stool output, the addition of soluble fiber and antidiarrheal agents such as loperamide and anticholinergics can be beneficial, although these drugs can increase the risk of bacterial overgrowth. Cholestyramine can be beneficial for patients with distal ileal resection, but its potential depletion of the bile acid pool can increase steatorrhea. Bacterial overgrowth is common in infants with a short bowel and can delay progression of enteral feedings. Empirical treatment with metronidazole or other antibiotics (nimoxanide, rifaximine) is often useful. Diets high in fat and lower in carbohydrate may be helpful in reducing bacterial overgrowth as well as enhancing adaptation.

COMPLICATIONS
Long-term complications of short bowel syndrome include those of parenteral nutrition: central catheter infection, thrombosis, hepatic cholestasis and cirrhosis, and gallstones. Appropriate care of the central line to prevent infection and catheter-related thrombosis is extremely important. Sepsis is a leading cause of death, can occur any time after treatment is initiated (months to years later), and is most often bacterial (single organism more common than polymicrobial), although fungal infection may be noted in 20-25% of septic episodes.

Some patients need long-term parenteral nutritional support, and lack of central line access is potentially life-threatening; inappropriate removal or changes of central lines in the neonatal period should be avoided. Other complications of terminal ileal resection include vitamin B₁₂ deficiency, which might not appear until 1-2 yr after parenteral nutrition is withdrawn. Long-term monitoring for deficiencies of vitamin B₁₂, folate, iron, fat-soluble vitamins, and trace minerals such as zinc and copper is important. Renal stones can occur as a result of hyperoxaluria secondary to steatorrhea (calcium binds to the excess fat and not to oxalate, so more oxalate is reabsorbed and excreted in the urine). Venous thrombosis and vitamin deficiency have been associated with hyperhomocystinemia in short bowel syndrome. Bloody diarrhea secondary to patchy, mild colitis can develop during the progression of enteral feedings. The pathogenesis of this “feeding colitis” is unknown, but it is usually benign and can improve with a hypoallergenic diet or treatment with mesalamine.

In patients who are unable to achieve full enteral feeding after several years of nutritional rehabilitation, surgical bowel lengthening procedures may be considered. In some children with complications of parenteral nutrition, especially impending liver failure, small intestinal and liver transplantation may be considered (see Chapter 331).

Bibliography is available at Expert Consult.

338.8 Chronic Malnutrition
Raanan Shamir and David Branski

Primary malnutrition (i.e., undernutrition) is very common in developing countries and is directly related to increased disease burden and mortality (see Chapter 46). In developed countries, chronic malnutrition occurs mainly as a result of decreased food intake, malabsorption syndromes, and increased nutritional needs in children with chronic diseases. Malnutrition is diagnosed in 11-50% of hospitalized children and recent reports from Europe suggest a prevalence of close to 20% in chronically ill children. Child neglect and improper preparation of formula can result in severe malnutrition. Malnutrition can be identified by evaluating dietary intake, by medical history (anorexia, vomiting, dysphagia, mood and behavioral changes, abdominal pain, diarrhea), by anthropometric measurements (e.g., reduced weight per age and weight per height, body mass index <5th percentile), and by clinical signs of nutrient deficiencies (atrophic tongue in iron-deficiency anemia or alopecia in zinc deficiency). Screening tools for malnutrition are used in adults to provide a simple and fast way of diagnosing those patients in need. Few such screening tools for the pediatric population were developed and are being studied.

Malnourished children suffer from impaired immunity, poor wound healing, muscle weakness, and diminished psychologic drive. Malnutrition has short-term consequences (increased disability, morbidity, and mortality) and long-term consequences (final adult size, lower IQ, economic productivity). Undernutrition in hospitalized children is related to increased infectious complications, delayed recovery, increased length of stay and costs, increased readmission rate, and increased mortality.

Nutritional rehabilitation in malnourished children is discussed in Chapter 46.

Chronic malnutrition complicated by diarrheal dehydration is a commonly observed phenomenon. Infectious diarrhea is common in tropical and subtropical countries, in the setting of poor hygiene practices, in immunocompromised hosts (e.g., HIV, congenital immunodeficiency), and when impairment of the immune response is due to chronic malnutrition itself. In children with chronic disorders, diarrhea may be related to the underlying disease that should be sought for. Examples include noncompliance with a gluten-free diet in celiac disease, noncompliance with pancreatic enzyme treatment in cystic fibrosis, and disease relapse in inflammatory bowel disease (IBD). In the case of IBD, relapse should be diagnosed only after infectious diarrhea and C. difficile infection have been ruled out. Malnutrition per se can lead to exocrine pancreatic insufficiency, which, in turn, aggravates malabsorption and diarrhea.

In infants and children with severe malnutrition, many of the signs normally used to assess the state of hydration or shock are unreliable.
Bibliography
Severe malnutrition might be accompanied by sepsis; thus, children with septic shock might not have diarrhea, thirst, or sunken eyes but may be hypothermic, hypoglycemic, or febrile. The electrocardiogram often shows tachycardia, low amplitude, and flat or inverted T waves. Cardiac reserve seems lowered, and heart failure is a common complication.

Despite clinical signs of dehydration, urinary osmolality may be low in the chronically malnourished child. Renal acidifying ability is also limited in patients with malnutrition.

Management of the diarrhea in chronically malnourished children is based on 3 principles: oral rehydration to correct dehydration, rapid resumption of feeds with avoidance of periods of nothing by mouth, and treating the etiology of the diarrhea.

When treating the dehydration, it must be remembered that in dehydrated and malnourished infants there appears to be overexpansion of the extracellular space accompanied by extracellular and presumably intracellular hypoosmolality. Thus, reduced or hypotonic osmolarity oral rehydration solutions are indicated in this setting. When oral rehydration is not possible, the route of choice is nasogastric, and intravenous therapy should be avoided if possible.

Initial intravenous therapy in profound dehydration is designed to improve the circulation and expand extracellular volume. For patients with edema, the quality of fluid and the rate of administration might need to be readjusted from recommended levels to avoid overhydration and pulmonary edema. Blood should be given if the patient is in shock and is severely anemic. Potassium salts can be given early if urine output is good. Clinical and electrocardiogram improvement may be more rapid with magnesium therapy.

Children with chronic malnutrition are at risk for the refeeding syndrome. Therefore, initial calorie provision should not exceed the previous daily intake and is usually begun at 50-75% of estimated resting energy expenditure, with rapid increase to caloric goals once there are no severe abnormalities in sodium, potassium, phosphorus, calcium, or magnesium. Correction of malnutrition and catch-up growth are not part of the primary treatment of these children, but a nutrition rehabilitation plan is necessary.

Bibliography is available at Expert Consult.

338.9 Enzyme Deficiencies
Michael J. Lentze and David Branski

CARBOHYDRATE MALABSORPTION
Symptoms of carbohydrate malabsorption include loose watery diarrhea, flatulence, abdominal distention, and pain. Some children are asymptomatic unless the malabsorbed carbohydrate is consumed in large amounts. Disaccharidases are present on the brush border membrane of the small bowel. Disaccharidase deficiency can be caused by a genetic defect or secondarily by damage to the small bowel epithelium, as occurs with infection or inflammatory disorders.

Unabsorbed carbohydrates enter the large bowel and are fermented by intestinal bacteria, producing organic acids and gases such as methane and hydrogen. The gases can cause discomfort and the unabsorbed carbohydrate and the organic acids cause osmotic diarrhea characterized by an acidic pH and presence of either reducing or non-reducing sugars in the stool. Hydrogen gas can be detected in the breath as a sign of fermentation of unabsorbed carbohydrates (H₂-breath test).

LACTASE DEFICIENCY
Congenital lactase deficiency is rare and is associated with symptoms occurring on exposure to lactose in milk. Fewer than 50 cases have been reported worldwide. In patients with congenital lactase deficiency, 5 distinct mutations in the coding region of the LCT gene were found. In most patients (84%), homozygosity for a nonsense mutation, 4170T-A (Y1390X; OMIM 223000), designated Fin (major), was found.

Primary adult type-hypolactasia is caused by a physiologic decline in lactase activity that occurs following weaning in most mammals. The brush-border lactase is expressed at low levels during fetal life; activity increases in late fetal life and peaks from term to 3 yr, after which levels gradually decrease with age. This decline in lactase levels varies between ethnic groups. Lactase deficiency occurs in approximately 15% of white adults, 40% of Asian adults, and 85% of black adults in the United States. Lactase is encoded by a single gene (LCT) of approximately 50 kb located on chromosome 2q21. C/T (−13910) polymorphisms of the MCM6 gene were found to be related to adult-type hypolactasia in most European populations. In 3 African populations—Tanzanians, Kenyans, and Sudanese—3 single-nucleotide polymorphisms, G/C (−14010), T/G (−13915), and C/G (−13907), were identified with lactase persistence and have derived alleles that significantly enhance transcription from the lactase gene promoter in vitro.

Secondary lactose intolerance follows small bowel mucosal damage (celiac disease, rotavirus infection) and is usually transient, improving with mucosal healing.

Lactase deficiency can be diagnosed by H₂-breath test or by measurement of lactase activity in mucosal tissue retrieved by small bowel biopsy. Diagnostic testing is not mandatory, and often simple dietary changes that reduce or eliminate lactose from the diet relieve symptoms.

Treatment of lactase deficiency consists of a milk-free diet. A lactose-free formula (based on either soy or cow's milk) can be used in infants. In older children, low-lactose milk can be consumed. Addition of lactase to dairy products usually abbreviates the symptoms.

Live-culture yogurt contains bacteria that produce lactase enzymes and is therefore tolerated in most patients with lactase deficiency. Hard cheeses have a small amount of lactose and are generally well tolerated.

FRUCTOSE MALABSORPTION
Children consuming a large quantity of juice rich in fructose, corn syrup, or natural fructose in fruit juices can present with diarrhea, abdominal distention, and slow weight gain. Restricting the amount of juice in the diet resolves the symptoms and helps avoid unnecessary investigations. Fructose H₂ breath test can be helpful in the diagnosis of fructose malabsorption. The reason for fructose malabsorption is the reduced abundance of GLUT-5 transporter on the surface of the intestinal brush-border membrane, which occurs in approximately 5% of the population.

SUCRASE-ISOMALTASE DEFICIENCY
Sucrase-isomaltase deficiency is a rare autosomal recessive disorder with a complete absence of sucrase and reduced maltase digestive activity. The sucrase-isomaltase complex is composed of 1,927 amino acids encoded by a 3,364 bp messenger RNA. The gene locus on chromosome 3 has 30 exons spanning 106.6 kb. The majority of sucrase-isomaltase mutations result in a lack of enzyme protein synthesis (null mutation). Posttranslational processing defects are also identified.

Approximately 2% of Europeans and Americans are mutant heterozygote. Sucrase deficiency is especially common in indigenous Greenlanders (estimated 5%) in whom it is often accompanied by lactase deficiency.

Symptoms of sucrase-isomaltase deficiency usually begin when the infant is exposed to sucrose or a glucose polymer diet. This can occur with ingestion of non–lactose-based infant formula or on the introduction of pureed food, especially fruits and sweets. Diarrhea, abdominal pain, and poor growth are observed. Occasional patients present with symptoms in late childhood or even adult life, but careful history often indicates that symptoms appeared earlier. Diagnosis of sucrase-isomaltase malabsorption requires acid hydrolysis of stool for reducing substances because sucrose is a nonreducing sugar. Alternatively, diagnosis can be achieved with hydrogen breath test or direct enzyme assay of small bowel biopsy.

The mainstay of treatment is lifelong dietary restriction of sucrose-containing foods. Enzyme replacement with a purified yeast
**Bibliography**


GLUCOSE–GALACTOSE MALABSORPTION

More than 30 different mutations of the sodium/glucose cotransporter gene (SGLT1) are identified. These mutations cause a rare autosomal recessive disorder of intestinal glucose and galactose/Na⁺ cotransport system that leads to osmotic diarrhea. Because most dietary sugars are poly saccharides or disaccharides with glucose or galactose moieties, diarrhea follows the ingestion of glucose, breast milk, or conventional lactose-containing formulas. Dehydration and acidosis can be severe, resulting in death.

The stools are acidic and contain sugar. Patients with the defect have normal absorption of fructose, and their small bowel function and structure are normal in all other aspects. Intermittent or permanent glycosuria after fasting or after a glucose load is a common finding because of the transport defect also being present in the kidney. The presence of reducing substances in watery stools and slight glycosuria despite low blood sugar levels is highly suggestive of glucose–galactose malabsorption. Malabsorption of glucose and galactose is easily identified using the breath hydrogen test. It is safe to perform the first test with a dose of 0.5 g/kg of glucose; if necessary, a second test can be performed using 2 g/kg. Breath H₂ will rise more than 20 ppm. The small intestinal biopsy is useful to document a normal villous architecture and normal disaccharidase activities. The identification of mutations of SGLT1 makes it possible to perform prenatal screening in families at risk for the disease.

Treatment consists of rigorous restriction of glucose and galactose. Fructose, the only carbohydrate that can be given safely, should be added to a carbohydrate-free formula at a concentration of 6–8%. Diarrhea immediately ceases when infants are given such a formula. Although the defect is permanent, later in life, limited amounts of glucose, such as starches or sucrose may be tolerated.

EXOCRINE PANCREATIC INSUFFICIENCY

Chapter 349 discusses disorders of exocrine pancreatic insufficiency. Cystic fibrosis is the most common congenital disorder associated with exocrine pancreatic insufficiency. Although rare, the next most common cause of pancreatic insufficiency in children is Shwachman-Diamond syndrome. Other rare disorders causing exocrine pancreatic insufficiency are Johanson-Blizzard syndrome (severe steatorrhea, aplasia of alae nasi, deafness, hypothyroidism, scalp defects), Pearson bone marrow syndrome (sideroblastic anemia, variable degree of neutropenia, thrombocytopenia), and isolated pancreatic enzyme deficiency (lipase, colipase and lipase–colipase, trypsinogen, amylase). Deficiency of enteropeptidase—a key enzyme that is produced in the small bowel and is responsible for the activation of tryps inogen to trypsin—manifests clinically as exocrine pancreatic insufficiency.

Autoimmune polyendocrinopathy syndrome type 1, a rare autosomal recessive disorder, is caused by mutation in the autoimmune regulator gene (AIRE). Chronic mucocutaneous candidiasis is associated with failure of parathyroid gland, adrenal cortex, pancreatic B cells, gonads, gastric parietal cells, and thyroid gland. Pancreatic insufficiency and steatorrhea are associated with this condition.

ENTEROKINASE (ENTEROPEPTIDASE) DEFICIENCY

Enterokinase (enteropeptidase) is a brush-border enzyme of the small intestine. It is responsible for the activation of tryps inogen into trypsin. Deficiency of this enzyme results in severe diarrhea, malabsorption, failure to thrive, and hypoproteinemid edema after birth.

Enterokinase deficiency is caused by mutation in the serine protease-7 gene (PRSS7) on chromosome 21q21. The diagnosis can be established by measuring the enzyme level in intestinal tissue. Treatment of this rare autosomal recessive disorder consists of replacement with pancreatic enzymes and administration of a protein hydrolysate formula with added MCT oil in infancy.

TRypsINOFEn DEFICIENCY

Trypsinogen deficiency is a rare syndrome with symptomatology similar to that of enterokinase deficiency. Enterokinase catalyzes the conversion of tryps inogen to trypsin, which, in turn, activates the various pancreatic proenzymes such as chymotrypsin, procarboxypeptidase, and proelastase for their active forms. Deficiency of tryps inogen results in severe diarrhea, malabsorption, failure to thrive, and hypo proteinemic edema soon after birth.

The tryps inogen gene is encoded on chromosome 7q35. Treatment is the same as for enterokinase deficiency, with pancreatic enzymes and protein hydrolysate formula with added MCT oil in infancy.

338.10 Liver and Biliary Disorders Causing Malabsorption

Anil Dhawan and David Branski

Absorption of fats and fat-soluble vitamins depends to a great extent on adequate bile flow providing bile acids to the small intestine. Most of the liver and biliary disorders lead to impairment of the bile flow, contributing to malabsorption of long-chain fatty acids and vitamins such as A, D, E, and K. Liver disorders that are associated with significant malabsorption and failure to thrive are: (1) progressive familial intrahepatic cholestasis (types 1, 2, and 3) and bile acid synthesis defects. Progressive familial intrahepatic cholestasis type 1 is also associated with chronic diarrhea caused by bile transport defect in the gut. It is not uncommon for these children to have symptomatic fat-soluble vitamin deficiencies like pathologic fractures and peripheral neuropathy. (2) Children with storage disorders such as Wolman disease also manifest with severe failure to thrive and multiple vitamin deficiencies. (3) Children with biliary disorders such as biliary atresia after a Kasai portoenterostomy, cystic fibrosis, neonatal sclerosing cholangitis, Alagille syndrome, and sclerosing cholangitis constitute another major group of disorders where malabsorption could be a significant problem. In addition, severe portal hypertension can lead to portal hypertensive enteropathy, resulting in poor absorption of the nutrients. Decompensated liver disease leads to anorexia and increased energy expenditures, further widening the gap between calorie intake and net absorption, leading to severe malnutrition. Adequate management of nutrition is essential to improve the outcome with or without liver transplantation. This is usually achieved by using MCT-rich milk formula, supplemental vitamins, and continuous or bolus enteral feed where oral intake is poor.

Vitamin D deficiency is commonly observed on biochemical tests, and children rarely present with pathologic fractures. Simultaneous administration of vitamin D with the water-soluble vitamin E preparation (TPGS, 1,000 succinate) enhances absorption of vitamin D. In young infants, oral vitamin D₃ is given at a dose of 1,000 IU/kg/24 hr. After 1 mo, if the serum 25-hydroxyvitamin D level is low, the same dose of oral vitamin D is mixed with TPGS. 25-Hydroxyvitamin D is then monitored every 3 mo, with adjustment of doses as necessary.

Vitamin E deficiency in patients with chronic cholestasis is not usually symptomatic, but it can manifest as a progressive neurologic syndrome, which includes peripheral neuropathy (manifesting as loss of deep tendon reflexes and ophthalmoplegia), cerebellar ataxia, and posterior column dysfunction. Early in the course, findings are partially reversible with treatment; late features might not be reversible. It may be difficult to identify vitamin E deficiency because the elevated blood lipid levels in cholestatic liver disease can falsely elevate the serum vitamin E level. Therefore, it is important to measure the ratio of serum vitamin E to total serum lipids; the normal level for patients younger than 12 yr of age is >0.6, and for patients older than 12 yr it is >0.8. The neurologic disease can be prevented with the use of an oral water-soluble vitamin E preparation (TPGS, Liqui-E) at a dose of 25–50 IU/day in neonates and 1 IU/kg/day in children.

Vitamin K deficiency can occur as a result of cholestasis and poor fat absorption. In children with liver disease it is very important to
differentiate between the coagulopathy related to vitamin K malabsorption and one secondary to the synthetic failure of the liver. A single dose of vitamin K administered intravenously does not correct the prolonged prothrombin time in liver failure, but the deficiency state responds within a few hours. Easy bruising may be the first sign. In neonatal cholestasis, coagulopathy as a result of vitamin K deficiency can manifest with intracranial bleeds with devastating consequences, and prothrombin time should be routinely measured to monitor for deficiency in children with cholestasis. All children with cholestasis should receive vitamin K supplements.

Vitamin A deficiency is rare and is associated with night blindness, xerophthalmia, and increased mortality if patients contract measles. Serum vitamin A levels should be monitored and adequate supplementation considered.

338.11 Rare Inborn Defects Causing Malabsorption
Klaus-Peter Zimmer and David Branski

Some congenital (primary) malabsorption disorders originate from a defect of integral membrane proteins, which fulfill a transport function as receptor or channel across the apical or basolateral membrane of enterocytes for nutritional components. Histologic examination of the small and large bowel is typically normal. Most of these disorders are inherited in an autosomal recessive pattern. Most are rare, and patients present with a broad phenotypic heterogeneity as a result of modifier genes and nutritional and other secondary factors.

DISORDERS OF CARBOHYDRATE ABSORPTION

Patients with Fanconi–Bickel syndrome present with tubular nephropathy; rickets; hepatomegaly; glycogen accumulation in liver, kidney, and small bowel; failure to thrive; and fasting hypoglycemia. The disorder is caused by homozygous mutations of GLUT2, the facilitative glucose (and galactose) transporter at the basolateral membrane of enterocytes hepatocytes, renal tubules, pancreatic islet cells, and cerebral neurons. Because severe osmotic diarrhea is not a feature of Fanconi–Bickel syndrome, a GLUT2-independent basolateral transport for glucose is suggested. GLUT2 seems to modulate insulin secretion, renal reabsorption, and glucose uptake from the apical membrane of enterocytes in response to the (postprandial) sugar environment. Diagnostic signs are elevated galactose levels in the blood (found in the neonatal screening program), neonatal bilateral cataracts, marked glycosuria, generalized aminoaciduria, and excessive renal losses of phosphate and calcium. Liver and kidneys are enlarged. Therapy includes substitution of electrolyte losses and vitamin D and supplying uncooked cornstarch to prevent hypoglycemia. Patients who present in the neonatal period need frequent small meals and galactose-free milk.

DISORDERS OF AMINO ACID AND PEPTIDE ABSORPTION

Owing to their ontogenic origins, enterocytes and renal tubules express amino acid transporter in common. Their highest intestinal transmembrane transport defect of cationic amino acids (lysine, arginine, ornithine, and proline, hydroxyproline, and glycine as a consequence of the proton gradient). This carrier is present in the small intestine, kidney, and brain, and transports the anionic acids glutamate, aspartate, and cysteine. There are single case reports indicating that this disorder could be associated with hyperprolinemia and neurologic symptoms such as POLIP (polyneuropathy, ophthalmoplegia, leukoencephalopathy, intestinal pseudoobstruction syndrome).

A histidine-specific transport system has also been proposed. A few patients have been reported with an intestinal and renal defect of this carrier. It has not been confirmed that patients with histidinuria, who have low plasma histidine levels, in contrast to histidinemia, develop neurologic symptoms (e.g., hearing loss, myoclonic seizures).

A methionine-prefering transporter in the small intestine was suggested to be affected in Smith–Strang disease (oatshole urine disease), which is characterized by purple, red-brown-colored urine with a cabbage-like odor, containing 2-hydroxybutyric acid, valine, and leucine. The potential symptoms of methionine malabsorption include neurologic signs, white hair, and diarrhea. Large amounts of methionine and branched-chain amino acids are present in the feces but not in the urine. A low-methionine diet is recommended to alleviate the symptoms.

Among the diseases (see the earlier discussion of cystinuria) with a membrane transport defect of cationic amino acids (lysine, arginine, ornithine), LPI is the second most common, with a prevalence in Finland of 1 in 60,000. The γ-LAT-1 (SLC7A7) carrier at the basolateral membrane of the intestinal and renal epithelium is affected, with failure to deliver cytosolic dibasic cationic amino acids into the paracellular space in exchange for Na+ and neutral amino. This defect is not compensated by the SLC3A1/SLC7A9 transporter (at the apical membrane), the latter being affected in cystinuria. The symptoms of
LPI, which appear after weaning, include diarrhea, failure to thrive, hepatosplenomegaly, nephritis, respiratory insufficiency, alveolar proteinosis, pulmonary fibrosis, and osteoporosis. Abnormalities of bone marrow have also been described in a subgroup of LPI patients. The disorder is characterized by low plasma concentrations of dibasic amino acids (in contrast to high levels of citrulline, glutamine, and alanine) and massive excretion of lysine (as well as orotic acid, ornithine, and arginine in moderate excess) in the urine. Hyperammonemia and coma usually develop after episodic attacks of vomiting, after fasting, or following administration of large amounts of protein (or alanine load), possibly because of a deficiency of intramitochondrial ornithine. Some patients show moderate retardation. Cutaneous manifestations can include alopecia, perianal dermatitis, and sparse hair. Some patients avoid protein-containing food. Treatment includes orally administered citrulline (200 mg/kg/day), which is well absorbed from the intestine; dietary protein restriction (<1.5 g/kg/day); and carnitine supplementation. One patient with isolated lysinuria has been reported with growth failure, seizures, and mental retardation.

**DISORDERS OF FAT TRANSPORT**
Chapter 86 describes abetalipoproteinemia, hypobetalipoproteinemia, and chylomicron retention disease. The long-chain fatty acid (FATP4) and cholesterol transporters, the latter being called Niemann-Pick Cl-like protein (NPC1L1), have been characterized at the intestinal brush-border in knockout mice models showing a hyperproliferative hyperkeratosis and an impaired fatty acid and cholesterol uptake. NPC1L1 is inhibited by ezetimibe, which is used to restrict the absorption of dietary cholesterol.

**Tangier disease** is characterized by the absence of high-density lipoprotein cholesterol, which is caused by mutations in the adenosine triphosphate–binding cassette transporter A1 (ABCA1) gene. The failure of intracellular phospholipids and cholesterol efflux to lipid-poor apolipoprotein acceptors such as high-density lipoprotein predisposes to premature coronary heart disease and accumulation of cholesterol in liver, spleen, lymph nodes (tonsils), and small intestine.

Features of Tangier disease include orange tonsils, hepatosplenomegaly, relapsing neuropathy, orange-brown spots on the colon and ileum, diarrhea in association with decreased plasma cholesterol levels (apolipoprotein A-1 and A-II), and normal or elevated triglyceride levels. Specific therapy for Tangier disease has not yet been established.

**Sitosterolemia**, defective efflux of sterol leads to increased absorption of dietary sterols; normally, <5% are retained by the GI tract. Patients carry mutations of the ABCG5 (sterolin-1) and ABCG8 (sterolin-2) transporters. The disorder is associated with tendon xanthomas, increased atherosclerosis, and hemolysis. Plasma levels of phytosterols (mainly sitosterol) are typically >10 mg/dL.

Congenital diarrhea in newborns with hyperlipidemia may indicate impaired fat (bile) absorption and mutations of the microsomal enzyme acyl-coenzyme A:diacylglycerol acyltransferase 1 (DGAT1), which catalyzes the final step in triglyceride synthesis.

**DISORDERS OF VITAMIN ABSORPTION**
Transporters and receptors of the intestinal epithelium have been described for water-soluble but not fat-soluble vitamins, the latter being absorbed primarily by enterocytes, by passive diffusion after emulsification of fats by bile salts. Transport proteins (retinol-binding protein, RBP4, and α-tocopherol transfer protein, TTP1) have been involved in deficiency states of vitamins E (spinocerebellar ataxia) and A (ophthalmologic signs), respectively.

Vitamin B<sub>12</sub> (cobalamin) is used exclusively by microorganisms and is acquired mostly from meat and milk. Its absorption starts with the removal of cobalamin from dietary protein by gastric acidity and its binding to haptocorrin. In the duodenum, pancreatic proteases hydrolyze the cobalamin-haptocorrin complex, allowing the binding of cobalamin to intrinsic factor (IF), which originates from parietal cells. The receptor of the cobalamin-IF complex is located at the apical membrane of the ileal enterocytes and represents a heterodimer consisting of cubilin and amnionless, with endocytic uptake of this ligand into endosomes, where it binds to megalin and forms a cobalamin–transcobalamin-2 complex (after cleavage of IF) for further transcytosis. As a cofactor for methionine synthase, cobalamin converts homocysteine to methionine. Cobalamin deficiency can be caused by inadequate intake of the vitamin (e.g., breastfeeding by mothers on a vegetarian diet), primary or secondary achlorhydria including autoimmune gastritis, exocrine pancreatic insufficiency, bacterial overgrowth (see Chapter 338.4), ileal disease (Crohn disease, see Chapter 336), ileal (or gastric) resection, infections (fish tapeworm), and Whipple disease (see Chapter 341).

Clinical signs of congenital cobalamin malabsorption, which usually appear from a few mo to 14 yr of age, are pancytopenia including megaloblastic anemia, fatigue, failure to thrive, and neurologic symptoms, including developmental delay. Recurrent infections and bruising may be present. Laboratory evaluation indicates low serum cobalamin, hyperhomocysteinemia, methylmalonic acidemia, and mild proteinuria. The Schilling test is useful to differentiate between lack of IF and malabsorption of cobalamin. Three rare autosomal recessive disorders of congenital cobalamin deficiency affect absorption and transport of cobalamin (in addition to 7 other inherited defects of cobalamin metabolism). These include mutations of the gastric IF (GIF) gene with absence of IF (but normal acid secretion and lack of autoantibodies against IF or parietal cells), mutations of the amnionless (AMN) and cobalmin (CUBN) genes (Imerslund-Grasbeck syndrome), and mutations in the transcobalamin 2 cDNA. These disorders require long-term parenteral cobalamin treatment: intramuscular injections of hydroxycobalamin 1 mg daily for 10 days and then once a month. High-dose substitution with oral cyanocobalamin (1 mg b.i.w.) does not seem to be sufficient for all patients with congenital cobalamin deficiency.

**Folate** is an essential vitamin required to synthesize methionine from homocysteine. It is found mainly in green leafy vegetables, legumes, and oranges. It is converted to 5- methyltetrahydrofolate after its uptake by enterocytes. Secondary folate deficiency is caused by insufficient folate intake, villous atrophy (e.g., celiac disease, IBD), treatment with phenytoin, and trimethoprim, among others (see Chapter 448.1). Several inherited disorders of folate metabolism and transport have been described.

Hereditary folate malabsorption is characterized by a defect of the proton-coupled folate transporter (formerly reported to be HCP1, a heme carrier) of the brush-border, leading to impaired absorption of folate in the upper small intestine as well as impaired transport of folate into the central nervous system. Mutations of the reduced folate carrier (RFC1, SLC19A1) have not been found in this entity. Sulfasalazine and metotrexate are potent inhibitors of proton-coupled folate transporter. Symptoms of congenital folate malabsorption are diarrhea, failure to thrive, megaloblastic anemia (in the 1st few mo of life), glossitis, infections (Pneumocystis jiroveci) with hypoinmunoglobulinemia, and neurologic abnormalities (seizures, mental retardation, and basal ganglia calcifications). Macrocytosis, with or without neutropenia, multilobulated polymorphonuclear cells, increased lactate dehydrogenase and bilirubin, increased saturation of transferrin, and decreased cholesterol can be found. Low levels of folate are present in serum and cerebrospinal fluid. Plasma homocysteine concentrations as well as urine excretion of formiminoglutamic acid and orotic acid are elevated. Long-lasting deficiency is best documented using red cell folate. Therapy involves large doses of oral (up to 100 mg/day) or systemic (intrathecal) folate.

The molecular basis of intestinal transport of other water-soluble vitamins such as vitamin C (Na<sup>+</sup>-dependent vitamin C transporters 1 and 2), pyridoxine/vitamin B<sub>6</sub>, and biotin/vitamin B<sub>12</sub> (Na<sup>+</sup>-dependent multivitamin transporter) have been described; however congenital defects of these transporter systems have not yet been found in humans. A thiamine/vitamin B<sub>1</sub>-responsive megaloblastic anemia syndrome, which is associated with early-onset type 1 diabetes mellitus and sensorineural deafness, is caused by mutations of the thiamine transporter protein, THTR-1 (SLC19A2), present in the brush-border.
DISORDERS OF ELECTROLYTE AND MINERAL ABSORPTION

Congenital chloride diarrhea belongs to the more common causes of severe congenital diarrhea, with prevalence in Finland of 1:20,000. It is caused by a defect of the SLC26A3 gene, which encodes a Na+-independent Cl-/HCO3- exchanger within the apical membrane of ileal and colonic epithelium. Founder mutations have been described in Finnish, Polish, and Arab patients: V317del, 1675-676ins, and G187X, respectively. The Cl-/HCO3- exchanger absorbs chloride originating from gastric acid and the cystic fibrosis transmembrane conductance regulator and secretes bicarbonate into the lumen, neutralizing the acidity of gastric secretion.

Prenatal clinical signs of this disorder are a dilated small bowel that can mislead to a diagnosis of intestinal obstruction. Newborns with congenital chloride diarrhea present with severe life-threatening secretory diarrhea during the 1st few wk of life. Laboratory findings are metabolic alkalosis, hypocloremia, hypokalemia, and hyponatremia (with high plasma renin and aldosterone activities). Fecal chloride concentrations are >90 mmol/L and exceed the sum of fecal sodium and potassium. Early diagnosis and aggressive lifelong enteral substitution of KCl in combination with NaCl (chloride doses of 6-8 mmol/kg/day for infants and 3-4 mmol/kg/day for older patients) prevent mortality and long-term complications (such as urinary infections, hyperuricemia with renal calcifications, renal insufficiency, and hypertension) and allow normal growth and development. Orally administered proton pump inhibitors, cholestyramine, and butyrate can reduce the severity of diarrhea. The diarrheal symptoms usually tend to regress with age. However, febrile diseases are likely to exacerbate symptoms as a consequence of severe dehydration and electrolyte imbalances. (See Chapter 52 for fluid and electrolyte management.)

The classic form of congenital sodium diarrhea manifests with polyhydramnios, massive secretory diarrhea, severe metabolic acidosis, alkaline stools (fecal pH >7.5) and hyponatremia as a result of fecal losses of Na+ (fecal Na+ >70 mmol/L). Urinary secretion of sodium is low to normal. There is partial villous atrophy. The molecular genetic defect could not be located in the Na+-H+ exchangers, which were thought to be impaired because they seem to be mainly responsible for Na+ absorption in the small intestine. In addition, a syndromic form of congenital sodium diarrhea with chonal or anal atresia, hypertelorism, and conneal erosions has been related to mutations of SPINT2, encoding a serine–protease inhibitor, whose pathophysiologic action on intestinal Na+ absorption is unclear. Some patients can be weaned from parenteral nutrition later in childhood but depend on oral sodium citrate supplementation.

The congenital form of acrodermatitis enteropathica manifests with severe deficiency of body zinc soon after birth in bottle-fed children or after weaning from breastfeeding. Clinical signs of this disorder are anorexia, diarrhea, failure to thrive, hemolysis and cell-mediated immunodeficiency (poor wound healing, recurrent infections), male hypogonadism, skin lesions (vesiculobullous dermatitis on the extremities and perirectal, perigenital, and perioral regions, and alopecia), and neurologic abnormalities (tremor, apathy, depression, irritability, nystagmus, photophobia, night blindness, and hypogeusia). The genetic defect of acrodermatitis enteropathica is caused by a mutation in the Zrt-Irt-like protein 4 (ZIP4, SLC39A4), normally expressed on the apical membrane, which enables the uptake of zinc into the cytosol of enterocytes. The zinc-dependent alkaline phosphatase and plasma zinc concentrations are low in contrast to an increase in mucosal cells, including enterocytes and fibroblasts. Plasma copper and ceruloplasmin levels decline postnatally. Clinical features of Menkes disease are progressive cerebral degeneration (convulsions), feeding difficulties, failure to thrive, hypothermia, apnea, infections (urinary tract), peculiar facies, hair abnormalities ( kinky hair), hypopigmentation, bone changes, and cutis laxa. Patients with the classic form of Menkes disease usually die before the age of 3 yr. A therapeutic trial with copper-histidinase should start before the age of 6 wk. In contrast to Menkes disease, occipital horn syndrome usually manifests during adolescence with borderline intelligence, craniofacial abnormalities, skeletal dysplasia (short clavicles, pectus excavatum, genu valgum), connective tissue abnormalities, chronic diarrhea, orthostatic hypotension, obstructive uropathy, and osteoporosis. It should be differentiated from Ehlers-Danlos syndrome type V.

Active calcium absorption is mediated by the transient receptor potential channel 6 (TRPV6) at the brush border membrane, calbindin, and the CaATPase, or the Na+-Ca2+ exchanger for calcium efflux at the basolateral membrane within the proximal small bowel. A congenital defect of these transporters has not yet been described.

Intestinal absorption of dietary magnesium, which occurs via the transient receptor potential channel TRPM6 at the apical membrane, is impaired in familial hypomagnesemia with secondary hypocalcemia, which manifests with neonatal seizures and tetany.

Intestinal iron absorption consists of several complex regulated processes starting with the uptake of heme-containing iron by heme carrier protein 1 (HCP1) and Fe2+ (after luminal reduction of oxidized Fe3+) by the divalent metal transporter 1 (DMT1) at the apical membrane, followed by the efflux of Fe3+ by ferroportin 1 (also called iron-regulated transporter) at the basolateral membrane of duodenal enterocytes. Mutations of the ferroportin 1 gene have been found in the autosomal dominant form of hemochromatosis type 4. Mutations of HFE (Cys282 Tyr, His63 Asn, Ser65Cys) of classic hemochromatosis reduce the endocytic uptake of diferric transferrin by the transferrin receptor-1 at the basolateral membrane of the intestinal epithelium. Hepcidin antimicrobial peptide encodes hepcidin, a hepatic peptide hormone, which inhibits the efflux of iron through ferroportin and can be induced by IL-6. It is the defective gene of juvenile hemochromatosis (type 2, subtype B).

Bibliography is available at Expert Consult.

338.12 Malabsorption in Eosinophilic Gastroenteritis

Ernest G. Seidman and David Branski

Eosinophilic digestive diseases are a group of rare and heterogeneous conditions characterized by patchy or diffuse eosinophilic infiltration of GI tissue. The diagnosis of eosinophilic gastroenteritis is based on GI symptoms, GI eosinophilic infiltrates, and the absence of other causes such as parasitic infection (most commonly Enterobius vermicularis in children) or a specific allergic response. Peripheral eosinophilia and elevated serum IgE levels are variably present are not diagnostic criteria. The majority (50-70%) of patients have a history of other allergic disorders, and others might have associated connective tissue diseases. Approximately 10% of patients with this disorder have an immediate family member affected, suggesting that eosinophilic GI disorders stem from a genetic predisposition, common environmental factors, or, most likely, a combination. Hypersensitivity to specific food allergens has been postulated as an etiologic factor. Symptoms depend on the severity and location of eosinophilic inflammation. Any region or layer (mucosa, submucosa, and serosa) of the gut may be involved, alone or in combination. Diagnosis requires pan-endoscopy with biopsies. Eosinophilic infiltrates dominate the histologic findings, and signs of other inflammatory diseases are absent; in particular, the crypt architecture remains normal, no parasites are identified, and no eggs or larvae are found.
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Bibliography


An increase in mast cells and IgE-containing plasma cells may be observed. Mucosal biopsies will only establish the diagnosis in cases with mucosal involvement. Small bowel capsule endoscopy is often very useful in that it characteristically reveals denuded mucosal erythema with marked focal villous atrophy in areas out of reach of standard endoscopes. The most common sites of involvement are the stomach and small intestine.

Symptoms may include abdominal pain (90%), vomiting (60%), nausea (50%), and abdominal distention (50%). Diarrhea with weight loss because of malabsorption can occur if small bowel involvement with villous blunting is extensive. Other than peripheral eosinophilia, hypoalbuminemia as a result of protein-losing enteropathy and iron-deficiency anemia are the more common laboratory findings.

Nutritional exclusion (or elemental) diets and corticosteroids are the mainstay of treatment. Approximately 50% of cases are complex, characterized by unpredictable relapses and a chronic course. Less-well-documented treatments, such as mast cell stabilizers and leukotriene antagonists (montelukast), have been used in small, uncontrolled trials. Clinical trials using biological modalities such as monoclonal anti-IgE (omalizumab) and anti-IL-5 (SCH55700/reslizumab and mepolizumab) are anticipated for severe cases.

Bibliography is available at Expert Consult.

### 338.13 Malabsorption in Inflammatory Bowel Disease

*Ernest G. Seidman and David Branski*

Crohn disease and ulcerative colitis represent the 2 forms of chronic, immune-mediated IBD that commonly affect pediatric patients (see Chapter 336). Because the small bowel is involved in the majority of pediatric Crohn disease patients, malabsorption of nutrients is far more of a problem than in ulcerative colitis. At the time of diagnosis, significant weight loss is observed in up to 85% of pediatric patients with Crohn disease and in approximately 65% with ulcerative colitis, due to inadequate intake of energy and micronutrients as well as diarrhea and malabsorption. Consequently, growth failure as a consequence of chronic undernutrition is far more common in Crohn disease than in ulcerative colitis, affecting up to 40% of cases.

In addition to malabsorption, energy intake is lower in patients with Crohn disease compared to healthy controls, in part due to lesser appetite. Excessive levels of proinflammatory cytokines are implicated in causing the anorexia as well as in mediating impaired growth. The symptoms, including abdominal pain, nausea, vomiting, and diarrhea, can cause affected children to have a lower desire to eat, which can lead to reduced food intake. This can, in turn, negatively affect nutritional status during a child’s critical period of growth and development.

Patients with IBD are also at risk of developing nutritional deficiencies because of restrictive diets imposed by caregivers or by the patients themselves.

In children with active disease, inadequate intakes of energy and of a number of micronutrients have been observed. Reduced energy intake during active disease can contribute to poor weight gain and impaired growth. Patients with IBD, particularly Crohn disease, often have multiple nutritional deficiencies and may be in negative nitrogen balance because of decreased intake and malabsorption of macro- and micronutrients. Quantifying nutrient intake, determining micronutrient deficiencies, and ascertaining requirements for nutritional supplementation are essential components of successful management in pediatric IBD.

Optimizing nutritional status and growth are key priorities in the management of IBD in children and adolescents. Energy intake should meet the added costs of catch-up growth and are usually in the range of 40-70 kcal/kg ideal body weight per day. Protein requirements are higher in Crohn disease (1-1.5 g/kg/day). Bone mineral density deficit is common, even in pediatric patients who have not been exposed to systemic corticosteroid therapy. Osteoporosis or osteopenia is best assessed by bone densitometry, and levels of vitamin 25-hydroxyvitamin D should be monitored. Table 338-10 shows other micronutrient deficiencies that result from inadequate intake, malabsorption, and gut losses.

Bile acid malabsorption is common in ileal Crohn disease, especially after small bowel resection. This leads to diarrhea and also places patients at increased risk for urolithiasis and cholelithiasis. The prevalence of recurrent calcium-oxalate urolithiasis is up to 5-fold higher in Crohn disease. Increased urinary oxalate and decreased citrate excretion, resulting from bowel resection with mainly preserved colon, were identified as crucial risk factors for stone formation. The hyperoxaluria predominantly results from increased colonic permeability to oxalate due to disturbed bile acid metabolism.

Enteral nutrition support is favored over parenteral for all but Crohn disease patients with extreme short gut. To induce remission, exclusive nutritional therapy given orally was reported to be as effective as when continuously administered by enteral feeding tube. However, weight gain was significantly greater for the latter group. Patients requiring hospitalization for a severe relapse should receive nutrition support if they are already malnourished or their intake is likely to be severely curtailed for ≥1 wk. Preoperative nutrition support is essential to the prevention of morbidity and mortality. However, clinicians must be aware of the risk of the refeeding syndrome in patients with severe malnutrition. In ulcerative colitis, nutrition support is adjunctive therapy; there is no evidence that bowel rest or total parenteral nutrition parenteral nutrition influences the outcome of severe ulcerative colitis.

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Bibliography
Bibliography


Chapter 339
Intestinal Transplantation in Children with Intestinal Failure
Jorge D. Reyes and André A.S. Dick

The introduction of tacrolimus and the development of the abdominal multiorgan procurement techniques allowed the tailoring of various types of intestine grafts that can contain other intraabdominal organs, such as the liver, pancreas, and stomach; this has been critical to the application of this type of organ transplant. The understanding that the liver protects the intestine against rejection demonstrates the interaction between recipient and donor immunocytes (host-versus-graft and graft-versus-host) which under the cover of immunosuppression allows varying degrees of graft acceptance and eventual minimization of drug therapy. Over the past several years the number of patients placed on the list for and those undergoing intestinal transplantation has decreased, which may be a result of (1) improvements in the care of patients with intestinal failure under a multidisciplinary intestinal care team management, (2) the introduction of new lipid management strategies for the treatment of cholestatic liver disease, and (3) corrective surgery enhancing absorptive surface and motility.

INDICATIONS FOR INTESTINAL TRANSPLANT
Intestinal failure describes a patient who has lost the ability to maintain nutritional support and adequate fluid requirements, needed to sustain growth, with their own intestine and is permanently dependent on total parenteral nutrition (TPN). The majority of these patients have short bowels as a result of a congenital deficiency or acquired condition (see Chapter 338.7). In others, the cause of intestinal failure is a functional disorder of motility or absorption (Table 339-1). Rarely do patients receive intestinal transplants for benign neoplasms. The complications of intestinal failure include loss of venous access, life-threatening infections, and TPN-induced cholestatic liver disease.

Table 339-1 Causes of Intestinal Failure in Children Requiring Transplantation

<table>
<thead>
<tr>
<th>SHORT BOWEL</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Congenital disorders</td>
<td>Volvulus</td>
</tr>
<tr>
<td>Gastrochisis</td>
<td>Necrotizing enterocolitis</td>
</tr>
<tr>
<td>Intestinal atresia</td>
<td>Trauma</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>INTESTINAL DYSMOTILITY</td>
<td></td>
</tr>
<tr>
<td>Intestinal pseudoobstruction</td>
<td>Intestinal aganglronosis (Hirschsprung disease)</td>
</tr>
<tr>
<td>ENTEROCYTE DYSFUNCTION</td>
<td></td>
</tr>
<tr>
<td>Microvillus inclusion disease</td>
<td>Tufting enteropathy</td>
</tr>
<tr>
<td>Autoimmune disorders</td>
<td>Crohn disease</td>
</tr>
<tr>
<td>TUMORS</td>
<td></td>
</tr>
<tr>
<td>Familial polyposis</td>
<td>Inflammatory pseudotumor</td>
</tr>
</tbody>
</table>

Paucity of Venous Access
Administration of TPN requires the insertion of a centrally placed venous catheter, there being only 6 readily accessible sites (bilateral internal jugulars, subclavians, iliac veins). The loss of venous access generally occurs in the setting of recurrent catheter sepsis and thrombosis; clinical convention suggests that loss of 50% of these venous access sites places the patient at risk of not being able to be treated with TPN.

Life-Threatening Infections
Life-threatening infections are usually catheter-related; the absence of significant lengths of intestine may be associated with abnormal motility of the residual bowel (producing both delayed or rapid emptying), with varying degrees of bacterial overgrowth and possible bacterial or fungal translocation as a consequence of loss of intestinal barrier function and/or loss of gut immunity. This situation can produce cholestatic liver disease, multisystem organ failure, and metastatic infectious foci in lungs, kidneys, liver, and the brain.

Liver Disease
The development of cholestatic liver disease is the most serious complication of intestinal failure and may be a consequence of the toxic drug effects of TPN on hepatocytes, a disruption of bile flow and bile acid metabolism, and the frequent occurrence of bacterial translocation and sepsis with endotoxin release into the portal circulation. This complication varies in frequency depending on the patient’s age and the etiology of the intestinal failure; it is most common in neonates with extreme short gut. The effects on the liver include fatty transformation, steatohepatitis and necrosis, fibrosis, and then cholestasis. The development of clinical jaundice (total bilirubin >3 mg/dL) and thrombocytopenia are significant risk factors for poor outcome, because these changes portend the development of portal hypertensive gastroenteropathy, hypersplenism, coagulopathy, and uncontrollable bleeding.

TRANSPLANTATION OPERATION
Donor Selection
Intestinal grafts are usually procured from hemodynamically stable, ABO-identical brain-dead donors who have minimal clinical or laboratory evidence suggesting intraabdominal ischemia; size matching varies according to age of the recipients; present surgical techniques allow for significant reductions of the graft in order to achieve abdominal closure. Human leukocyte antigen has been random, and cross-matching has not been a determinant of graft acceptance. Exclusion criteria include a history of malignancy and intraabdominal evidence of infection; systemic viral or bacterial infections are not excluded. Donor preparation has been limited to the administration of systemic and enteral antibiotics. Propylxylisis for graft-versus-host disease with graft pretreatment using irradiation or a monoclonal antilymphocyte antibody has varied over time. Grafts have been preserved with the University of Wisconsin solution, as is the case with other types of abdominal organs.

Types of Intestinal Grafts
Intestinal allografts are used in various forms, either alone (as an isolated intestine graft) or as a composite graft, which can include the liver, duodenum, and pancreas (liver-intestine graft); when this composite graft includes the stomach, and the recipient operation requires the removal of all of the patient’s gastrointestinal tract (as with intestinal pseudoobstruction) and liver, then this replacement graft is known as a multivisceral graft.

The procurement of these various types of grafts focuses on the preservation of the arterial vessels of celiac and/or superior mesenteric arteries, as well as appropriate venous outflow, which would include the superior mesenteric vein or the hepatic veins in the composite grafts. The larger composite grafts inherently retain the celiac and superior mesenteric arteries; this includes multivisceral grafts, liver plus small bowel grafts, and “modified multivisceral grafts” in which the liver is excluded but the entire gastrointestinal tract is replaced,
including the stomach. The isolated intestine graft retains the superior mesenteric artery and vein; this graft can be accomplished with preservation of the vessels going to the pancreas, when that organ has been allocated to another recipient. The graft that is to be used in a particular recipient is dissected out in situ and then removed after cardiac arrest of the donor, with core cooling of the organs, using an infusion of preservation solution (Fig. 339-1).

Various modifications in these grafts have included the preservation of visceral ganglia at the base of the arteries, the inclusion of donor duodenum and pancreas for the liver and intestine graft, the inclusion of colon, the reduction of the liver graft (into left or right side) and variable reduction of the intestine graft, and the development of living donor intestine grafts.

The Recipient Operation
Because many children have had multiple previous abdominal operations, intestinal transplantation can be a formidable technical challenge; most children require replacement of the liver because of TPN-induced disease and often present with advanced liver failure. Transplantation of an isolated intestinal allograft involves exposure of the lower abdomen, infrarenal aorta, and inferior vena cava. Placement of vascular homografts using donor iliac artery and vein to these vessels allows arterialization and venous drainage of the intestinal graft. In patients who have retained their intestine and then undergo an enterectomy at the time of transplantation, use of the native superior mesenteric vessels is feasible.

Transplantation of a larger composite graft requires the removal and replacement of the native liver in the liver with intestine transplant, and complete abdominal exenteration in the multivisceral transplant. In a similar fashion, the infrarenal aorta is exposed for placement of an arterial conduit graft (donor thoracic aorta) for arterialization of the graft. The venous drainage is achieved to the retained hepatic veins, which are fashioned to a single conduit for anastomosis to the allograft liver.

The intestinal anastomosis to native proximal and distal bowel are performed, leaving an enterostomy of distal allograft ileum; this will be used for routine posttransplantation surveillance endoscopy and biopsy. This ostomy is closed 3-6 mo after transplantation (Fig. 339-2).

POSTOPERATIVE MANAGEMENT

Immunosuppression
Successful immunosuppression for intestinal transplantation is initiated with tacrolimus and corticosteroids. This required high levels of tacrolimus (in the nephrotoxic range), and although initial success rates were high they were followed by rejection rates of >80%, infection, and late drug toxicities, resulting in a gradual loss of grafts and patients. The next generation of protocols incorporated the addition of other agents, such as azathioprine, cyclophosphamide, induction with an interleukin-2 antibody antagonist, mycophenolate mofetil, and rapamycin. This modification resulted in a decreased incidence in the severity of initial rejection; the ability to decrease immunosuppression

Small Bowel Transplantation Surgery

Isolated Intestine

Combined with Liver

Multivisceral

Figure 339-2 The 3 basic intestinal transplant procedures (the graft is shaded). With the isolated intestine, the venous outflow may be to the recipient portal vein (main figure), inferior vena cava (inset left), or superior mesenteric vein (inset right). With the composite grafts, which include the liver, the arterialization is from the aorta with venous drainage out from the liver graft to the recipient inferior vena cava.
later did not allow for stabilization of long-term survival. The introduction of recipient pretreatment using antilymphocyte antibodies and the elimination of recipient therapy with steroids have resulted in improved transplant survival as a result of a significant decrease in the incidence of rejection and infection, permitting the gradual decrease of immunosuppressive drug therapy within 3 mo, and a decline in drug toxicity events. The most common initial maintenance regimen used is tacrolimus and prednisone dual therapy. By 1yr the majority of patients are on tacrolimus monotherapy.

**Allograft Assessment**

There are no simple laboratory tools that allow assessment of the intestinal allograft. The gold standard for diagnosis of intestinal allograft rejection has been serial endoscopic surveillance and biopsies through the allograft ileostomy. Clinical signs and symptoms of rejection or infection of the allograft can overlap and mimic each other, producing either rapid diarrhea or complete ileus with pseudoobstruction syndromes, or gastrointestinal bleeding. Any changes in clinical status should warrant thorough evaluation for rejection with endoscopic biopsies and an evaluation for opportunistic infection, malabsorption, and other enteral infections.

The diagnosis of acute rejection is based on seeing destruction of crypt epithelial cells from apoptosis, in association with a mixed lymphocytic infiltrate. These histologic findings may or may not correlate with endoscopic evidence of injury, which varies from diffuse erythema and friability to ulcers and, in cases of severe rejection, exfoliation of the intestinal mucosa. Chronic rejection of the allograft can be diagnosed only through full thickness sampling of the intestine, which shows the typical vasculopathy that can result in progressive ischemia of the allograft.

**Rejection and Graft-Versus-Host Disease**

Acute rejection rates for the intestinal allograft are significantly higher than with any other organ, in the range of 80–90%, and severe rejection requiring the use of antilymphocyte antibody preparations may be as high as 30%. Triple-drug regimens and the use of interleukin-2 antibody inhibitors have resulted in significant decreases in rejection rates; nonetheless, the amount of immunosuppression was incompatible with improvements in long-term patient and graft survival. Rejection rates of 40% are achievable with the use of antilymphocyte globulin. These protocols induce varying degrees of “proper tolerance,” which can eventually allow for minimization of immunosuppression, thus reducing the risk of drug toxicity and infection. Vascular rejection has been an uncommon occurrence, and chronic rejection has been seen in approximately 15% of cases. Graft-versus-host disease is infrequent but potentially life-threatening. The mortality rate exceeds 80% and most recipients die from infectious complications from bone marrow failure. The incidence seen in intestinal transplantation is 5–6%. Although no standard treatment is available, early diagnosis, prevention of infection, and initiation of treatment as soon as possible may improve outcomes.

**Infections**

Infectious complications are the most significant cause of morbidity and mortality after intestinal transplantation. The most common infections (bacterial, fungal, polymicrobial) occur as a result of the continuing need for venous catheter placement for as long as 1yr posttransplantation. Infections as a consequence of immunosuppressive drug management are from cytomegalovirus (CMV) infection (22% incidence), Epstein-Barr virus (EBV)−induced infections (21% incidence), and adenovirus enteritis (40% incidence). Despite improvements in monitoring and preventative measures, CMV remains the most common viral infection post–intestinal transplantation. CMV may be acquired from blood transfusions, reactivation of endogenous viruses, or the donated allograft. The highest risk recipients for CMV infection are those who are immunologically naïve and receive an allograft from a donor who is seropositive. The 2 mainstay CMV prevention strategies commonly employed are universal prophylaxis and preemptive therapy. Current consensus guidelines recommend prophylaxis treatment for high-risk patients (donor+/recipient−). The preferred drugs for CMV prophylaxis are ganciclovir and oral valganciclovir.

Patients at the highest risk for EBV infection are similarly those who are seronegative at the time of transplantation and those requiring a high-burden immunosuppressive therapy to maintain their graft. EBV disease varies from asymptomatic viremia to posttransplant lymphoproliferative disorder (PTLD). The incidence of EBV-related PTLD is highest in patients receiving intestinal allografts compared to liver, heart, or kidney. Children have a higher incidence of PTLD compared to adults, and are most likely to have EBV+PTLD. Early diagnosis and prevention of PTLD is essential and the mainstay of therapy is to reduce immunosuppression, although some patients have required chemotherapy. The use of anti−B-cell monoclonal antibodies, such as the anti-CD20 antibody rituximab, in PTLD has been successful as noted in anecdotal reports. Successful management of these viral infections is achieved through early detection and preemptive therapy, for both CMV and EBV, before the development of a serious life-threatening infection. This approach has improved outcomes for CMV, eliminating the mortality in the pediatric patient population (see Chapters 178, 254, and 255).

**Outcomes**

Intestinal transplantation is the standard of care for children with intestinal failure who have significant complications of TPN and can no longer tolerate such therapy. Data from the Organ Procurement and Transplantation Network (OPTN)/Scientific Registry of Transplant Recipients (SRTR) Annual Report 2011, and center-specific data reports have documented significant improvements with short- and long-term survivals for transplantations occurring principally in the last 10 yr; intestinal transplantation (liver-intestine and isolated intestinal transplants) graft failure rates for deceased donor transplants in 2010−2011 were 26% at 1yr, 46% at 3 yr for transplants in 2008−2009, and 48% at 5yr for transplants in 2006−2007 (Fig. 339−3). It is hoped that with the minimization strategies currently used the long-term survival will plateau as occurs with other organ transplants; rehabilitation and quality-of-life studies have shown that more than 80% of survivors reach total independence from TPN and have meaningful

![Graft Failure Among Intestinal Transplant Recipients: Deceased Donor](http://srtr.transplant.hrsa.gov/annual_reports/2011/default.aspx)
life activities. Consequently, there has been a shift in efforts to improve long-term outcomes and quality of life.

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Diarrheal disorders in childhood account for a large proportion (9%) of childhood deaths, with an estimated 0.71 million deaths per year globally, making it the second most common cause of child deaths worldwide. Almost 1.731 billion episodes of diarrhea occurred in 2010 in children younger than 5 yr of age in developing countries, with more than 80% of the episodes occurring in Africa and South Asia (50.5% and 32.5%, respectively) and 36 million of the total episodes progress to severe episodes. Global mortality may be declining rapidly, but the overall incidence of diarrhea has only declined from 3.4 to 2.9 episodes per child-year in the past 2 decades, and it is estimated to account for 23 million childhood disability-adjusted life years.

The decline in diarrheal mortality, despite the lack of significant changes in incidence, is the result of preventive rotavirus vaccination and improved case management of diarrhea, as well as improved nutrition of infants and children. These interventions have included widespread home- and hospital-based oral rehydration therapy and improved nutritional management of children with diarrhea.

In addition to the risk of mortality, persistently high rates of diarrhea, especially prolonged and persistent diarrhea among young children may be associated with long-term adverse outcomes. Diarrheal illnesses, especially early and repeated episodes among young children can be associated with malnutrition, micronutrient deficiencies, and significant deficits in psychomotor and cognitive development.

**ETIOLOGY OF DIARRHEA**

Gastroenteritis is the result of infection acquired through the fecal–oral route or by ingestion of contaminated food or water. Gastroenteritis is associated with poverty, poor environmental hygiene, and development indices. Enteropathogens that are infectious in a small inoculum (Shigella, enterohemorrhagic Escherichia coli, Campylobacter jejuni, noroviruses, rotavirus, Giardia lamblia, Cryptosporidium parvum, Entamoeba histolytica) can be transmitted by person-to-person contact, whereas others, such as cholera, are generally a consequence of contamination of food or water supply (see Tables 340-1 to 340-3).

In the United States, rotavirus and the noroviruses (small round viruses such as Norwalk-like virus and caliciviruses) are the most common viral agents, followed by sapoviruses, enteric adenoviruses, and astroviruses (see Table 340-2). Foodborne outbreaks in the United States are mostly caused by norovirus, accounting for 58% of all episodes, and by bacterial causes, which are most commonly Salmonella, Clostridium perfringens, Campylobacter, and Staphylococcus aureus, followed much less often by E. coli, Clostridium botulinum, Shigella, Cryptosporidium, Yersinia, Listeria, Vibrio, and Cyclospora, species, in that order. Food sources include poultry, leafy vegetables, beef, fruits and nuts, vine-stalk vegetables, and many other foods.

Direct person-to-person contact outbreaks of gastroenteritis are usually caused by norovirus and Shigella species. Unknown agents are seen in 30–40%; other pathogens include Salmonella, rotavirus, Giardia, Cryptosporidium, Clostridium difficile, and C. jejuni.

The exact etiologic fractions of diarrhea among children in developing countries are a subject of much research, and our knowledge of the various pathogens that cause moderate to severe childhood diarrhea has grown considerably (Fig. 340-1; Table 340-5). There are indications that rates of hospitalization and deaths caused by Shigella infections, especially Shigella dysenteriae type 1, the most severe form of shigellosis, may be declining; however, it accounts for nearly 28,000 deaths annually. Enteropathogenic E. coli is responsible for 79,000 and enterotoxigenic E. coli (ETEC) may be responsible for 42,000 deaths annually among children younger than 5 yr. Rotavirus infections (the most common identifiable viral cause of gastroenteritis in all children) account for 197,000 deaths annually or 28% of all deaths caused by diarrhea among children younger than 5 yr of age.

**PATHOGENESIS OF INFECTIOUS DIARRHEA**

Pathogenesis and severity of bacterial disease depend on whether organisms have preformed toxins (S. aureus, Bacillus cereus), produce secretory (cholera, E. coli, Salmonella, Shigella) or cytotoxic (Shigella, S. aureus, Vibrio parahaemolyticus, C. difficile, E. coli, C. jejuni) toxins, or are invasive, and on whether they replicate in food. Enteropathogens can lead to either an inflammatory or noninflammatory response in the intestinal mucosa (Table 340-6).

Enteropathogens elicit noninflammatory diarrhea through enterotoxin production by some bacteria, destruction of villus (surface) cells by viruses, adherence by parasites, and adherence and/or translocation by bacteria. Inflammatory diarrhea is usually caused by bacteria that directly invade the intestine or produce cytotoxins with consequent fluid, protein, and cells (erythrocytes, leukocytes) that enter the intestinal lumen. Some enteropathogens possess more than 1 virulence property. Some viruses, such as rotavirus, target the microvillus tips of the enterocytes and can enter the cells by direct invasion or calcium-dependent endocytosis. This can result in villus shortening and loss of enterocyte absorptive surface through cell shortening and loss of microvilli (Fig. 340-2).

Most bacterial pathogens elaborate enterotoxins; the rotavirus protein NSP4 acts as a viral enterotoxin. Bacterial enterotoxins can selectively activate enterocyte intracellular signal transduction and can also affect cytoskeletal rearrangements with subsequent alterations in the water and electrolyte fluxes across enterocytes. In toxigenic diarrhea, enterotoxin produced by Vibrio cholerae, increased mucosal levels of cyclic adenosine monophosphate, inhibit electroneutral NaCl absorption but have no effect on glucose-stimulated Na+ absorption. In inflammatory diarrhea (e.g., Shigella spp. or Salmonella spp.) there is extensive histologic damage, resulting in altered cell morphology and reduced glucose-stimulated Na+ and electroneutral NaCl absorption. The role of 1 or more cytokines in this inflammatory response is critical. In secretory cells from crypts, Cl secretion is minimal in normal subjects and is activated by cyclic adenosine monophosphate in toxigenic and inflammatory diarrhea (Fig. 340-3).

ETEC colonizes and adheres to enterocytes of the small bowel via its surface fimbriae (pili) and induces hypersecretion of fluids and electrolytes into the small intestine through 1 of 2 toxins: the heat-labile enterotoxin or the heat-stable enterotoxin. Heat-labile enterotoxin is structurally similar to the V. cholerae toxin, and activates adenylate cyclase, resulting in an increase in intracellular cyclic guanosine monophosphate (Fig. 340-4). In contrast, Shigella spp. cause...
### Table 340-1 | Foodborne Bacterial Illnesses

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Incubation Period</th>
<th>Signs and Symptoms</th>
<th>Duration of Illness</th>
<th>Associated Foods</th>
<th>Laboratory Testing</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bacillus anthracis</strong></td>
<td>2 days to weeks</td>
<td>Nausea, vomiting, malaise, bloody diarrhea, acute abdominal pain</td>
<td>Weeks</td>
<td>Insufficiently cooked contaminated meat</td>
<td>Blood</td>
<td>Penicillin is first choice for naturally acquired GI anthrax but use beta lactams with high index of suspicion for resistance. Ciprofloxacin is second option.</td>
</tr>
<tr>
<td><strong>Bacillus cereus</strong> (preformed enterotoxin)</td>
<td>1-6 hr</td>
<td>Sudden onset of severe nausea and vomiting. Diarrhea may be present</td>
<td>24 hr</td>
<td>Improperly refrigerated cooked or fried rice, meats</td>
<td>Normally a clinical diagnosis. Clinical laboratories do not routinely identify this organism. If indicated, send stool and food specimens to reference laboratory for culture and toxin identification.</td>
<td>Supportive care</td>
</tr>
<tr>
<td><strong>Bacillus cereus</strong> (diarrheal toxin)</td>
<td>10-16 hr</td>
<td>Abdominal cramps, watery diarrhea, nausea</td>
<td>24-48 hr</td>
<td>Meats, stews, gravies, vanilla sauce</td>
<td>Testing not necessary, self-limiting. Consider testing food and stool for toxin in outbreaks.</td>
<td>Supportive care</td>
</tr>
<tr>
<td><strong>Brucella abortus, Brucella melitensis, and Brucella suis</strong></td>
<td>7-21 days</td>
<td>Fever, chills, sweating, weakness, headache, muscle and joint pain, diarrhea, bloody stools during acute phase</td>
<td>Weeks</td>
<td>Raw milk, goat cheese made from unpasteurized milk, contaminated meats</td>
<td>Blood culture and positive serology</td>
<td>Acute: Rifampin and doxycycline daily for ≥ 6 wk. Infections with complications require combination therapy with rifampin, tetracycline, and an aminoglycoside.</td>
</tr>
<tr>
<td><strong>Campylobacter jejuni</strong></td>
<td>2-5 days</td>
<td>Diarrhea, cramps, fever, and vomiting; diarrhea may be bloody</td>
<td>2-10 days</td>
<td>Raw and undercooked poultry, unpasteurized milk, contaminated water</td>
<td>Routine stool culture; Campylobacter requires special media and incubation at 42°C (107.6°F) to grow</td>
<td>Supportive care. For severe cases, antibiotics, such as azithromycin and quinolones, may be indicated early in the diarrheal disease. Guillain-Barré syndrome can be a sequela.</td>
</tr>
<tr>
<td><strong>Clostridium botulinum: children and adults</strong> (preformed toxin)</td>
<td>12-72 hr</td>
<td>Vomiting, diarrhea, blurred vision, diplopia, dysphagia, descending muscle weakness</td>
<td>Variable (days to months)</td>
<td>Home-canned foods with a low acid content, improperly canned commercial foods, home-canned or fermented fish, herb-infused oils, baked potatoes in aluminum foil, cheese sauce, bottled garlic, foods held warm for extended periods (e.g., in a warm oven)</td>
<td>Stool, serum, and food can be tested for toxin. Stool and food can also be cultured for the organism. These tests can be performed at some state health department laboratories and CDC.</td>
<td>Supportive care. Botulinum antitoxin is helpful if given early in the course of the illness. Antitoxin for children and adults is available through CDC. Contact the state health department. The 24-hr number for CDC is (800) 232-4636 (800-CDC-INFO).</td>
</tr>
<tr>
<td><strong>Clostridium botulinum: infants</strong></td>
<td>3-30 days</td>
<td>In infants &lt;12 mo, lethargy, weakness, poor feeding, constipation, hypotonia, poor head control, poor gag and sucking reflex</td>
<td>Variable</td>
<td>Honey, home-canned vegetables and fruits, corn syrup</td>
<td>Stool, serum, and food can be tested for toxin. Stool and food can also be cultured for the organism. These tests can be performed at some state health department laboratories and CDC.</td>
<td>Supportive care. Botulinum antitoxin for infants can be obtained from the Infant Botulism Prevention Program, Health and Human Services, California (510-540-2646).</td>
</tr>
</tbody>
</table>

Continued
<table>
<thead>
<tr>
<th>Etiology</th>
<th>Incubation Period</th>
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<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Clostridium perfringens</em> toxin</td>
<td>8-16 hr</td>
<td>Watery diarrhea, nausea, abdominal cramps; fever is rare</td>
<td>24-48 hr</td>
<td>Meats, poultry, gravy, dried or precooked foods, time- and/or temperature-abused food</td>
<td>Stools can be tested for enterotoxin and cultured for organism</td>
<td>Supportive care. Antibiotics not indicated.</td>
</tr>
<tr>
<td>Enterohemorrhagic Escherichia coli (EHEC) including E. coli O157:H7 and other Shiga toxin-producing E. coli (STEC)</td>
<td>1-8 days</td>
<td>Severe diarrhea that is often bloody, abdominal pain and vomiting</td>
<td>5-10 days</td>
<td>Undercooked beef especially hamburger, unpasteurized milk and juice, raw fruits and vegetables (e.g., sprouts), salami (rarely), contaminated water</td>
<td>Stool culture; E. coli O157:H7 requires special media to grow. If E. coli O157:H7 is suspected, specific testing must be requested. Shiga toxin testing may be done using commercial kits; positive isolates should be forwarded to public health laboratories for confirmation and serotyping.</td>
<td>Supportive care, monitor renal function, hemoglobin, and platelets closely. E. coli O157:H7 infection is also associated with hemolytic uremic syndrome (HUS), which can cause lifelong complications. Studies indicate that antibiotics might promote the development of HUS. Antibiotics like Imodium may also increase the risk of developing HUS.</td>
</tr>
<tr>
<td>Enterotoxigenic E. coli (ETEC)</td>
<td>1-3 days</td>
<td>Watery diarrhea, abdominal cramps, some vomiting</td>
<td>3 to &gt;7 days</td>
<td>Water or food contaminated with human feces</td>
<td>Stool culture ETEC requires special laboratory techniques for identification that may not be widely available; consequently, physicians may make the diagnosis based on a patient’s history and symptoms. If ETEC is suspected, must alert microbiology laboratory that is testing the specimen</td>
<td>Supportive care. Antibiotics are rarely needed except in severe cases. Recommended antibiotics include quinolones although these are rarely required unless there is severe infection and should be administered early. Antimotility medications should be avoided by persons with high fevers or bloody diarrhea, and should be discontinued if diarrhea symptoms persist more than 48 hr. Bismuth subsalicylate compounds (e.g., Pepto-Bismol) can help reduce the number of bowel movements.</td>
</tr>
<tr>
<td>Pathogen: Organism</td>
<td>GI Symptoms</td>
<td>Fever, Muscle Aches, and Nausea or Diarrhea</td>
<td>Variable</td>
<td>Fresh Soft Cheeses, Unpasteurized Milk, Inadequately Pasteurized Milk, Ready-to-Eat Deli Meats, Hot Dogs</td>
<td>Blood or Cerebrospinal Fluid Cultures. Selective Enrichment Media Improve Rates of Isolation from Contaminated Specimens</td>
<td>Supportive Care and Antibiotics; Intravenous Ampicillin, Penicillin G, or TMP-SMX Is Recommended for Invasive Disease</td>
</tr>
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</tr>
<tr>
<td>Listeria monocytogenes</td>
<td>9-48 hr for GI symptoms, 2-6 wk for invasive disease</td>
<td>At birth and infancy</td>
<td>Infants infected from mother at risk for sepsis or meningitis</td>
<td>Fever, muscle aches, and nausea or diarrhea</td>
<td>Pregnant women might have mild flu-like illness, and infection can lead to premature delivery or stillbirth</td>
<td>Antibody to listeriolysin O may be helpful to identify outbreak retrospectively</td>
</tr>
<tr>
<td>Salmonella spp.</td>
<td>1-3 days</td>
<td>Diarrhea, fever, abdominal cramps, vomiting</td>
<td>4-7 days</td>
<td>Contaminated eggs, poultry, unpasteurized milk or juice, cheese, contaminated raw fruits and vegetables (alfalfa sprouts, melons)</td>
<td>Routine Stool Cultures</td>
<td>Supportive care. Other than for S. typhi and S. paratyphi, antibiotics are not indicated unless there is extraintestinal spread, or the risk of extraintestinal spread of the infection</td>
</tr>
<tr>
<td>Shigella spp.</td>
<td>24-48 hr</td>
<td>Abdominal cramps, fever, diarrhea</td>
<td>4-7 days</td>
<td>Food or water contaminated with human fecal material</td>
<td>Routine Stool Cultures</td>
<td>Supportive care. Antibiotics are recommended for severe disease, bloody diarrhea, or compromised immune systems. Resistance to traditional first-line drugs like ampicillin and TMP-SMX is common. When susceptibility is unknown or when an ampicillin- or TMP-SMX-resistant strain is isolated, choices for therapy include fluoroquinolones, ceftriaxone, and azithromycin. Antidiarrheal agents such as Imodium or Lomotil can worsen the illness and should be avoided</td>
</tr>
<tr>
<td>Staphylococcus aureus (preformed enterotoxin)</td>
<td>1-6 hr</td>
<td>Sudden onset of severe nausea and vomiting</td>
<td>24-48 hr</td>
<td>Unrefrigerated or improperly refrigerated meats, potato and egg salads, cream pastries</td>
<td>Normally a clinical diagnosis</td>
<td>Supportive care</td>
</tr>
</tbody>
</table>

**Continued**
Table 340-1 | Foodborne Bacterial Illnesses—cont’d

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Incubation Period</th>
<th>Signs and Symptoms</th>
<th>Duration of Illness</th>
<th>Associated Foods</th>
<th>Laboratory Testing</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vibrio cholerae (toxin)</td>
<td>24-72 hr</td>
<td>Profuse watery diarrhea and vomiting, which can lead to severe dehydration and death within hours</td>
<td>3-7 days</td>
<td>Contaminated water, fish, shellfish, street-vended food typically from Latin America or Asia</td>
<td>Stool culture</td>
<td>Supportive care with aggressive oral and intravenous rehydration. Doxycycline is recommended as first-line treatment for adults, whereas azithromycin is recommended as first-line treatment for children and pregnant women. Ciprofloxacin and doxycycline recommended as second-line drugs for children.</td>
</tr>
<tr>
<td>Vibrio parahaemolyticus</td>
<td>2-48 hr</td>
<td>Watery diarrhea, abdominal cramps, nausea, vomiting</td>
<td>2-5 days</td>
<td>Undercooked or raw seafood, such as fish, shellfish</td>
<td>Stool cultures. V. parahaemolyticus requires special media (TCBS agar) to grow; must request specific testing</td>
<td>Supportive care</td>
</tr>
<tr>
<td>Vibrio vulnificus</td>
<td>1-7 days</td>
<td>Vomiting, diarrhea, abdominal pain, bacteremia, and wound infections; More common and potentially fatal in the immunocompromised or in patients with chronic liver disease (presenting with septic shock and hemorrhagic bullous skin lesions)</td>
<td>2-8 days</td>
<td>Undercooked or raw shellfish, especially oysters, other contaminated seafood, and open wounds exposed to seawater</td>
<td>Stool, wound, or blood cultures. V. vulnificus requires special media (TCBS agar) to grow; if V. vulnificus is suspected, must request specific testing</td>
<td>Supportive care and antibiotics: doxycycline, and a third-generation cephalosporin such as ceftazidime is recommended</td>
</tr>
<tr>
<td>Yersinia enterocolitica and Yersinia pseudotuberculosis</td>
<td>24-48 hr</td>
<td>Appendicitis-like symptoms (diarrhea and vomiting, fever, abdominal pain) occur primarily in older children and young adults; Might have a scarlatiniform rash or erythema nodosum with Y. pseudotuberculosis</td>
<td>1-3 wk, usually self-limiting</td>
<td>Undercooked pork, unpasteurized milk, tofu, contaminated water; Infection has occurred in infants whose caregivers handled chitterlings</td>
<td>Stool, vomitus, or blood culture, throat, lymph nodes, joint fluid, urine, and bile Yersinia requires special media to grow; must request specific testing. Serology is available in research and reference laboratories.</td>
<td>Supportive care</td>
</tr>
</tbody>
</table>

CDC, Centers for Disease Control and Prevention; GI, gastrointestinal; TMP-SMX, trimethoprim-sulfamethoxazole.

### Table 340-2  Foodborne Viral Illnesses

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Incubation Period</th>
<th>Signs and Symptoms</th>
<th>Duration of Illness</th>
<th>Associated Foods</th>
<th>Laboratory Testing</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatitis A</td>
<td>28 days average (15-50 days)</td>
<td>Diarrhea, dark urine, jaundice, and flu-like symptoms, i.e., fever, headache, nausea, and abdominal pain</td>
<td>Variable, 2 wk-3 mo</td>
<td>Shellfish harvested from contaminated waters, raw produce, contaminated drinking water, uncooked foods, and cooked foods that are not reheated after contact with infected food handler</td>
<td>Increase in ALT, bilirubin Positive IgM and anti-hepatitis A antibodies</td>
<td>Supportive care Prevention with immunization (vaccine available for persons 1 year and older)</td>
</tr>
<tr>
<td>Caliciviruses (including noroviruses and sapoviruses)</td>
<td>12-48 hr</td>
<td>Nausea, vomiting, abdominal cramping, diarrhea, fever, myalgia, and some headache</td>
<td>12-60 hr</td>
<td>Shellfish, fecally contaminated foods, ready-to-eat foods touched by infected food workers (salads, sandwiches, ice, cookies, fruit)</td>
<td>Routine RT-PCR. RT-PCR assays are the preferred laboratory method for detecting norovirus. Conventional RT-PCR followed by sequence analysis of the RT-PCR products is used for norovirus genotyping. Rapid commercial assays, such as enzyme immunoassays (EIAs), have poor sensitivity and are not recommended for establishing diagnosis</td>
<td>Supportive care such as rehydration. Avoid giving antimotility agents to children younger than 3 yr old. However, these agents may be helpful in older children and adults, particularly when used along with rehydration treatment Good hygiene</td>
</tr>
<tr>
<td>Rotavirus (groups A-C)</td>
<td>1-3 days</td>
<td>Vomiting, watery diarrhea, low-grade fever Temporary lactose intolerance can occur Infants and children, elderly, and immunocompromised are especially vulnerable</td>
<td>4-8 days</td>
<td>Fecally contaminated foods Ready-to-eat foods touched by infected food workers (salads, fruits)</td>
<td>Diagnosis may be made by rapid antigen detection of rotavirus in stool specimens.</td>
<td>Supportive care Severe diarrhea can require fluid and electrolyte replacement</td>
</tr>
<tr>
<td>Other viral agents (astroviruses, adenoviruses, parvoviruses)</td>
<td>10-70 hr</td>
<td>Nausea, vomiting, diarrhea, malaise, abdominal pain, headache, fever</td>
<td>2-9 days</td>
<td>Fecally contaminated foods Ready-to-eat foods touched by infected food workers Some shellfish</td>
<td>Identification of the virus in early acute stool samples Serology Commercial ELISA kits are available for adenoviruses and astroviruses</td>
<td>Supportive care, usually mild, self-limiting Good hygiene</td>
</tr>
</tbody>
</table>

ALT, alanine aminotransferase; ELISA, enzyme-linked immunosorbent assay; IgM, immunoglobulin M; RT-PCR, reverse transcriptase polymerase chain reaction; WBCs, white blood cells.

*From Centers for Disease Control and Prevention: Diagnosis and management of foodborne illnesses. MMWR 53(RR-4):1-33, 2004.*
<table>
<thead>
<tr>
<th>Etiology</th>
<th>Incubation Period</th>
<th>Signs and Symptoms</th>
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<th>Associated Foods</th>
<th>Laboratory Testing</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angiostrongylus cantonensis</td>
<td>1 wk-1 mo</td>
<td>Severe headaches, nausea, vomiting, neck stiffness, paresthesias, hyperesthesias, seizures, and other neurologic abnormalities</td>
<td>Several weeks to several months</td>
<td>Raw or undercooked intermediate hosts (e.g., snails or slugs), infected paratenic (transport) hosts (e.g., crabs, freshwater shrimp), fresh produce contaminated with intermediate or transport hosts</td>
<td>No readily available blood tests. History is major guide to diagnosis. Examination of CSF for elevated pressure, protein, leukocytes, and eosinophils; serologic testing using ELISA to detect antibodies to <em>Angiostrongylus cantonensis</em></td>
<td>Supportive care. There is no specific treatment. Repeat lumbar punctures and use of corticosteroid therapy may be used for more severely ill patients</td>
</tr>
<tr>
<td>Cryptosporidium</td>
<td>2-10 days</td>
<td>Diarrhea (usually watery), stomach cramps, upset stomach, slight fever</td>
<td>May be remitting and relapsing over weeks to months</td>
<td>Any uncooked food or food contaminated by an ill food handler after cooking; drinking water</td>
<td>Request specific examination of the stool for <em>Cryptosporidium</em>. Most often, stool specimens are examined microscopically using different techniques (e.g., acid-fast staining, direct fluorescent antibody [DFA], and/or enzyme immunoassays for detection of <em>Cryptosporidium</em> sp. antigens) May need to examine water or food</td>
<td>Supportive care, self-limited. If severe, nitazoxanide can be prescribed for all patients 1 yr of age or older</td>
</tr>
<tr>
<td>Cyclospora cayetanensis</td>
<td>1-14 days, usually at ≥1 wk</td>
<td>Diarrhea (usually watery), loss of appetite, substantial loss of weight, stomach cramps, nausea, vomiting, fatigue</td>
<td>May be remitting and relapsing over weeks to months</td>
<td>Various types of fresh produce (imported berries, lettuce)</td>
<td>Request specific examination of the stool for <em>Cyclospora</em>. May need to examine <em>Cyclospora</em> May need to examine water or food</td>
<td>TMP-SMX for 7 days</td>
</tr>
<tr>
<td>Entamoeba histolytica</td>
<td>2-3 days-1-4 wk</td>
<td>Diarrhea (often bloody), frequent bowel movements, lower abdominal pain</td>
<td>May be protracted (several weeks to several months)</td>
<td>Any uncooked food or food contaminated by an ill food handler after cooking; drinking water</td>
<td>Examination of fresh stool for cysts and parasites; may need at least 3 samples Serology for long-term infections</td>
<td>For asymptomatic infections, paromomycin and iodoquinol are the drugs of choice. For symptomatic intestinal disease or extraintestinal infections (e.g., hepatic abscess), the drugs of choice are metronidazole and tinidazole, immediately followed by treatment with paromomycin or iodoquinol</td>
</tr>
<tr>
<td>Pathogen</td>
<td>Incubation</td>
<td>Signs and Symptoms</td>
<td>Duration of Illness</td>
<td>Etiology</td>
<td>Treatment and Diagnostics</td>
<td></td>
</tr>
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</tr>
<tr>
<td>Giardia lamblia</td>
<td>1-2 wk</td>
<td>Diarrhea, stomach cramps, gas, weight loss</td>
<td>Days to weeks</td>
<td>Any uncooked food or food contaminated by an ill food handler after cooking; drinking water</td>
<td>Examination of stool for ova and parasites; may need at least 3 samples</td>
<td></td>
</tr>
<tr>
<td>Toxoplasma gondii</td>
<td>5-23 days</td>
<td>Generally asymptomatic, 20% develop cervical lymphadenopathy and/or a flu-like illness</td>
<td>Months</td>
<td>Accidental ingestion of contaminated substances (e.g., soil contaminated with cat feces on fruits and vegetables), raw or partially cooked meat (especially pork, lamb, and venison)</td>
<td>The diagnosis of toxoplasmosis is typically made by serologic testing. However, IgM antibodies can persist for 6-18 mo and thus do not necessarily indicate recent infection. PCR of bodily fluids. Diagnosis can also be made by isolation of parasites from blood or other body fluids; observation of parasites in patient specimens via microscopy or histology. Detection of organisms is rare. Asymptomatic healthy, but infected, persons do not require treatment. Spiramycin or pyrimethamine plus sulfadiazine may be used for pregnant women. Pyrimethamine plus sulfadiazine may be used for immunocompromised persons, in specific cases. Pyrimethamine plus sulfadiazine (with or without steroids) may be given for ocular disease when indicated. Folinic acid is given with pyrimethamine plus sulfadiazine to counteract bone marrow suppression.</td>
<td></td>
</tr>
<tr>
<td>Toxoplasma gondii (congenital infection)</td>
<td>In infants at birth</td>
<td>Treatment of the mother can reduce severity and/or incidence of congenital infection. Most infected infants have few symptoms at birth; later, they generally develop signs of congenital toxoplasmosis (mental retardation, severely impaired eyesight, cerebral palsy, seizures), unless the infection is treated.</td>
<td>Months</td>
<td>Passed from mother (who acquired acute infection during pregnancy) to child</td>
<td>Isolation of T. gondii from placenta, umbilical cord, or infant blood; PCR of white blood cells, CSF, or amniotic fluid, or IgM and IgA serology, performed by a reference laboratory.</td>
<td></td>
</tr>
<tr>
<td>Trichinella spiralis</td>
<td>1-2 days for initial symptoms; others begin 2-8 wk after infection</td>
<td>Acute: nausea, diarrhea, vomiting, fatigue, fever, abdominal discomfort followed by muscle soreness, weakness, and occasional cardiac and neurologic complications</td>
<td>Months</td>
<td>Raw or undercooked contaminated meat, usually pork or wild game meat (e.g., bear or moose)</td>
<td>Positive serology or demonstration of larvae via muscle biopsy; increase in eosinophils. Supportive care plus mebendazole or albendazole. In addition to antiparasitic medication, treatment with steroids is sometimes required in more severe cases.</td>
<td></td>
</tr>
</tbody>
</table>

CNS, central nervous system; CSF, cerebrospinal fluid; ELISA, enzyme-linked immunosorbent assay; IgA, immunoglobulin A; IgM, immunoglobulin M; PCR, polymerase chain reaction; TMP-SMX, trimethoprim-sulfamethoxazole.

<table>
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</tr>
</thead>
<tbody>
<tr>
<td>Antimony</td>
<td>5 min–8 hr usually &lt;1 hr</td>
<td>Vomiting, metallic taste</td>
<td>Usually self-limited</td>
<td>Metallic container</td>
<td>Identification of metal in beverage or food</td>
<td>Supportive care</td>
</tr>
<tr>
<td>Arsenic</td>
<td>Few hours</td>
<td>Vomiting, colic, diarrhea</td>
<td>Several days</td>
<td>Contaminated food</td>
<td>Urine; Can cause eosinophilia</td>
<td>Gastric lavage, BAL (dimercaprol)</td>
</tr>
<tr>
<td>Cadmium</td>
<td>5 min–8 hr usually &lt;1 hr</td>
<td>Nausea, vomiting, myalgia, increase in salivation, stomach pain</td>
<td>Usually self-limited</td>
<td>Seafood, oysters, clams, lobster, grains, peanuts</td>
<td>Identification of metal in food</td>
<td>Supportive care</td>
</tr>
<tr>
<td>Ciguatera fish poisoning (ciguatera toxin)</td>
<td>2-6 hr</td>
<td>GI: abdominal pain, nausea, vomiting, diarrhea</td>
<td>Days to weeks to months</td>
<td>A variety of large reef fish: grouper, red snapper, amberjack, and barracuda (most common)</td>
<td>Radioassay for toxin in fish or a consistent history</td>
<td>Supportive care, IV mannitol Children more vulnerable</td>
</tr>
<tr>
<td></td>
<td>3 hr</td>
<td>Neurologic: paresthesias, reversal of hot or cold, pain, weakness, Cardiovascular: bradycardia, hypotension, increase in T-wave abnormalities</td>
<td></td>
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<tr>
<td></td>
<td>2-5 days</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Copper</td>
<td>5 min–8 hr usually &lt;1 hr</td>
<td>Nausea, vomiting, blue or green vomitus</td>
<td>Usually self-limited</td>
<td>Metallic container</td>
<td>Identification of metal in beverage or food</td>
<td>Supportive care</td>
</tr>
<tr>
<td>Mercury</td>
<td>1 wk or longer</td>
<td>Numbness, weakness of legs, spastic paralysis, impaired vision, blindness, coma</td>
<td>May be protracted</td>
<td>Fish exposed to organic mercury, grains treated with mercury fungicides</td>
<td>Analysis of blood, hair</td>
<td>Supportive care</td>
</tr>
<tr>
<td>Mushroom toxins, short-acting (muscimol, muscarine, psilocybin, Coprinus atramentaria, ibotenic acid)</td>
<td>&lt;2 hr</td>
<td>Vomiting, diarrhea, confusion, visual disturbance, salivation, diaphoresis, hallucinations, disulfiram-like reaction, confusion, visual disturbance</td>
<td>Self-limited</td>
<td>Wild mushrooms (cooking might not destroy these toxins)</td>
<td>Typical syndrome and mushroom identified or demonstration of the toxin</td>
<td>Supportive care</td>
</tr>
<tr>
<td>Mushroom toxins, long-acting (amanitin)</td>
<td>4-8 hr diarrhea; 24-48 hr liver failure</td>
<td>Diarrhea, abdominal cramps, leading to hepatic and renal failure</td>
<td>Often fatal</td>
<td>Mushrooms</td>
<td>Typical syndrome and mushroom identified and/or demonstration of the toxin</td>
<td>Supportive care, life-threatening, may need life support</td>
</tr>
<tr>
<td>Nitrite poisoning</td>
<td>1-2 hr</td>
<td>Nausea, vomiting, cyanosis, headache, dizziness, weakness, loss of consciousness, chocolate-brown blood</td>
<td>Usually self-limited</td>
<td>Cured meats, any contaminated foods, spinach exposed to excessive nitrification</td>
<td>Analysis of the food, blood</td>
<td>Supportive care, methylene blue</td>
</tr>
</tbody>
</table>

**Table 340-4: Foodborne Noninfectious Illnesses**

**ETIOLOGY**
- Antimony
- Arsenic
- Cadmium
- Ciguatera fish poisoning (ciguatera toxin)
- Copper
- Mercury
- Mushroom toxins, short-acting (muscimol, muscarine, psilocybin, Coprinus atramentaria, ibotenic acid)
- Mushroom toxins, long-acting (amanitin)
- Nitrite poisoning

**INCUBATION PERIOD**
- 5 min–8 hr usually <1 hr
- Few hours
- 5 min–8 hr usually <1 hr
- 2-6 hr
- 3 hr
- 2-5 days
- 5 min–8 hr usually <1 hr
- 1 wk or longer
- <2 hr
- 4-8 hr diarrhea; 24-48 hr liver failure
- 1-2 hr

**SIGNS AND SYMPTOMS**
- Vomiting, metallic taste
- Vomiting, colic, diarrhea
- Nausea, vomiting, myalgia, increase in salivation, stomach pain
- GI: abdominal pain, nausea, vomiting, diarrhea
- Neurologic: paresthesias, reversal of hot or cold, pain, weakness
- Nausea, vomiting, blue or green vomitus
- Numbness, weakness of legs, spastic paralysis, impaired vision, blindness, coma
- Nausea, vomiting, confusion, visual disturbance, salivation, diaphoresis, hallucinations, disulfiram-like reaction, confusion, visual disturbance
- Nausea, vomiting, cyanosis, headache, dizziness, weakness, loss of consciousness, chocolate-brown blood

**DURATION OF ILLNESS**
- Usually self-limited
- Several days
- Usually self-limited
- Days to weeks to months
- May be protracted
- Self-limited
- Often fatal
- Usually self-limited

**ASSOCIATED FOODS**
- Metallic container
- Contaminated food
- Seafood, oysters, clams, lobster, grains, peanuts
- A variety of large reef fish: grouper, red snapper, amberjack, and barracuda (most common)
- Metallic container
- Fish exposed to organic mercury, grains treated with mercury fungicides
- Wild mushrooms (cooking might not destroy these toxins)
- Mushrooms
- Cured meats, any contaminated foods, spinach exposed to excessive nitrification

**LABORATORY TESTING**
- Identification of metal in beverage or food
- Identification of metal in food
- Radioassay for toxin in fish or a consistent history
- Typical syndrome and mushroom identified or demonstration of the toxin
- Analysis of blood, hair
- Typical syndrome and mushroom identified and/or demonstration of the toxin
- Analysis of the food, blood

**TREATMENT**
- Supportive care
- Supportive care, IV mannitol Children more vulnerable
- Supportive care
- Supportive care
- Supportive care
- Supportive care
- Supportive care

**Notes:**
- BAL, bronchoalveolar lavage; GI, gastrointestinal.
- From Centers for Disease Control and Prevention: Diagnosis and management of foodborne illnesses, MMWR.
<table>
<thead>
<tr>
<th>Poison</th>
<th>Symptoms/Signs</th>
<th>Duration</th>
<th>Associated Foods</th>
<th>Testing/Diagnosis</th>
<th>Supportive Care</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pesticides (organophosphates or carbamates)</td>
<td>Nausea, vomiting, abdominal cramps, diarrhea, headache, nervousness, blurred vision, twitching, convulsions, salvation, meiosis</td>
<td>Usually self-limited</td>
<td>Any contaminated food</td>
<td>Analysis of the food, blood</td>
<td>Atropine; 2-PAM (pralidoxime) is used when atropine is not able to control symptoms; rarely necessary in carbamate poisoning</td>
</tr>
<tr>
<td>Puffer fish (tetrodotoxin)</td>
<td>Paresthesias, vomiting, diarrhea, abdominal pain, ascending paralysis, respiratory failure</td>
<td>Death usually in 4-6 hr</td>
<td>Puffer fish</td>
<td>Detection of tetrodotoxin in fish</td>
<td>Life-threatening, may need respiratory support</td>
</tr>
<tr>
<td>Scombroid (histamine)</td>
<td>Flushing, rash, burning sensation of skin, mouth and throat, dizziness, urticaria, paresthesias</td>
<td>3-6 hr</td>
<td>Fish: bluefin, tuna, skipjack, mackerel, marlin, escolar, and mahi mahi</td>
<td>Demonstration of histamine in food or clinical diagnosis</td>
<td>Supportive care, antihistamines</td>
</tr>
<tr>
<td>Shellfish toxins (diarrheic, neurotoxic, amnesic)</td>
<td>Nausea, vomiting, diarrhea, and abdominal pain accompanied by chills, headache, and fever</td>
<td>hr to 2-3 days</td>
<td>A variety of shellfish, primarily mussels, oysters, scallops, and shellfish from the Florida coast and the Gulf of Mexico</td>
<td>Detection of the toxin in shellfish; high-pressure liquid chromatography</td>
<td>Supportive care, generally self-limiting</td>
</tr>
<tr>
<td>Shellfish toxins (paralytic shellfish poisoning)</td>
<td>Nausea, vomiting, diarrhea leading to paresthesias of mouth and lips, weakness, dysphasia, dysphonia, respiratory paralysis</td>
<td>Days</td>
<td>Scallops, mussels, clams, cockles</td>
<td>Detection of toxin in food or water where fish are located; high-pressure liquid chromatography</td>
<td>Life-threatening, may need respiratory support</td>
</tr>
<tr>
<td>Sodium fluoride</td>
<td>Salty or soapy taste, numbness of mouth, vomiting, diarrhea, dilated pupils, spasms, pallor, shock, collapse</td>
<td>Usually self-limited</td>
<td>Dry foods (e.g., dry milk, flour, baking powder, cake mixes) contaminated with NaF-containing insecticides and rodenticides</td>
<td>Testing of vomitus or gastric washings</td>
<td>Supportive care</td>
</tr>
<tr>
<td>Thallium</td>
<td>Nausea, vomiting, diarrhea, painful paresthesias, motor polyneuropathy, hair loss</td>
<td>Several days</td>
<td>Contaminated food</td>
<td>Urine, hair</td>
<td>Supportive care</td>
</tr>
<tr>
<td>Tin</td>
<td>Nausea, vomiting, diarrhea</td>
<td>Usually self-limited</td>
<td>Metallic container</td>
<td>Analysis of the food</td>
<td>Supportive care</td>
</tr>
<tr>
<td>Vomitoxin</td>
<td>Nausea, headache, abdominal pain, vomiting</td>
<td>Usually self-limited</td>
<td>Grains such as wheat, corn, barley</td>
<td>Analysis of the food</td>
<td>Supportive care</td>
</tr>
<tr>
<td>Zinc</td>
<td>Stomach cramps, nausea, vomiting, diarrhea, myalgias</td>
<td>Usually self-limited</td>
<td>Metallic container</td>
<td>Analysis of the food, blood and feces, saliva or urine</td>
<td>Supportive care</td>
</tr>
</tbody>
</table>

BAL: bronchoalveolar lavage; GI: gastrointestinal.

*From Centers for Disease Control and Prevention: Diagnosis and management of foodborne illnesses, MMWR 53(RR-4):1-33, 2004.*
Part XVIII ♦ The Digestive System

1864

The Digestive System

vitamin A deficiency, and accounts for 157,000 deaths from diarrhea, measles, and malaria. Zinc deficiency is estimated to cause 116,000 deaths from diarrhea and pneumonia. Table 340-7 summarizes some of the key risk factors associated with childhood diarrhea globally.

The majority of cases of diarrhea resolve within the 1st wk of the illness. A smaller proportion of diarrheal illnesses fail to resolve and persist for longer than 2 wk. Persistent diarrhea is defined as episodes that began acutely but last for 14 or more days. Such episodes account for 3-19% of all diarrheal episodes in children younger than 5 yr of age and up to 50% of all diarrhea-related deaths; persistent diarrhea has a case fatality rate of 60%. Many children (especially infants and toddlers) in developing countries have frequent episodes of acute diarrhea. Although few individual episodes persist beyond 14 days, frequent episodes of acute diarrhea, as well as prolonged diarrhea (lasting between 7-13 days of age), can result in nutritional compromise and can predispose these children to develop persistent diarrhea, protein-calorie malnutrition, and secondary infections.

Figure 340-1 Attributable incidence of pathogen-specific moderate-to-severe diarrhea per 100 child-yr by age stratum, all sites combined. The bars show the incidence rates and the error bars show the 95% confidence intervals. (From Kotloff KL, Nataro JP, Blackwelder WC, et al. Burden and aetiology of diarrhoeal disease in infants and young children in developing countries [the Global Enteric Multicenter Study, GEMS]: a prospective, case-control study. Lancet 382(9888):209–222, 2013, Fig. 4.)

gastroenteritis via a superficial invasion of colonic mucosa, which they invade through M cells located over Peyer patches. After phagocytosis, a series of events occurs, including apoptosis of macrophages, multiplication and spread of bacteria into adjacent cells, release of inflammatory mediators (interleukin-1 and -8), transmigration of neutrophils into the lumen of the colon, neutrophil necrosis and degranulation, further breach of the epithelial barrier, and mucosal destruction (Fig. 340-5).

RISK FACTORS FOR GASTROENTERITIS

In developed countries, episodes of infectious diarrhea can occur through seasonal exposure to organisms such as rotavirus, or exposure to pathogens in settings of close contact (e.g., daycare centers). Major risks include environmental contamination and increased exposure to enteropathogens. Additional risks include young age, immunodeficiency, measles, malnutrition, and lack of exclusive or predominant breastfeeding. Malnutrition increases the risk of diarrhea and associated mortality, and moderate to severe stunting increases the odds of diarrhea-associated mortality. The fraction of such infectious diarrhea deaths that are attributable to nutritional deficiencies varies with the prevalence of deficiencies; the highest attributable fractions are in sub-Saharan Africa, south Asia, and Andean Latin America. The risks are particularly higher with micronutrient malnutrition; in children with vitamin A deficiency, and accounts for 157,000 deaths from diarrhea, measles, and malaria. Zinc deficiency is estimated to cause 116,000 deaths from diarrhea and pneumonia. Table 340-7 summarizes some of the key risk factors associated with childhood diarrhea globally.

The majority of cases of diarrhea resolve within the 1st wk of the illness. A smaller proportion of diarrheal illnesses fail to resolve and persist for longer than 2 wk. Persistent diarrhea is defined as episodes that began acutely but last for 14 or more days. Such episodes account for 3-19% of all diarrheal episodes in children younger than 5 yr of age and up to 50% of all diarrhea-related deaths; persistent diarrhea has a case fatality rate of 60%. Many children (especially infants and toddlers) in developing countries have frequent episodes of acute diarrhea. Although few individual episodes persist beyond 14 days, frequent episodes of acute diarrhea, as well as prolonged diarrhea (lasting between 7-13 days of age), can result in nutritional compromise and can predispose these children to develop persistent diarrhea, protein-calorie malnutrition, and secondary infections.

CLINICAL MANIFESTATION OF DIARRHEA

Most of the clinical manifestations and clinical syndromes of diarrhea are related to the infecting pathogen and the dose or inoculum (see Tables 340-1 to 340-3). Additional manifestations depend on the development of complications (e.g., dehydration and electrolyte imbalance)
## Table 340-5

Weighted Annual Incidence (Per 100 Child-Years) of Moderate-to-Severe Diarrhea Attributable to a Specific Pathogen, with 95% Confidence Interval, By Age Stratum and Country

<table>
<thead>
<tr>
<th>AGE GROUP</th>
<th>PATHOGEN</th>
<th>GAMBIA</th>
<th>MALI</th>
<th>MOZAMBIQUE</th>
<th>KENYA</th>
<th>INDIA</th>
<th>BANGLADESH</th>
<th>PAKISTAN</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;12 mo</td>
<td>VIRUSES</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Rotavirus</td>
<td>3.2 (1.7-4.6)</td>
<td>8.4 (3.5-13.3)</td>
<td>3.5 (1.5-5.4)</td>
<td>10.1 (5.4-14.8)</td>
<td>25.4 (14.7-36.2)</td>
<td>2.1 (1.0-3.2)</td>
<td>5.5 (2.6-8.5)</td>
</tr>
<tr>
<td></td>
<td>Norovirus GII</td>
<td>1.2 (0.4-2.0)</td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td></td>
<td>Adenovirus 40/41</td>
<td>0.3 (0.1-0.6)</td>
<td>0.7 (0.1-1.3)</td>
<td>0.3 (0.0-0.5)</td>
<td></td>
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</tr>
<tr>
<td>BACTERIA</td>
<td>ST-ETEC (ST-only or LT/ST)</td>
<td>0.7 (0.1-1.2)</td>
<td>1.4 (0.3-2.5)</td>
<td></td>
<td>3.6 (1.4-5.8)</td>
<td>2.8 (0.9-4.8)</td>
<td>0.2 (0.0-0.4)</td>
<td>1.7 (0.6-2.8)</td>
</tr>
<tr>
<td></td>
<td>Shigella</td>
<td>0.5 (0.2-0.9)</td>
<td></td>
<td></td>
<td>2.3 (0.8-3.8)</td>
<td>1.9 (0.4-3.3)</td>
<td>1.7 (0.8-2.6)</td>
<td>1.9 (0.8-2.9)</td>
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<tr>
<td></td>
<td>Aeromonas</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.2 (0.3-2.2)</td>
<td>2.8 (1.0-4.5)</td>
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<tr>
<td></td>
<td>Campylobacter jejuni</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>1.1 (0.1-2.2)</td>
<td>1.7 (0.0-3.3)</td>
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<tr>
<td></td>
<td>Typical EPEC</td>
<td></td>
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<tr>
<td></td>
<td>Nontyphoidal salmonella</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>0.5 (0.2-0.9)</td>
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<tr>
<td></td>
<td>Vibrio cholera O1</td>
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<tr>
<td>PROTOZOA</td>
<td>Cryptosporidium</td>
<td>1.6 (0.7-2.4)</td>
<td>5.4 (2-1.8)</td>
<td>1.8 (0.7-3.0)</td>
<td>4.6 (2.0-7.2)</td>
<td>11.1 (5.4-16.9)</td>
<td>0.7 (0.2-1.2)</td>
<td>1.4 (0.1-2.6)</td>
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<td></td>
<td>Entamoeba histolytica</td>
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<tr>
<td>12-23 mo</td>
<td>VIRUSES</td>
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<td></td>
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</tr>
<tr>
<td></td>
<td>Rotavirus</td>
<td>3.3 (1.3-5.2)</td>
<td>4.1 (1.0-7.1)</td>
<td></td>
<td>3.0 (1.6-4.3)</td>
<td>12.4 (7.1-17.7)</td>
<td>3.0 (1.1-4.9)</td>
<td>1.6 (0.6-2.7)</td>
</tr>
<tr>
<td></td>
<td>Norovirus GII</td>
<td>1.7 (0.5-2.8)</td>
<td></td>
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<tr>
<td></td>
<td>Adenovirus 40/41</td>
<td>0.4 (0.0-0.8)</td>
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<tr>
<td>BACTERIA</td>
<td>ST-ETEC (ST-only or LT/ST)</td>
<td>1.5 (0.3-2.8)</td>
<td>0.8 (0.0-1.7)</td>
<td>0.7 (0.2-1.2)</td>
<td>1.5 (0.6-2.5)</td>
<td>2.8 (1.1-4.6)</td>
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<td>0.9 (0.2-1.7)</td>
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<td>EAEC</td>
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<td>1.6 (0.0-3.2)</td>
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<tr>
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<td>Shigella</td>
<td>2.5 (0.9-4.1)</td>
<td>0.8 (0.0-1.6)</td>
<td>0.5 (0.1-0.9)</td>
<td>1.0 (0.3-1.8)</td>
<td>3.5 (1.7-5.4)</td>
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<td></td>
<td>Aeromonas</td>
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<td>1.9 (0.2-3.7)</td>
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<td>Campylobacter jejuni</td>
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<td>Typical EPEC</td>
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<td>0.5 (0.2-0.9)</td>
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<td>Vibrio cholera O1</td>
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<tr>
<td>PROTOZOA</td>
<td>Cryptosporidium</td>
<td>1.5 (0.4-2.5)</td>
<td>1.6 (0.0-3.3)</td>
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<td>2.0 (0.9-3.0)</td>
<td>4.1 (1.2-6.9)</td>
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<td>Entamoeba histolytica</td>
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<td>24–59 mo</td>
<td>VIRUSES</td>
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<td>Rotavirus</td>
<td>0.4 (0.1-0.6)</td>
<td>0.4 (0.0-3.2)</td>
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<td>0.3 (0.1-0.4)</td>
<td>3.5 (0.0-7.1)</td>
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<td>Norovirus GII</td>
<td>0.3 (0.0-0.5)</td>
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<td>Sapovirus</td>
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<td>0.8 (0.0-1.8)</td>
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<td>Adenovirus 40/41</td>
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<td>BACTERIA</td>
<td>ST-ETEC (ST-only or LT/ST)</td>
<td>0.3 (0.0-0.5)</td>
<td></td>
<td></td>
<td>0.4 (0.1-0.6)</td>
<td>1.5 (0.0-3.1)</td>
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<td>0.1 (0.0-0.3)</td>
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<td></td>
<td>EAEC</td>
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<td></td>
<td>Shigella</td>
<td>0.4 (0.1-0.7)</td>
<td>0.3 (0.0-2.9)</td>
<td>0.4 (0.0-0.9)</td>
<td>0.7 (0.4-1.1)</td>
<td>2.9 (0.0-5.9)</td>
<td>3.1 (0.0-6.3)</td>
<td>0.2 (0.0-0.4)</td>
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<tr>
<td></td>
<td>Aeromonas</td>
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<td>0.8 (0.0-1.8)</td>
<td>0.5 (0.2-0.9)</td>
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<td>Campylobacter jejuni</td>
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<td></td>
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<td></td>
<td>0.4 (0.0-0.7)</td>
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<td>Typical EPEC</td>
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<tr>
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<td>Vibrio cholera O1</td>
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<tr>
<td>PROTOZOA</td>
<td>Cryptosporidium</td>
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</tr>
<tr>
<td></td>
<td>Entamoeba histolytica</td>
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</tr>
</tbody>
</table>

EAEC, enteroadherent *Escherichia coli*; EPEC, enteropathogenic *Escherichia coli*; ETEC, enterotoxigenic *Escherichia coli*; LT, heat-labile; ST, heat stable.
### Table 340-6 Comparison of 3 Types of Enteric Infection

<table>
<thead>
<tr>
<th>PARAMETER</th>
<th>TYPE OF INFECTION</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>I</td>
</tr>
<tr>
<td>Mechanism</td>
<td>Noninflammatory (enterotoxin or adherence/superficial invasion)</td>
</tr>
<tr>
<td>Location</td>
<td>Proximal small bowel</td>
</tr>
<tr>
<td>Illness</td>
<td>Watery diarrhea</td>
</tr>
<tr>
<td>Stool examination</td>
<td>No fecal leukocytes</td>
</tr>
<tr>
<td></td>
<td>Mild or no ↑ lactoferrin</td>
</tr>
<tr>
<td>Examples</td>
<td><em>Vibrio cholerae</em></td>
</tr>
<tr>
<td></td>
<td><em>Escherichia coli</em> (ETEC, LT, ST)</td>
</tr>
<tr>
<td></td>
<td><em>Clostridium perfringens</em></td>
</tr>
<tr>
<td></td>
<td><em>Bacillus cereus</em></td>
</tr>
<tr>
<td></td>
<td><em>Staphylococcus aureus</em></td>
</tr>
<tr>
<td></td>
<td><em>Also</em>‡</td>
</tr>
<tr>
<td></td>
<td><em>Giardia lamblia</em></td>
</tr>
<tr>
<td></td>
<td><em>Rotavirus</em></td>
</tr>
<tr>
<td></td>
<td><em>Norwalk-like viruses</em></td>
</tr>
<tr>
<td></td>
<td><em>Cryptosporidium parvum</em></td>
</tr>
<tr>
<td></td>
<td><em>E. coli</em> (EPEC, EAEC)</td>
</tr>
<tr>
<td></td>
<td><em>Microsporidia</em></td>
</tr>
<tr>
<td></td>
<td><em>Cyclospora cayetanensis</em></td>
</tr>
<tr>
<td></td>
<td><em>Shigella</em></td>
</tr>
<tr>
<td></td>
<td><em>E. coli</em> (EIEC, EHEC)</td>
</tr>
<tr>
<td></td>
<td><em>Salmonella enteritidis</em></td>
</tr>
<tr>
<td></td>
<td><em>Vibrio parahaemolyticus</em></td>
</tr>
<tr>
<td></td>
<td><em>Clostridium difficile</em></td>
</tr>
<tr>
<td></td>
<td><em>Campylobacter jejuni</em></td>
</tr>
<tr>
<td></td>
<td><em>Entamoeba histolytica</em></td>
</tr>
</tbody>
</table>

*Although amebic dysentery involves tissue inflammation, the leukocytes are characteristically pyknotic or absent, having been destroyed by the virulent amebae.

‡ Although not typically enterotoxigenic, these pathogens alter bowel physiology via adherence, superficial cell entry, cytokine induction, or toxins that inhibit cell function.

EAEC, enteraggregative E. coli; EHEC, enterohemorrhagic E. coli; EIEC, enteroinvasive E. coli; EPEC, enteropathogenic E. coli; ETEC, enterotoxigenic E. coli; LT, heat-labile; ST, heat-stable.


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**Figure 340-2 Pathogenesis of rotavirus infection and diarrhea.** ENS, enteric nervous system; ER, endoplasmic reticulum; PLC, phospholipase C; TJ, tight junction. (Adapted from Ramig RF: Pathogenesis of intestinal and systemic rotavirus infection, J Virol 78:10213–10220, 2004.)

**Figure 340-4** Movement of Na\(^+\) and Cl\(^-\) in the small intestine. **A**, Movement in normal subjects. Na\(^+\) is absorbed by 2 different mechanisms in absorptive cells from villi: glucose-stimulated absorption and electroneutral absorption (which represents the coupling of Na\(^+\)/H\(^+\) and Cl\(^-\)/HCO\(_3\)\(^-\) exchanges). **B**, Movement during diarrhea caused by a toxin and inflammation. (From Petri WA, Miller M, Binder HJ, et al: Enteric infections, diarrhea and their impact on function and development, J Clin Invest 118:1277–1290, 2008.)

and the nature of the infecting pathogen (Table 340-8). Usually the ingestion of preformed toxins (e.g., those of S. aureus) is associated with the rapid onset of nausea and vomiting within 6 hr, with possible fever, abdominal cramps, and diarrhea within 8-72 hr. Watery diarrhea and abdominal cramps after an 8-16 hr incubation period are associated with enterotoxin-producing C. perfringens and B. cereus. Abdominal cramps and watery diarrhea after a 16-48 hr incubation period can be associated with noroviruses, several enterotoxin-producing bacteria, Cryptosporidium, and Cyclospora, and also have been a notable feature of influenza virus H1N1 infections. Several organisms, including Salmonella, Shigella, C. jejuni, Yersinia enterocolitica, enteroinvasive or hemorrhagic (Shigatoxin-producing) E. coli, and V. parahaemolyticus, produce diarrhea that can contain blood as well as fecal leukocytes in association with abdominal cramps, tenesmus, and fever; these features suggest bacterial dysentery and fever (Table 340-8). Bloody diarrhea and abdominal cramps after a 72-120 hr incubation period are associated with infections from Shigella and also Shigatoxin-producing E. coli, such as E. coli O157:H7. Organisms associated with dysentery or hemorrhagic diarrhea can also cause watery diarrhea alone without fever or that precedes a more complicated course that results in dysentery.

Although many of the manifestations of acute gastroenteritis in children are nonspecific, some clinical features can help identify major categories of diarrhea and allow rapid triage for antibiotic or specific dietary therapy (see Tables 340-1 to 340-4). There is considerable overlap in the symptomatology. The positive predictive values for the features of dysentery are very poor; the negative predictability for bacterial pathogens is much better in the absence of signs of dysentery. If warranted and if facilities and resources permit, the etiology can be verified by appropriate laboratory testing.

### Table 340-7 Proven Risk Factors with Direct Biologic Links to Diarrhea: Relative Risks (RR) or Odds Ratios (OR) and 95% Confidence Intervals

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Relative Risk</th>
<th>Odds Ratio</th>
<th>95% Confidence Intervals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lack of exclusive breastfeeding (0-5 mo)</td>
<td>RR = 2.65 (1.72-4.07)</td>
<td>compared to not breastfed infants</td>
<td></td>
</tr>
<tr>
<td>No breastfeeding (6-23 mo)</td>
<td>RR = 1.32 (1.06-1.63)</td>
<td>compared to not breastfed infants</td>
<td></td>
</tr>
<tr>
<td>Underweight (WAZ)</td>
<td>RR = 1.23 (1.12-1.35)</td>
<td>OR = 2.1 (1.6)</td>
<td></td>
</tr>
<tr>
<td>Stunted (HAZ)</td>
<td>OR = 1.2 (0.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wasted (WHZ)</td>
<td>OR = 1.2 (0.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitamin A deficiency</td>
<td>Inconsistent evidence</td>
<td>RR = 1.47 (1.25-175)</td>
<td></td>
</tr>
<tr>
<td>Zinc deficiency</td>
<td>RR = 0.87 (0.81-0.94)</td>
<td>RR = 0.82 (0.64-1.05)</td>
<td></td>
</tr>
<tr>
<td>Crowding (&gt;8 persons/kitchen)</td>
<td>Indoor air pollution</td>
<td>Unwashed hands</td>
<td>Poor water quality</td>
</tr>
<tr>
<td>Indoor air pollution</td>
<td>RR = 0.58 (0.49-0.69)</td>
<td>Risk relationship suggested but studies of poor methodologic quality</td>
<td></td>
</tr>
<tr>
<td>Poor water quality</td>
<td>RR = 0.73 (0.53-1.01)</td>
<td>Inconsistent evidence from blinded studies</td>
<td></td>
</tr>
<tr>
<td>Inappropriate excreta disposal</td>
<td>Limited evidence suggests risk relationship</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

HAZ, height-for-age Z-score; WAZ, weight-for-age Z score; WHZ, weight-for-height Z-score.


### Complications

Most of the complications associated with gastroenteritis are related to delays in diagnosis and delays in the institution of appropriate therapy. Without early and appropriate rehydration, many children with acute diarrhea would develop dehydration with associated complications (see Chapter 57). These can be life-threatening in infants and young children. Inappropriate therapy can lead to prolongation of the diarrheal episodes, with consequent malnutrition and complications such as secondary infections and micronutrient deficiencies (iron, zinc, vitamin A). In developing countries and HIV-infected populations, associated bacteremias are well-recognized complications in malnourished children with diarrhea.

Specific pathogens are associated with extraintestinal manifestations and complications. These are not pathognomonic of the infection, nor do they always occur in close temporal association with the diarrheal episode (Table 340-9).

### Diagnosis

The diagnosis of gastroenteritis is based on clinical recognition, an evaluation of its severity by rapid assessment and by confirmation by appropriate laboratory investigations, if indicated.
Clinical Evaluation of Diarrhea

The most common manifestations of gastrointestinal tract infection in children are diarrhea, abdominal cramps, and vomiting. Systemic manifestations are varied and associated with a variety of causes. The evaluation of a child with acute diarrhea includes:

- Assessing the degree of dehydration and acidosis and providing rapid resuscitation and rehydration with oral or intravenous fluids as required (Tables 340-10 and 340-11).
- Obtaining appropriate contact, travel, or exposure history. This includes information on exposure to contacts with similar symptoms, intake of contaminated foods or water, child-care center attendance, recent travel of patient or contact with a person who traveled to a diarrhea-endemic area, and use of antimicrobial agents.
- Clinically determining the etiology of diarrhea for institution of prompt antibiotic therapy, if indicated.

Although nausea and vomiting are nonspecific symptoms, they indicate infection in the upper intestine. Fever suggests an inflammatory process but also occurs as a result of dehydration or coinfection (e.g., urinary tract infection, otitis media). Fever is common in patients with inflammatory diarrhea. Severe abdominal pain and tenesmus indicate involvement of the large intestine and rectum. Features such as nausea and vomiting and absent or low-grade fever with mild to moderate periumbilical pain and watery diarrhea indicate small intestine involvement and also reduce the likelihood of a serious bacterial infection.

This clinical approach to the diagnosis and management of diarrhea in young children is a critical component of the Integrated Manage-

**Table 340-8** Differential Diagnosis of Acute Dysentery and Inflammatory Enterocolitis

<table>
<thead>
<tr>
<th>SPECIFIC INFECTIOUS PROCESSES</th>
<th>PROCTITIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacillary dysentery (Shigella flexneri, Shigella sonnei, Shigella boydii; invasive Escherichia coli)</td>
<td>Gonococcal (Neisseria gonorrhoeae)</td>
</tr>
<tr>
<td>Campylobacteriosis (Campylobacter jejuni)</td>
<td>Herpetic (herpes simplex virus)</td>
</tr>
<tr>
<td>Amebic dysentery (Entamoeba histolytica)</td>
<td>Chlamydial (Chlamydia trachomatis)</td>
</tr>
<tr>
<td>Ciliary dysentery (Balantidium coli)</td>
<td>Syphilitic (Treponema pallidum)</td>
</tr>
<tr>
<td>Bilharzial dysentery (Schistosoma japonicum, Schistosoma mansoni)</td>
<td>OTHER SYNDROMES</td>
</tr>
<tr>
<td>Other parasitic infections (Trichinella spiralis)</td>
<td>Necrotizing enterocolitis of the newborn</td>
</tr>
<tr>
<td>Vibrosis (Vibrio parahaemolyticus)</td>
<td>Enteritis necroticans</td>
</tr>
<tr>
<td>Salmonellosis (Salmonella typhimurium)</td>
<td>Pseudomembranous enterocolitis (Clostridium difficile)</td>
</tr>
<tr>
<td>Typhoid fever (Salmonella typhi)</td>
<td>Typhilitis</td>
</tr>
<tr>
<td>Enterc fever (Salmonella choleraesuis, Salmonella paratyphi)</td>
<td>CHRONIC INFLAMMATORY PROCESSES</td>
</tr>
<tr>
<td>Yersiniosis (Yersinia enterocolitica)</td>
<td>Enteropathogenic and enteroaggregative E. coli</td>
</tr>
<tr>
<td>Spirill dysentery (Spirillum spp.)</td>
<td>Gastrointestinal tuberculosis</td>
</tr>
<tr>
<td></td>
<td>Gastrointestinal mycosis</td>
</tr>
<tr>
<td></td>
<td>Parastic enteritis</td>
</tr>
<tr>
<td>SYNDROMES WITHOUT KNOWN INFECTIOUS CAUSE</td>
<td>SYNDROMES WITH UNKNOWN INFECTIOUS CAUSE</td>
</tr>
<tr>
<td>Idiopathic ulcerative colitis</td>
<td>Crohn disease</td>
</tr>
<tr>
<td>Crohn disease</td>
<td>Radiation enteritis</td>
</tr>
<tr>
<td>Ischemic colitis</td>
<td>Ischemic enteritis</td>
</tr>
<tr>
<td>Allergic enteritis</td>
<td>Idiopathic ulcerative colitis</td>
</tr>
</tbody>
</table>


**Stool Examination**

Microscopic examination of the stool and cultures can yield important information on the etiology of diarrhea. Stool specimens could be examined for mucus, blood, and leukocytes. Fecal leukocytes indicate bacterial invasion of colonic mucosa, although some patients with shigellosis have minimal leukocytes at an early stage of infection, as do patients infected with Shigatoxin-producing E. coli and E. histolytica.

Recent advances in rapid molecular methods of diagnosis for bacterial and parasitic infections have made the role of traditional microscopy less important; however, this is still a useful test in developing countries. XTAG GPP is an FDA-approved gastrointestinal pathogen panel using multiplexed nucleic acid technology that detects Campylobacter, C. difficile, toxin A/B, E. coli 0157, enterotoxigenic E. coli, Salmonella, Shigella, Shiga-like toxin E. coli, norovirus, rotavirus A, Giardia, and Cryptosporidium. Stool cultures should be obtained as early in the course of disease as possible from children with bloody diarrhea in whom stool microscopy indicates fecal leukocytes, in outbreaks with suspected hemolytic-uremic syndrome, and in immunosuppressed children with diarrhea. Stool specimens for culture need to be transported and plated quickly; if the latter is not quickly available, specimens might need to be transported in special transport media. The yield and diagnosis of bacterial diarrhea is improved by using molecular diagnostic procedures such as real-time polymerase chain reaction. In most previously healthy children with uncomplicated watery diarrhea, no laboratory evaluation is needed except for epidemiologic purposes.

**TREATMENT**

The broad principles of management of acute gastroenteritis in children include oral rehydration therapy, enteral feeding and diet selection, zinc supplementation, and additional therapies such as probiotics.

**Oral Rehydration Therapy**

Children, especially infants, are more susceptible than adults to dehydration because of the greater basal fluid and electrolyte requirements per kg and because they are dependent on others to meet these demands. Dehydration must be evaluated rapidly and corrected in 4-6 hr according to the degree of dehydration and estimated daily requirements. A small minority of children, especially those in shock or unable to tolerate oral fluids, require initial intravenous rehydration, but oral rehydration is the preferred mode of rehydration and replacement of ongoing losses (see Tables 340-8 and 340-9). Risks associated with severe dehydration that might necessitate intravenous resuscitation include: age <6 mo; prematurity; chronic illness; fever >38°C (100.4°F) if younger than 3 mo or >39°C (102.2°F) if 3-36 mo of age; bloody diarrhea; persistent emesis; poor urine output; sunken eyes; and a depressed level of consciousness. The low-osmolality World Health Organization (WHO) oral rehydration solution (ORS) containing 75 mEq of sodium, 64 mEq of chloride, 20 mEq of potassium, and 75 mmol of glucose per liter, with total osmolality of 245 mOsm/L, is now the global standard of care and more effective than home fluids, including deionized soda beverages, fruit juices, and tea. These are not suitable for rehydration or maintenance therapy because they have inappropriately high osmolarities and low sodium concentrations. Figure 340-7 and Tables 340-10 and 340-11 outline a clinical evaluation plan and management strategy for children with moderate to severe diarrhea. Oral rehydration should be given to infants and children slowly, especially if they have emesis. It can be given initially by a dropper, teaspoon, or syringe, beginning with as little as 5 mL at a time. The volume is increased as tolerated. Replacement for emesis or stool losses is noted in Table 340-11. Oral rehydration can also be given by a nasogastric tube if needed; this is not the usual route.

Limitations to oral rehydration therapy include shock, an ileus, intussusception, carbohydrate intolerance (rare), severe emesis, and...
### Table 340-9 Extraintestinal Manifestations of Enteric Infections

<table>
<thead>
<tr>
<th>MANIFESTATION</th>
<th>ASSOCIATED ENTERIC PATHOGEN(S)</th>
<th>ONSET AND PROGNOSIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Focal infections from systemic spread of bacterial pathogens, including vulvovaginitis, urinary tract infection, endocarditis, osteomyelitis, meningitis, pneumonia, hepatitis, peritonitis, chorioamnionitis, soft-tissue infection, and septic thrombophlebitis</td>
<td>All major pathogens can cause such direct extraintestinal infections, including <em>Salmonella</em>, <em>Shigella</em>, <em>Yersinia</em>, <em>Campylobacter</em>, <em>Clostridium difficile</em></td>
<td>Onset usually during the acute infection but can occur subsequently. Prognosis depends on infection site.</td>
</tr>
<tr>
<td>Reactive arthritis</td>
<td><em>Salmonella</em>, <em>Shigella</em>, <em>Yersinia</em>, <em>Campylobacter</em>, <em>Cryptosporidium</em>, <em>C. difficile</em></td>
<td>Typically occurs 1-3 wk after infection. Relapses after reinfection can develop in 15-50% of people, but most children recover fully within 2-6 mo after the first symptoms appear.</td>
</tr>
<tr>
<td>Guillain-Barré syndrome</td>
<td><em>Campylobacter</em></td>
<td>Usually occurs a few weeks after the original infection. Prognosis is good although 15-20% may have sequelae.</td>
</tr>
<tr>
<td>Glomerulonephritis</td>
<td><em>Shigella</em>, <em>Campylobacter</em>, <em>Yersinia</em></td>
<td>Can be of sudden onset in acute, referring to a sudden attack of inflammation, or chronic, which comes on gradually. In most cases, the kidneys heal with time.</td>
</tr>
<tr>
<td>Immunoglobulin A (IgA) nephropathy</td>
<td><em>Campylobacter</em></td>
<td>Characterized by recurrent episodes of blood in the urine, this condition results from deposits of the protein IgA in the glomeruli. IgA nephropathy can progress for years with no noticeable symptoms. Men seem more likely to develop this disorder than women.</td>
</tr>
<tr>
<td>Erythema nodosum</td>
<td><em>Yersinia</em>, <em>Campylobacter</em>, <em>Salmonella</em></td>
<td>Although painful, is usually benign and more commonly seen in adolescents. Resolves with 4-6 wk.</td>
</tr>
<tr>
<td>Hemolytic uremic syndrome</td>
<td><em>Shigella dysenteriae</em> 1, <em>Escherichia coli</em> O157:H7, others</td>
<td>Sudden onset, short-term renal failure. In severe cases, renal failure requires several sessions of dialysis to take over the kidney function, but most children recover without permanent damage to their health.</td>
</tr>
<tr>
<td>Hemolytic anemia</td>
<td><em>Campylobacter</em>, <em>Yersinia</em></td>
<td>Relatively rare complication and can have a chronic course.</td>
</tr>
</tbody>
</table>


### Table 340-10 Symptoms Associated with Dehydration

<table>
<thead>
<tr>
<th>SYMPTOM</th>
<th>MINIMAL OR NO DEHYDRATION (&lt;3% LOSS OF BODY WEIGHT)</th>
<th>MILD TO MODERATE DEHYDRATION (3-9% LOSS OF BODY WEIGHT)</th>
<th>SEVERE DEHYDRATION (&gt;9% LOSS OF BODY WEIGHT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mental status</td>
<td>Well; alert</td>
<td>Normal, fatigued or restless, irritable</td>
<td>Apathetic, lethargic, unconscious</td>
</tr>
<tr>
<td>Thirst</td>
<td>Drinks normally; might refuse liquids</td>
<td>Thirsty; eager to drink</td>
<td>Drinks poorly; unable to drink</td>
</tr>
<tr>
<td>Heart rate</td>
<td>Normal</td>
<td>Normal to increased</td>
<td>Tachycardia, with bradycardia in most severe cases</td>
</tr>
<tr>
<td>Quality of pulses</td>
<td>Normal</td>
<td>Normal to decreased</td>
<td>Weak, thready, or impalpable</td>
</tr>
<tr>
<td>Breathing</td>
<td>Normal</td>
<td>Normal; fast</td>
<td>Deep</td>
</tr>
<tr>
<td>Eyes</td>
<td>Normal</td>
<td>Slightly sunken</td>
<td>Deeply sunken</td>
</tr>
<tr>
<td>Tears</td>
<td>Present</td>
<td>Decreased</td>
<td>Absent</td>
</tr>
<tr>
<td>Mouth and tongue</td>
<td>Moist</td>
<td>Dry</td>
<td>Parched</td>
</tr>
<tr>
<td>Skinfold</td>
<td>Instant recoil</td>
<td>Recoil in &lt;2 sec</td>
<td>Recoil in &gt;2 sec</td>
</tr>
<tr>
<td>Capillary refill</td>
<td>Normal</td>
<td>Prolonged</td>
<td>Prolonged; minimal</td>
</tr>
<tr>
<td>Extremities</td>
<td>Warm</td>
<td>Cool</td>
<td>Cold; mottled; cyanotic</td>
</tr>
<tr>
<td>Urine output</td>
<td>Normal to decreased</td>
<td>Decreased</td>
<td>Minimal</td>
</tr>
</tbody>
</table>

high stool output (>10 mL/kg/hr). Ondansetron (oral mucosal absorption preparation) reduces the incidence of emesis, thus permitting more effective oral rehydration and is well established in emergency management of acute gastroenteritis in developed countries.

**Enteral Feeding and Diet Selection**

Continued enteral feeding in diarrhea aids in recovery from the episode, and a continued age-appropriate diet after rehydration is the norm. Although intestinal brush-border surface and luminal enzymes can be affected in children with prolonged diarrhea, there is evidence that satisfactory carbohydrate, protein, and fat absorption can take place on a variety of diets. Once rehydration is complete, food should be reintroduced while oral rehydration is continued to replace ongoing losses from emesis or stools and for maintenance. Breastfeeding or nondiluted regular formula should be resumed as soon as possible. Foods with complex carbohydrates (rice, wheat, potatoes, bread, and cereals), lean meats, yogurt, fruits, and vegetables are also tolerated. Fatty foods or foods high in simple sugars (juices, carbonated sodas)

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**Table 340-11  Summary of Treatment Based on Degree of Dehydration**

<table>
<thead>
<tr>
<th>Degree of Dehydration</th>
<th>Rehydration Therapy</th>
<th>Replacement of Losses</th>
<th>Nutrition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimal or no dehydration</td>
<td>Not applicable</td>
<td>&lt;10 kg body weight: 60-120 mL ORS for each diarrheal stool or vomiting episode &gt;10 kg body weight: 120-240 mL ORS for each diarrheal stool or vomiting episode</td>
<td>Continue breastfeeding or resume age-appropriate normal diet after initial hydration, including adequate caloric intake for maintenance*</td>
</tr>
<tr>
<td>Mild to moderate dehydration</td>
<td>ORS, 50-100 mL/kg body weight over 3-4 hr</td>
<td>Same; if unable to drink, administer through nasogastric tube or administer 5% dextrose in normal saline with 20 mEq/L potassium chloride IV</td>
<td>Same</td>
</tr>
<tr>
<td>Severe dehydration</td>
<td>Lactated Ringer solution or normal saline in 20 mL/kg body weight IV until perfusion and mental status improve; then administer 100 mL/kg body weight ORS over 4 hr or 5% dextrose normal saline IV at twice maintenance fluid rates</td>
<td>Same, if unable to drink, administer through nasogastric tube or administer 5% dextrose in normal saline with 20 mEq/L potassium chloride IV</td>
<td>Same</td>
</tr>
</tbody>
</table>

*Overly restricted diets should be avoided during acute diarrheal episodes. Breastfed infants should continue to nurse ad libitum even during acute rehydration. Infants too weak to eat can be given milk or formula through a nasogastric tube. Lactose-containing formulas are usually well tolerated. If lactose malabsorption appears clinically substantial, lactose-free formulas can be used. Complex carbohydrates, fresh fruits, lean meats, yogurt, and vegetables are all recommended. Carbonated drinks or commercial juices with a high concentration of simple carbohydrates should be avoided.


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**Figure 340-6** Integrated Management of Childhood Illnesses (IMCI) protocol for the recognition and management of diarrhea in developing countries. ORS, Oral rehydration solution.
should be avoided. The usual energy density of any diet used for the therapy of diarrhea should be around 1 kcal/g, aiming to provide an energy intake of a minimum of 100 kcal/kg/day and a protein intake of 2-3 g/kg/day. In selected circumstances when adequate intake of energy-dense food is problematic, the addition of amylase to the diet through germination techniques can also be helpful.

With the exception of acute lactose intolerance in a small subgroup, most children with diarrhea are able to tolerate milk and lactose-containing diets. Withdrawal of milk and replacement with specialized (and expensive) lactose-free formulations are unnecessary. Although children with persistent diarrhea are not lactose intolerant, administration of a lactose load exceeding 5 g/kg/day may be associated with higher purging rates and treatment failure. Alternative strategies for reducing the lactose load while feeding malnourished children who have prolonged diarrhea include addition of milk to cereals and replacement of milk with fermented milk products such as yogurt.

Rarely, when dietary intolerance precludes the administration of cow’s milk–based formulations or whole milk it may be necessary to administer specialized milk-free diets such as a comminuted or blended chicken-based diet or an elemental formulation. Although effective in some settings, the latter are unaffordable in most developing countries. In addition to rice-lentil formulations, the addition of green banana or pectin to the diet has also been shown to be effective in the treatment of persistent diarrhea. Figure 340-7 gives an algorithm for managing children with prolonged diarrhea in developing countries.

Among children in low- and middle-income countries, where the dual burden of diarrhea and malnutrition is greatest and where access to proprietary formulas and specialized ingredients is limited, the use of locally available age-appropriate foods should be promoted for the majority of acute diarrhea cases. Lactose intolerance is an important complication in some cases, but even among those children for whom lactose avoidance may be necessary, nutritionally complete diets comprised of locally available ingredients can be used at least as effectively as commercial preparations or specialized ingredients. These same conclusions may also apply to the dietary management of children with persistent diarrhea, but the evidence remains limited.

**Zinc Supplementation**

Zinc supplementation in children with diarrhea in developing countries leads to reduced duration and severity of diarrhea and could potentially prevent a large proportion of cases from recurring. Zinc administration for diarrhea management can significantly reduce all-cause mortality by 46% and hospital admission by 23%. In addition to improving diarrhea recovery rates, administration of zinc in community settings leads to increased use of ORS and reduction in the inappropriate use of antimicrobials. All children older than 6 mo of age with acute diarrhea in at-risk areas should receive oral zinc (20 mg/
day) in some form for 10-14 days during and continued after diarrhea. The role of zinc in well nourished, zinc replete populations in developed countries is less certain.

**Additional Therapies**
The use of probiotic nonpathogenic bacteria for prevention and therapy of diarrhea has been successful in some settings although the evidence is inconclusive to recommend their use in all settings. In addition to restoring beneficial intestinal flora, probiotics can enhance host protective immunity such as downregulation of proinflammatory cytokines and upregulation of anti inflammatory cytokines. A variety of organisms (Lactobacillus, Bifidobacterium) have a good safety record; therapy has not been standardized and the most effective (and safe) organism has not been identified. Saccharomyces boulardii is effective in antibiotic-associated and in C. difficile diarrhea, and there is some evidence that it might prevent diarrhea in daycare centers. Lactobacillus rhamnosus GG is associated with reduced diarrheal duration and severity, which reduction is more evident in cases of childhood rotavirus diarrhea.

**Antimotility agents** (loperamide) are contraindicated in children with dysentery and probably have no role in the management of acute watery diarrhea in otherwise healthy children. Similarly, **antiemetic agents**, such as the phenothiazines, are of little value and are associated with watery diarrhea in otherwise healthy children. Similarly, with dysentery and probably have no role in the management of acute virus diarrhea.

**Antimotility agents** (loperamide) are contraindicated in children with dysentery and probably have no role in the management of acute watery diarrhea in otherwise healthy children. Similarly, **antiemetic agents**, such as the phenothiazines, are of little value and are associated with potentially serious side effects (lethargy, dystonia, malignant hyperpyrexia). Nonetheless, ondansetron is an effective and less-toxic antiemetic agent and as indicated previously, is a useful adjunct to the treatment of vomiting in ambulatory settings with reduced risk of intravenous fluid requirements and hospitalization. Because persistent vomiting can limit oral rehydration therapy, a single sublingual dose of an oral dissolvable tablet of ondansetron (4 mg 4-11 yr and 8 mg for children older than 11 yr [generally 0.2 mg/kg]) may be given. However, most children do not require specific antiemetic therapy; careful oral rehydration therapy is usually sufficient.

Racemadotril, an enkephalin inhibitor, has inconsistently been shown to reduce stool output in patients with diarrhea. Experience with this drug in children is limited, and for the average child with acute diarrhea it may be unnecessary.

**Antibiotic Therapy**
Timely antibiotic therapy in select cases of diarrhea related to bacterial infections can reduce the duration and severity of illness and prevent complications (Table 340-12). Although these agents are important to use in specific cases, their widespread and indiscriminate use leads to the development of antimicrobial resistance. Nitazoxanide, an antifungal agent, is effective in the treatment of a wide variety of pathogens, including C. parvum, G. lamblia, E. histolytica, Blastocystis hominis, C. difficile, and rotavirus.

**PREVENTION**
In many developed countries, diarrhea caused by pathogens such as C. botulinum, E. coli O157:H7, Salmonella, Shigella, V. cholerae, Cryptosporidium, and Cyclospora is a notifiable disease and, thus, contact tracing and source identification is important in preventing outbreaks.

Many developing countries struggle with huge disease burdens of diarrhea where a wider approach to diarrhea prevention may be required. Preventive strategies may be of relevance to both developed and developing countries.

**Promotion of Exclusive Breastfeeding**
Exclusive breastfeeding (administration of no other fluids or foods for the 1st 6 mo of life) is not common, especially in many developed countries. Exclusive breastfeeding protects very young infants from diarrheal disease through the promotion of passive immunity and through reduction in the intake of potentially contaminated food and water. Breast milk contains all the nutrients needed in early infancy, and when continued during diarrhea, it also diminishes the adverse impact on nutritional status. Exclusive breastfeeding for the 1st 6 mo of life is widely regarded as one of the most effective interventions to reduce the risk of premature childhood mortality and the potential to prevent 12% of all deaths of children younger than 5 yr of age.

**Improved Complementary Feeding Practices**
There is a strong inverse association between appropriate, safe complementary feeding and mortality in children age 6-11 mo; malnutrition is an independent risk for the frequency and severity of diarrheal illness. Complementary foods should be introduced at 6 mo of age, and breastfeeding should continue for up to 2 yr. Complementary foods in developing countries are generally poor in quality and often are heavily contaminated, thus predisposing to diarrhea. Contamination of complementary foods can be potentially reduced through caregivers’ education and improving home food storage. Improved vitamin A status has been shown to reduce the frequency of severe diarrhea. Vitamin A supplementation reduces all-cause childhood mortality by 25% (95% confidence interval [CI], 12-36%) and diarrhea-specific mortality by 30% (95% CI, 14-42%).

**Rotavirus Immunization**
Most infants acquire rotavirus diarrhea early in life; an effective rotavirus vaccine would have a major effect on reducing diarrhea mortality in developing countries. In 1998, a quadrivalent Rhesus rotavirus-derived vaccine was licensed in the United States but subsequently withdrawn because of an increased risk of intussusception. Subsequent development and testing of newer rotavirus vaccines have led to their introduction in most developed countries and approval by the WHO in 2009 for widespread use in developing countries. It is now clear that the introduction of these vaccines is associated with a significant reduction in severe diarrhea and associated mortality.

The institution of large-scale rotavirus vaccination programs has led to major reduction in the burden of disease and associated mortality. In an evaluation of large-scale rotavirus vaccine introduction, coverage rate of 74% was achieved in infants younger than 12 mo of age, with 41% reduction (95% CI, 36-47%) in diarrhea-related mortality. In an evaluation of the vaccine in Africa, overall protective efficacy against rotavirus gastroenteritis ranged from 49-61%, with 30% protective efficacy against all-cause severe gastroenteritis in infancy. Vaccine (live virus) associated rotavirus infection has been reported in children with severe combined immunodeficiency disease, but the vaccine has been shown to be safe in HIV-infected populations.

Other vaccines that could potentially reduce the burden of severe diarrhea and mortality in young children are vaccines against cholera, Shigella, and ETEC. Preventive use of cholera vaccines in endemic countries can reduce the risk of developing cholera by 52% (95% CI, 36-65%).

**Improved Water and Sanitary Facilities and Promotion of Personal and Domestic Hygiene**
Much of the reduction in diarrhea prevalence in the developed world is the result of improvement in standards of hygiene, sanitation, and water supply. Strikingly, an estimated 88% of all diarrheal deaths worldwide can be attributed to unsafe water, inadequate sanitation, and poor hygiene. Improving water quality can reduce the risk of diarrhea by 17%, whereas hand washing with soap and safe excreta disposal reduce the risk of diarrhea by 48% and 36%, respectively. Behavioral change strategies through promotion of handwashing indicate that handwashing promotion and access to soap reduces the burden of diarrhea in developing countries.

**Improved Case Management of Diarrhea**
Improved management of diarrhea through prompt identification and appropriate therapy significantly reduces diarrhea duration, its nutritional penalty, and risk of death in childhood. Improved management of acute diarrhea is a key factor in reducing the burden of prolonged episodes and persistent diarrhea. The WHO/UNICEF recommendations to use low-osmolality ORS and zinc supplementation for the management of diarrhea, coupled with selective and appropriate use of antibiotics, have the potential to reduce the number of diarrheal
Table 340-12  Antibiotic Therapy for Infectious Diarrhea

<table>
<thead>
<tr>
<th>ORGANISM</th>
<th>DRUG OF CHOICE</th>
<th>DOSAGE AND DURATION OF TREATMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shigella (severe dysentry and EIEC dysentery)</td>
<td>Ciprofloxacin, ampicillin, ceftriaxone, azithromycin, or TMP-SMX</td>
<td>Most strains are resistant to several antibiotics</td>
</tr>
<tr>
<td>EPEC, ETEC, EIEC</td>
<td>TMP-SMX or ciprofloxacin</td>
<td></td>
</tr>
<tr>
<td>Salmonella</td>
<td>No antibiotics for uncomplicated gastroenteritis in normal hosts caused by nontyphoidal species</td>
<td>Treatment indicated in infants younger than 3 mo, and patients with malignancy, chronic G1 disease, severe colitis hemoglobinopathies, or HIV infection, and other immunocompromised patients. Most strains are resistant to multiple antibiotics.</td>
</tr>
<tr>
<td>Aeromonas/Plesiomonas</td>
<td>TMP-SMX</td>
<td>Ciprofloxacin</td>
</tr>
<tr>
<td>Yersinia spp.</td>
<td>Erythromycin</td>
<td>Antibiotics are not usually required for diarrhea. Deferoxamine therapy should be withheld for severe infections or associated bacteremia. Treat sepsis as for immunocompromised hosts, using combination therapy with parenteral doxycycline, aminoglycoside, TMP-SMX, or fluoroquinolone.</td>
</tr>
<tr>
<td>Campylobacter jejuni</td>
<td>Erythromycin or azithromycin</td>
<td></td>
</tr>
<tr>
<td>Clostridium difficile</td>
<td>Metronidazole (first line)</td>
<td>PO 30 mg/kg/day divided qid × 5 days; max 2 g</td>
</tr>
<tr>
<td>Entamoeba histolytica</td>
<td>Vancomycin (second line)</td>
<td>PO 40 mg/kg/day qid × 7 days, max 125 mg</td>
</tr>
<tr>
<td>Giardia lamblia</td>
<td>Metronidazole followed by iodoquinol or paromomycin</td>
<td>Metronidazole PO 30-40 mg/kg/day tid × 7-10 days Iodoquinol PO 30-40 mg/kg/day tid × 20 days Paromomycin PO 25-35 mg/kg/day tid × 7 days</td>
</tr>
<tr>
<td>Cryptosporidium spp.</td>
<td>Nitazoxanide</td>
<td>PO TMP 5 mg/kg/day and SMX 25 mg/kg/day, bid × 7-10 days</td>
</tr>
<tr>
<td>Isospora spp.</td>
<td>TMP-SMX</td>
<td></td>
</tr>
<tr>
<td>Cyclospora spp.</td>
<td>Metronidazole or iodoquinol</td>
<td></td>
</tr>
</tbody>
</table>

EIEC, Enteroinvasive Escherichia coli; EPEC, enteropathogenic E. coli; ETEC, enterotoxigenic E. coli; GI, gastrointestinal; max, maximum; SMX, sulfamethoxazole; TMP, trimethoprim.

**340.1 Traveler’s Diarrhea**

**Zulfiqar Ahmed Bhutta**

Traveler’s diarrhea is a common complication of visitors to developing countries and is caused by a variety of pathogens, in part depending on the season and the region visited (see Table 340-12). Traveler’s diarrhea has a high attack rate among travelers from higher-income countries visiting, during the summer, countries in a warmer climate that have a high prevalence of indigenous infectious diarrhea. Traveler’s diarrhea can manifest with watery diarrhea or as dysentery. Without treatment, 90% will have resolved within a week and 98% within a month of onset. Some individuals develop more severe diarrhea and become dehydrated or unwell and may experience systemic complications that warrant further attention. Most cases of traveler’s diarrhea resolve spontaneously and a simple stool culture may be the only investigation required. For those individuals with ongoing symptoms, further tests should be requested depending on the history and clinical presentation.

**TREATMENT**

Traveler’s diarrhea is often self-limiting but requires particular attention to avoid dehydration. For infants and children, rehydration, as

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discussed in Chapter 340, is appropriate, followed by a standard diet. Adolescents and adults should increase their intake of electrolyte-rich fluids. Kaolin-pectin, anticholinergic agents, *Lactobacillus*, and bismuth salicylate have not been effective therapies. Loperamide, an antimotility and antisecretory agent, reduces the number of stools in older children with watery diarrhea and improves outcomes when used in combination with antibiotics in traveler’s diarrhea. However, loperamide should be used with great caution or not at all in febrile or toxic patients with dysentery and in those with bloody diarrhea.

Antibiotics, with or without loperamide, can also reduce the number of unformed stools. Short-duration (3 days) therapy with fluoroquinolones, trimethoprim-sulfamethoxazole, azithromycin, or rifaximin is effective; the choice of antibiotic depends on the age of the patient, the potential organism, and the organism’s local resistance patterns. However, antibiotics often have a negative risk-benefit ratio when weighing potential side effects vs treatment need for a short-lasting and self-limiting disease such as traveler’s diarrhea. Azithromycin has several advantages over other antibiotics. It is taken only once (1,000 mg), the rate of antimicrobial resistance is low, and it has a good safety profile. Furthermore, in contrast to rifaximin, it can be used in severe cases of diarrhea with fever or bloody stools and can even be administered in children. Optionally, azithromycin can be combined with antimotility medications such as loperamide. Travelers should be reminded that diarrhea can be a symptom of other severe diseases, such as malaria. Therefore, if diarrhea persists or additional symptoms such as fever occur, travelers should seek medical advice. For up-to-date information on local pathogens and resistant patterns, see www.cdc.gov/travel.

**PREVENTION**

Travelers should drink bottled or canned beverages or boiled water. They should avoid ice, salads, and fruit they did not peel themselves. Food should be eaten hot, if possible. Raw or poorly cooked seafood is a risk, as is eating in a restaurant rather than a private home. Swimming pools and other recreational water sites can also be contaminated.

Chemoprophylaxis is not routinely recommended for previously healthy children or adults. Nonetheless, travelers should bring azithromycin (younger than 16 yr of age) or ciprofloxacin (older than 16 yr of age) and begin antimicrobial therapy if diarrhea develops.

*Bibliography is available at Expert Consult.*
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DEFINITION AND EPIDEMIOLOGY
Chronic diarrhea is defined as stool volume of more than 10 g/kg/day in toddlers/infants and greater than 200 g/day in older children that lasts for 14 days or more. In practice, this usually means having loose or watery stools more than 3 times a day. Awakening at night to pass stool is often a sign of an organic cause of diarrhea. The epidemiology has 2 distinct patterns. In developing countries, chronic diarrhea is, in many cases, the result of an intestinal infection that persists longer than expected. This syndrome is often defined as protracted diarrhea, but there is no clear distinction between protracted and chronic diarrhea. In countries with higher socioeconomic conditions, chronic diarrhea is less frequent and the etiology often varies with age. The outcome of diarrhea depends on the cause and ranges from benign, self-limited conditions, such as toddler’s diarrhea, to severe congenital diseases, such as microvillus inclusion disease, that may lead to progressive intestinal failure.

PATHOPHYSIOLOGY
The mechanisms of diarrhea are generally divided into secretory and osmotic, but often diarrhea is a combination of both mechanisms. In addition, inflammation and motility disorders may contribute to diarrhea. Secretory diarrhea is usually associated with large volumes of watery stools and persists when oral feeding is withdrawn. Osmotic diarrhea is dependent on oral feeding, and stool volumes are usually not as massive as in secretory diarrhea (Fig. 341-1).

Secretory diarrhea is characterized by active electrolyte and water fluxes toward the intestinal lumen, resulting from either the inhibition of neutral NaCl absorption in villous enterocytes or an increase in electronegic chloride secretion in secretory crypt cells as a result of the opening of the cystic fibrosis transmembrane regulator (CFTR) chloride channel or both. The result is more secretion from the crypts than absorption in the villous that persists during fasting. The other components of the enterocyte ion secretory machinery are (1) the Na-K 2Cl cotransporter for the electroneutral chloride entrance into the enterocyte; (2) the Na-K pump, which decreases the intracellular Na+ concentration, determining the driving gradient for further Na+ influx; and (3) the K+ selective channel, that enables K+, once it has entered the cell together with Na+, to return to the extracellular fluid.

Electrogeneic secretion is induced by an increase of intracellular concentration of cyclic adenosine monophosphate, cyclic guanosine monophosphate, or calcium in response to microbial enterotoxins, or to endogenous endocrine or nonendocrine moieties, including inflammatory cytokines. Another mechanism of secretory diarrhea is the inhibition of the electroneutral NaCl-coupled pathway that involves the Na+/H+ and the Cl-/HCO3- exchangers. Defects in the genes of the Na+/H+ and the Cl-/HCO3- exchangers are responsible for congenital Na+ and Cl- diarrhea, respectively.

Osmotic diarrhea is caused by nonabsorbed nutrients in the intestinal lumen as a result of 1 or more of the following mechanisms: (1) intestinal damage (e.g., enteric infection); (2) reduced absorptive surface area (e.g., active celiac disease); (3) defective digestive enzyme or nutrient carrier (e.g., lactase deficiency); (4) decreased intestinal transit time (e.g., functional diarrhea); and (5) nutrient overload, exceeding the digestive capacity (e.g., overfeeding, sorbitol in fruit juice). Whatever the mechanism, the osmotic force generated by nonabsorbed solutes drives water into the intestinal lumen. A very common
example of osmotic diarrhea is lactose intolerance. Lactose, if not absorbed in the small intestine, reaches the colon, where it is fermented to short-chain organic acids, releasing hydrogen that is detected in the lactose breath test, and generating an osmotic overload. In many children chronic diarrhea may be caused by multiple mechanisms.

ETIOLOGY

Enteric infections are by far the most frequent cause of chronic diarrhea, both in developing and industrialized countries but, outcomes are often very different. In the former, comorbid conditions, such as HIV/AIDS, malaria, or tuberculosis, result in malnutrition that impairs the child’s immune response, thereby potentiating the likelihood of prolonging diarrhea or acquiring another enteric infection. In children with HIV/AIDS, the viral infection itself impairs immune function and may trigger a vicious circle with malnutrition. Sequential infections with the same or different pathogens may also be responsible for chronic diarrhea.

In developing countries, enterohedherent Escherichia coli and Giardia lamblia have been implicated in chronic diarrhea, whereas, in developed countries, chronic infectious diarrhea usually runs a more benign course and the etiology is often viral, with a major role of rotavirus and norovirus (Table 341-1). Opportunistic microorganisms induce diarrhea exclusively, more severely or for more prolonged periods, in specific populations, such as immunocompromised children. Specific agents cause chronic diarrhea or exacerbate diarrhea in many chronic diseases. Clostridium difficile or cytomegalovirus act as opportunistic agents in oncologic patients as well as in patients with inflammatory bowel diseases. Cryptosporidium may induce severe and protracted diarrhea in AIDS patients.

In small intestinal bacterial overgrowth, diarrhea may be the result of either a direct interaction between the microorganism and the enterocyte or the consequence of deconjugation and dehydroxylation of bile salts, and hydroxylation of fatty acids due to increased proliferation of bacteria in the proximal intestine. Postenteritis diarrhea syndrome is a clinicopathologic condition in which small intestinal mucosal damage persists after acute gastroenteritis. Sensitization to food antigens, secondary disaccharidase deficiency, persistent infections, reinfestation with an enteric pathogen, or side effects of medication may be responsible for causing postenteritis diarrhea syndrome, thought to be related to perturbations of the intestinal microbiome. Functional diarrhea which may be related to the pathogenesis of irritable bowel syndrome may be caused by complications of an acute gastroenteritis. Noninfectious chronic diarrhea is the manifestation of a broad number of heterogeneous conditions that vary with the age of the patient (Table 341-2; see also Table 336-5).

Table 341-1

A Comparative List of Prevalent Agents and Conditions in Children with Persistent Infectious Diarrhea in Industrialized and Developing Countries

<table>
<thead>
<tr>
<th>AGENT/DISEASE</th>
<th>INDUSTRIALIZED COUNTRIES</th>
<th>DEVELOPING COUNTRIES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clostridium difficile</td>
<td>Enterohedherent E. coli</td>
<td>Enterohedherent E. coli</td>
</tr>
<tr>
<td>Enteroaggregative Escherichia coli</td>
<td>Typical E. coli</td>
<td>Shigella</td>
</tr>
<tr>
<td>Postenteritis diarrhea syndrome</td>
<td>Enterotoxin-producing E. coli</td>
<td></td>
</tr>
<tr>
<td>Astrovirus</td>
<td>Rotavirus*</td>
<td></td>
</tr>
<tr>
<td>Norovirus</td>
<td>Cryptosporidium</td>
<td></td>
</tr>
<tr>
<td>Rotavirus*</td>
<td>Giardia lamblia</td>
<td></td>
</tr>
<tr>
<td>Small intestinal bacterial overgrowth (SIBO)</td>
<td>Tropical sprue</td>
<td></td>
</tr>
</tbody>
</table>

*More frequent in industrialized than in developing countries as agent of chronic diarrhea.

A reduction of intestinal absorptive surface is responsible for diarrhea in celiac disease, a genetically determined permanent gluten intolerance that affects as many as 1 in 100 individuals, depending on geographic origin. In the genetically susceptible host, gliadin, the major protein of gluten, reacts with the immune system to cause villous atrophy. The reduction of functional absorptive surface area is reversible upon restriction of gluten from the diet. Celiac disease presents with more severe intestinal symptoms in younger children. Allergy to cow’s milk protein and other food proteins also may present during infancy with chronic diarrhea. Eosinophilic gastroenteritis is characterized by eosinophil infiltration of the intestinal wall and is strongly associated with atopy. However, whereas diarrhea in food allergy responds to withdrawal of the responsible food, this does not always occur in eosinophilic gastroenteritis, in which immune suppression may be needed.

Lactose intolerance or carbohydrate malabsorption may be caused by a brush-border enzyme defect in lactase, sucrase-isomaltase, or to a defect in the sodium/glucose cotransporter protein (SLC5A1) that is transcribed from the SLC5A1 gene causing congenital glucose-galactose malabsorption. The result of these genetic mutations is chronic diarrhea. More commonly, lactose intolerance is secondary to lactase deficiency caused by intestinal mucosal damage. Depending on ethnicity, a progressive, age-related, loss of lactase activity may begin around age 7 yr and affects approximately 80% of the nonwhite population, and acquired hypolactasia may be responsible for chronic diarrhea in older children receiving cow’s milk (adult-type lactase deficiency).

In older children and adolescents, inflammatory bowel diseases, including Crohn disease, ulcerative colitis, and inflammatory bowel disease–undetermined, cause chronic diarrhea that is often associated with abdominal pain, elevated inflammatory markers, and increased concentrations of fecal calprotectin or lactoferrin (see Chapter 336). The age of onset of inflammatory bowel disease is broad, with rare cases described in the 1st few mo of life, but the peak incidence in childhood occurring in adolescence. The severity of the symptoms is highly variable with a pattern characterised by long periods of well-being followed by exacerbations. Growth retardation and delays in sexual maturation may precede the onset of gastrointestinal symptoms by up to 18 mo.

Chronic diarrhea may be the manifestation of malabsorption caused by exocrine pancreatic disorders. In most patients with cystic fibrosis, exocrine pancreatic insufficiency results in steatorrhea and protein malabsorption. In Shwachman-Diamond syndrome, exocrine pancreatic hypoplasia may be associated with neutropenia, bone changes, and intestinal protein-losing enteroptathy. Specific isolated pancreatic enzyme defects, such as lipase deficiency, result in fat and/or protein malabsorption. Familial pancreatitis, associated with a mutation in the trypsinogen gene, may be associated with exocrine pancreatic insufficiency and chronic diarrhea. Mutations in CFTR, CTRC, PRSS1, SPINK 1, and SPINK 5 are all associated with hereditary pancreatitis.

Liver disorders may lead to a reduction in the bile salts pool resulting in fat malabsorption. Bile acid loss may be associated with diseases affecting the terminal ileum, such as Crohn disease, or following ileal resection. In primary bile acid malabsorption, neonates and young infants present with chronic diarrhea and fat malabsorption caused by mutations of ileal bile transporter.

The most benign etiology of chronic diarrhea is nonspecific diarrhea that encompasses functional diarrhea (or toddler’s diarrhea) in children younger than 4 yr of age and irritable bowel syndrome in those 5 yr of age and older. The diseases fall under the umbrella of functional disorders, in that in older children abdominal pain is often associated with diarrhea alternating with constipation and growth and weight gain are normal.

Diarrhea may be the result from an excessive intake of fluid and carbohydrate. If the child’s fluid intake were >150 mL/kg/24 hr, fluid intake should be reduced not to exceed 90 mL/kg/24 hr. The child is often irritable in the 1st days of the fluid restriction; however, persistence results in a decrease in the stool frequency and volume. If the dietary history suggests that the child is ingesting significant amounts of fruit juice, especially apple juice, then the consumption of juice
should be decreased. Sorbitol, which is a nonabsorbable sugar, is found in apple, pear, and prune juices, and often causes diarrhea in toddlers. Moreover, apple and pear juices contain higher amounts of fructose than glucose, a feature postulated to cause diarrhea in toddlers. In older children, irritable bowel syndrome is often associated with abdominal pain and may be related to anxiety, depression, and other psychologic disturbances.

The most severe etiology of chronic diarrhea includes a number of heterogeneous congenital conditions leading to syndromes related to intractable diarrhea. This is often the result of a permanent defect in the structure or function of the enterocyte, leading to progressive, potentially irreversible intestinal failure. The main etiologies of intractable diarrhea include structural enterocyte defects, disorders of intestinal motility, immune-based disorders, short gut syndrome, and disorders without demonstrable abnormalities.

**Structural enterocyte defects** are caused by specific molecular defects responsible for early onset, severe diarrhea. In microvillus inclusion disease, microvilli are sequestered in vacuoles as a consequence of autophagocytosis because of a defect in protein trafficking disrupting enterocyte polarity (Fig. 341-2). Intestinal epithelial dysplasia (or tufting enteropathy) is caused by focal crowding of enterocytes that produce epithelial abnormalities resembling tufts (tears). Abnormal deposition of laminin and heparan sulfate proteoglycan on the basement membrane has been detected in intestinal epithelia. An abnormal intestinal distribution of αβ1 and αβ6 integrins is implicated in tufting enteropathy. These ubiquitous proteins are involved in cell–cell and cell–matrix interactions, and play a crucial role in cell development and differentiation.

**Table 341-2 Main Etiologies of Noninfectious Chronic Diarrhea in Children Older and Younger Than 2 Yr of Age**

<table>
<thead>
<tr>
<th>ETIOLOGY</th>
<th>YOUNGER THAN 2 YR</th>
<th>OLDER THAN 2 YR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abnormal digestive processes</td>
<td>Shwachman-Diamond syndrome, isolated pancreatic enzyme deficiency, chronic pancreatitis, Johanson-Blizzard syndrome, Pearson syndrome. Trypsinogen and enterokinase deficiency: chronic cholestasis; use of bile acids sequestrants; primary bile acid malabsorption</td>
<td>Cystic fibrosis, terminal ileum resection</td>
</tr>
<tr>
<td>Nutrient malabsorption</td>
<td>Congenital sucrase-isomaltase deficiency; congenital lactase deficiency; glucose-galactose malabsorption; fructose malabsorption; congenital short bowel</td>
<td>Hypoalactasia; acquired short bowel</td>
</tr>
<tr>
<td>Immune/inflammatory</td>
<td>Food allergy; autoimmune enteropathy; primary and secondary immunodeficiencies; IPEX syndrome</td>
<td>Celiac disease; eosinophilic gastroenteritis, inflammatory bowel diseases</td>
</tr>
<tr>
<td>Structural defects</td>
<td>Microvillus inclusion disease, tufting enteropathy, phenotypic diarrhea, heparan-sulphate deficiency, αβ1 and αβ6 integrin deficiency, lymphangiectasia, enteric anendocrinosis (neurogenin-3 mutation)</td>
<td>Rare</td>
</tr>
<tr>
<td>Defects of electrolyte and metabolite transport</td>
<td>Congenital chloride diarrhea, congenital sodium diarrhea, acrodermatitis enteropathica, selective folate deficiency, abetalipoproteinemia, activating guanylate cyclase mutation</td>
<td>Late onset chloride diarrhea</td>
</tr>
<tr>
<td>Motility disorders</td>
<td>Hirschsprung disease, chronic intestinal pseudoobstruction (neurogenic and myopathic)</td>
<td>Thyrotoxicosis</td>
</tr>
<tr>
<td>Neoplastic diseases</td>
<td>Neuroendocrine hormone-secreting tumors: Apudomas such as VIPoma, Zollinger-Ellison, and mastocytosis</td>
<td>Neuroendocrine hormone-secreting tumors: Apudomas such as VIPoma, Zollinger-Ellison, and mastocytosis</td>
</tr>
<tr>
<td>Diarrhea associated with exogenous substances</td>
<td>Excessive intake of carbonated fluid, foods or drinks containing sorbitol, mannitol, or xylitol; excessive intake of antacids or laxatives containing lactulose or Mg(OH)2; excessive intake of methylxanthines-containing drinks (cola, tea, coffee)</td>
<td>Excessive intake of carbonated fluid, foods or drinks containing sorbitol, mannitol, or xylitol; excessive intake of antacids or laxatives containing lactulose or Mg(OH)2; excessive intake of methylxanthines-containing drinks (cola, tea, coffee)</td>
</tr>
<tr>
<td>Chronic nonspecific diarrhea</td>
<td>Functional diarrhea*</td>
<td>Irritable bowel syndrome†</td>
</tr>
</tbody>
</table>

*Until 4 yr of age, according to Rome III criteria.
†Older than 3 yr of age according to Rome III criteria.
IPEX, immunodysregulation polyendocrinopathy enteropathy X-linked syndrome; VIPoma, vasoactive intestinal polypeptide.
The villous enterocyte lack brush-border microvilli, whereas their apical cytoplasm contains a microvillus inclusion. Periodic acid-Schiff (PAS) staining highlights abundant PAS-positive material in the apical part of the enterocyte cytoplasm. The villous enterocyte lack brush-border microvilli, whereas their apical cytoplasm contains a microvillus inclusion and numerous lysosomes.

Figure 341-2 Microvillus inclusion disease. A, From top to bottom: microvillus inclusion (a), a granule with few microvilli (b), and a lysosome (c) detected in the same enterocyte. Inset: Higher magnification of b and c ×11,000, inset ×21,500. B, Microvillus inclusion disease. Periodic acid-Schiff (PAS) staining highlights abundant PAS-positive material (arrows) in the apical part of the enterocyte cytoplasm. C, Microvillus inclusion disease. The villous enterocyte lack brush-border microvilli, whereas their apical cytoplasm contains a microvillus inclusion and numerous lysosomes. (L) ×5,500. (A from Morroni M, Cangiotti AM, Guarino A, et al. Unusual ultrastructural features in microvillous inclusion disease: a report of two cases. Virchows Arch 448:805–810, 2006.)

Immune-dysregulation, polyendocrinopathy, and enteropathy (IPEX syndrome) is associated with variable gene mutations and phenotypes of chronic diarrhea. Other immunoregulatory defects, found in patients with agammaglobulinemia, isolated immunoglobulin A deficiency, and combined immunodeficiency disorders, may result in persistent infectious diarrhea.

Phenotypic diarrhea, also defined as syndromic diarrhea or trichohepatoenteric syndrome, is a rare disease presenting with facial dysmorphism, woolly hair, severe diarrhea, and malabsorption (Fig. 341-3). Half of the patients have liver disease.

**Short bowel syndrome** is the single most frequent etiology of chronic diarrhea and intestinal failure (see Chapter 338.7). Many intestinal abnormalities such as stenosis, segmental atresia, and malrotation may require surgical resection, but the most frequent primary cause of short bowel is necrotizing enterocolitis. In these conditions, the residual intestine may be insufficient to carry on its digestive-absorptive functions. Rarely, a child may be born with a congenitally short small bowel resulting in delayed growth. In rare cases of severe chronic diarrhea, the gastrointestinal symptoms may be the initial manifestation of mitochondrial disease, carbohydrate deficient glycoproteins, or a primary immune deficiency. **Multiple food protein hypersensitivity** is also included in the list of causes of protracted diarrhea syndrome. The disease is believed to be the result of a reaction against specific proteins contained in foods. Diarrhea often resolves with fasting or when an amino-acid–based formula is started. Although most children with food intolerance in infancy are eventually able to resume a regular diet, some require restrictions throughout their lives. When the cause of the diarrhea remains undetermined and the clinical course is inconsistent with organic disorders, factitious disorder by proxy should be considered.

**GENETIC AND MOLECULAR BASIS OF THE PROTRACTED DIARRHEA SYNDROME**

The genetic and molecular basis of many causes of protracted diarrhea have been identified recently and a new classification of congenital diarrhea disorders (CDDs) has been proposed (Table 341-3). CDDs are a group of rare, but severe enteropathies, with a similar clinical presentation despite a different outcome. However, diarrhea is the result of structural and functional abnormalities resulting in either secretory or osmotic diarrhea. Often diarrhea presents at birth or shortly thereafter, but in milder forms diarrhea may go unrecognized for years. CDDs are rare diseases, however in most specific disorders the specific genetic defect and transmission are known. Hereditary fructose intolerance is associated with mutations in the ASDOB gene that encodes for the aldolase B enzyme that is found primarily in the liver and is involved in the metabolism of fructose. Individuals with hereditary fructose intolerance may have nausea, abdominal pain/bloating, vomiting, diarrhea, and hypoglycemia. Continued ingestion of fructose results in hepatomegaly and eventually cirrhosis. The incidence of hereditary fructose intolerance is estimated to be 1 in 20,000-30,000. In contrast, fructose malabsorption is common in Western countries with estimates as high as 40% of the population. These individuals cannot absorb fructose and often develop bloating, abdominal pain, diarrhea, and flatulence. They do not have liver disease.

The incidence of other genetic disorders associated with CDD ranges from 1 in 2,500 for cystic fibrosis, 1 in 5,000 for sucrose-isomaltase deficiency, 1 in 60,000 for congenital lactase deficiency, to 1 in 400,000 to trichohepatoenteric syndrome. For most CDDs, such as polyendocrinopathy, X-linked (IPEX) syndrome, or autoimmune polyglandular syndrome type 1, the clinical application of exome
Table 341-3 Classification of Congenital Diarrheal Disorders Based on Their Molecular Defect and Their Inheritance

<table>
<thead>
<tr>
<th>DEFECTS OF DIGESTION, ABSORPTION, AND TRANSPORT OF NUTRIENTS AND ELECTROLYTES</th>
<th>GENOME</th>
<th>TRANSMISSION AND INCIDENCE</th>
<th>MECHANISM</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DEFECTS OF DIGESTION, ABSORPTION, AND TRANSPORT OF NUTRIENTS AND ELECTROLYTES</strong></td>
<td><strong>GENE</strong></td>
<td><strong>OMIM NUMBER</strong></td>
<td><strong>TRANSMISSION AND INCIDENCE</strong></td>
</tr>
<tr>
<td>Genes Encoding Brush-Border Enzymes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Congenital lactase deficiency (LD)</td>
<td>LCT</td>
<td>2q21.3</td>
<td>AR, 1 in 60,000 in Finland; lower in other ethnic groups</td>
</tr>
<tr>
<td>Congenital sucrase-isomaltase deficiency (SID)</td>
<td>SI</td>
<td>3q26.1</td>
<td>AR, 1 in 5,000; higher incidence in Greenland, Alaska, and Canada</td>
</tr>
<tr>
<td>Congenital maltase-glucoamylase deficiency (MGD)</td>
<td>Not defined</td>
<td>—</td>
<td>Few cases described</td>
</tr>
<tr>
<td>Genes Encoding Membrane Carriers</td>
<td>Glucose-galactose malabsorption (GGM)</td>
<td>SLC5A1</td>
<td>22q13.1</td>
</tr>
<tr>
<td>Fructose malabsorption (FM)</td>
<td>Not defined</td>
<td>—</td>
<td>Up to 40%</td>
</tr>
<tr>
<td>Fanconi-Bickel syndrome (FBS)</td>
<td>SLC2A2</td>
<td>3q26.2</td>
<td>AR, rare, higher frequency in consanguineous</td>
</tr>
<tr>
<td>Acrodermatitis enteropathica (ADE)</td>
<td>SLC39A4</td>
<td>8q24.3</td>
<td>AR, 1 in 500,000</td>
</tr>
<tr>
<td>Congenital chloride diarrhea (CCD, DIAR 1)</td>
<td>SLC26A3</td>
<td>7q31.1</td>
<td>AR, sporadic; frequent in some ethnicities</td>
</tr>
<tr>
<td>Lysinuric protein intolerance (LPI)</td>
<td>SLC7A7</td>
<td>14q11.2</td>
<td>AR, about 1 in 60,000 in Finland and Japan; rare in other ethnic groups</td>
</tr>
<tr>
<td>Primary bile acid malabsorption (PBAM)</td>
<td>SLC10A2</td>
<td>7q33.1</td>
<td>AR</td>
</tr>
<tr>
<td>Cystic fibrosis (CF)</td>
<td>CFTR</td>
<td>7q31.2</td>
<td>AR, 1 in 2,500</td>
</tr>
<tr>
<td>Genes Encoding Pancreatic Enzymes</td>
<td>Enterokinase deficiency (EKD)</td>
<td>PRSS7</td>
<td>21q21</td>
</tr>
<tr>
<td>Hereditary pancreatitis (HP)</td>
<td>PRSS1</td>
<td>7q34</td>
<td>AR</td>
</tr>
<tr>
<td></td>
<td>SPINK1</td>
<td>5q32</td>
<td>AR</td>
</tr>
<tr>
<td>Congenital absence of pancreatic lipase (APL)</td>
<td>PNLIP</td>
<td>10q25.3</td>
<td>—</td>
</tr>
<tr>
<td>Genes Encoding Proteins of Lipoprotein Metabolism</td>
<td>Abetalipoproteinemia (ALP)</td>
<td>MTTP</td>
<td>4q27</td>
</tr>
<tr>
<td>Hypobetalipoproteinemia (HLP)</td>
<td>Apo B</td>
<td>2p24.1</td>
<td>AR</td>
</tr>
<tr>
<td>Chylomicron retention disease (CRD)</td>
<td>SAR1B</td>
<td>5q31.1</td>
<td>AR, about 40 cases described</td>
</tr>
<tr>
<td>Genes Encoding Other Types of Proteins</td>
<td>Congenital sodium diarrhea (CSD, DIAR 3)</td>
<td>SPINT2 (only syndromic CSD)</td>
<td>19q13.2</td>
</tr>
<tr>
<td>Shwachman-Diamond syndrome (SDS)</td>
<td>SBDS</td>
<td>7q11</td>
<td>AR</td>
</tr>
<tr>
<td>Activating GUCY2C mutation</td>
<td>Guanylate cyclase-C</td>
<td>Unknown</td>
<td>AD</td>
</tr>
<tr>
<td>Genes Encoding for Other Enzymes</td>
<td>Defect in triglyceride synthesis</td>
<td>DGAT1</td>
<td>Splice variant (chromosome 8, 145541756 A G) in the splice donor site 32 of exon 8, altering the invariant GT to GC</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>DISEASE</th>
<th>OMIM NUMBER</th>
<th>TRANSMISSION AND INCIDENCE</th>
<th>MECHANISM</th>
</tr>
</thead>
<tbody>
<tr>
<td>DEFECTS OF ENTEROCYTE DIFFERENTIATION AND POLARIZATION</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Microvillous inclusion disease (MVID, DIAR 2)</td>
<td>251850</td>
<td>AR; rare; higher frequency among Navajo</td>
<td>Secretory</td>
</tr>
<tr>
<td>Congenital tufting enteropathy (CTE, DIAR 5)</td>
<td>613217</td>
<td>AR; 1 in 50,000-100,000; higher among Arabians</td>
<td>Secretory</td>
</tr>
<tr>
<td>Trichohepatoenteric syndrome (THE)</td>
<td>222470</td>
<td>AR; 1 in 400,000</td>
<td>Secretory</td>
</tr>
<tr>
<td>Proprotein convertase 1/3 deficiency (PCD)</td>
<td>600955</td>
<td>AR</td>
<td>Osmotic</td>
</tr>
<tr>
<td>DEFECTS OF ENTEROENDOCRINE CELL DIFFERENTIATION</td>
<td>610370</td>
<td>AR; few cases described</td>
<td>Osmotic</td>
</tr>
<tr>
<td>Congenital malabsorptive diarrhea (CMD, DIAR 4)</td>
<td>AR</td>
<td>Osmotic</td>
<td></td>
</tr>
<tr>
<td>Proprotein convertase 1/3 deficiency (PCD)</td>
<td>600955</td>
<td>AR</td>
<td>Osmotic</td>
</tr>
<tr>
<td>DEFECTS OF MODULATION OF INTESTINAL IMMUNE RESPONSE</td>
<td>240300</td>
<td>AR; AD (1 family)</td>
<td>Secretory</td>
</tr>
<tr>
<td>Autoimmune polyglandular syndrome type 1 (APS1)</td>
<td>601410</td>
<td>X-linked (autosomal cases described), very rare</td>
<td>Secretory</td>
</tr>
<tr>
<td>Immune dysfunction, polyendocrinopathy, X-linked (IPEX)</td>
<td>601410</td>
<td>X-linked (autosomal cases described), very rare</td>
<td>Secretory</td>
</tr>
<tr>
<td>IPEX-like syndrome</td>
<td>Not X-linked</td>
<td>—</td>
<td>Secretory</td>
</tr>
</tbody>
</table>

AD, autosomal dominant; AR, autosomal recessive.
prompt supportive interventions to stabilize the patient. Nutritional support functional diarrhea that may respond to simple dietary and growth. The amount of weight loss over time provides an estimate of diarrhea with specific foods may indicate a nutrient basis, such as demonstrated by increased fecal calprotectin or lactoferrin, sup- porting intestinal inflammation. 

Most cases of protracted diarrhea syndrome are not easily treated. The natural history of protracted diarrhea is related to the primary intestinal disease and the specific defect in nutrient absorption. Treatment is more favorable for motility disorders and autoimmune enteropathy than for structural enterocyte defects. Children with motility disorders may have persistent symptoms, but they are rarely fatal; whereas children with structural enterocyte defects have a more severe course, poorer prognosis, and are more likely to be candidates for intestinal transplantation (see Chapter 339). Some late-onset CDDs may be relatively mild and are recognized only later in life.

**EVALUATION OF PATIENTS**

Because of the spectrum of etiologies, the medical approach should be based on diagnostic algorithms that begin with assessment for infectious causes, and then consider the age of the child, growth, and clinical and epidemiologic factors. Early onset may suggest a congenital or severe condition. In later infancy and up to 2 yr of age, infections and allergies are more common; inflammatory diseases are more frequent in older children and adolescents. Celiac disease and chronic nonspecific diarrhea should always be considered independently of age because of their relatively high frequency at all ages.

Specific clues in the family and personal history may provide useful indications, suggesting a congenital, allergic or inflammatory etiology. A history of polyhydramnios is consistent with congenital chloride-sodium diarrhea, or cystic fibrosis. An acute onset of diarrhea that runs a protracted course suggests post-enteritis diarrhea or small intestinal overgrowth or the onset of chronic nonspecific diarrhea (toddler's diarrhea). In children, with chronic nonspecific diarrhea there is often a history of an acute gastroenteritis. The association of diarrhea with specific foods may indicate a nutrient basis, such as intolerance to selected nutrients (fructose). Anthropometric evaluation is essential to understand if diarrhea has affected weight gain and growth. The amount of weight loss over time provides an estimate of the severity of diarrhea. Normal weight and growth strongly support functional diarrhea that may respond to simple dietary management.

Initial clinical examination should include the evaluation of general and nutritional status. Dehydration, marasmus, or kwashiorkor require prompt supportive interventions to stabilize the patient. Nutritional evaluation should start with the evaluation of the weight and height curves, and of the weight-for-height index to determine the impact of diarrhea on growth. Weight is generally impaired before height, but with time, linear growth also becomes affected, and both parameters may be equally abnormal in the long-term. Assessment of nutritional status includes a dietary history and biochemical and nutritional investigations. Caloric intake should be quantitatively determined and the relationship between weight modifications and energy intake should be carefully considered.

Biochemical markers may assist in grading malnutrition (Table 341-4) as the half-life of serum proteins may distinguish between short- and long-term malnutrition. Assessment of body composition may be performed by measuring mid-arm circumference and triceps skinfold thickness or, more accurately, by bioelectrical impedance analysis or dual-emission x-ray absorptiometry scans. Evaluation of micronutrient concentrations should always be considered. Zinc, magnesium, vitamin A, and folate deficiency are associated with chronic diarrhea and should be provided if needed.

Diagnosis of functional diarrhea is based on clinical assessment using established age-related criteria. It should be noted that a child with functional diarrhea may be inappropriately “treated” with a diluted hypocaloric diet in an effort to reduce the diarrhea, resulting in impaired growth.

The search for an etiology may be based on the relevant causes of diarrhea for the age of the child. Continued diarrhea with fasting or fecal electrolyte concentrations discriminate between secretory and osmotic diarrhea. Associated symptoms and selected investigations provide important diagnostic clues. Signs of general inflammation such as fever, mucoid or bloody stools, and abdominal pain may suggest inflammatory bowel disease. The presence of eczema or asthma is associated with an allergic disorder, whereas specific extraintestinal manifestations (arthritis, diabetes, thrombocytopenia, etc.) may suggest an autoimmune disease. Specific skin lesions may be suggestive of acrodermatitis enteropathica that might respond to zinc replacement. Typical facial abnormalities and woolly hair are associated with phenotypic diarrhea (see Fig. 341-3).

**INVESTIGATIONS**

Microbiologic investigation should include a thorough list of intestinal bacterial, viral, and protozoan pathogens. Proximal intestinal bacterial overgrowth may be determined using the hydrogen breath test, after an oral glucose or lactulose load, but either substrate may give false results.

Initial investigations of a child with chronic diarrhea should always include an assessment of intestinal inflammation using fecal calprotectin or lactoferrin, and serology for celiac disease (see Chapter 338.2). The role of a mucosal biopsy is determined by the noninvasive diagnostic evaluation in consultation with a pediatric gastroenterologist.

Noninvasive assessment of digestive-absorptive function and of intestinal inflammation plays a key role in the diagnostic work-up (Table 341-5). Abnormalities in the digestive-absorptive function tests suggest small bowel involvement, whereas intestinal inflammation, as demonstrated by increased fecal calprotectin or lactoferrin, supports colitis. Histology is important in establishing mucosal involvement, noting changes in the epithelial cells, or in identifying specific
intracellular inclusion bodies caused by pathogens, such as cytomegalovirus, or the presence of parasites. Electron microscopy is essential to detect subcellular structural abnormalities such as microvillous inclusion disease. Immunohistochemistry allows the study of mucosal immunity as well as of other cell types (smooth muscle cells and enteric neuronal cells).

Imaging has a major role in the diagnostic approach. Abdominal ultrasound may help in detecting liver and pancreatic abnormalities or an increase in distal ileal wall thickness that suggests inflammatory bowel disease. A preliminary plain abdominal x-ray is useful for detection of abdominal distention, suggestive of intestinal obstruction, or increased retention of colonic feces. Intramural or portal gas may be seen in necrotizing enterocolitis or intussusception. Structural abnormalities such as diverticula, malrotation, stenosis, blind loop, inflammatory bowel disease, as well as motility disorders, may be investigated through a barium meal and a small bowel follow-through. Capsule endoscopy allows the exploration of the entire intestinal tract searching for structural changes, inflammation or bleeding and the new SmartPill measures pressure, pH, and temperature as it moves through the gastrointestinal tract, assessing motility.

Specific investigations should be carried out for specific diagnostic indications. Prick and patch test may support a diagnosis of food allergy. However, elimination diet with withdrawal of the suspected harmful food from the diet and subsequent challenge is the most reliable strategy by which to establish a diagnosis. Bile malabsorption may be explored by the retention of the bile acid analog $^{75}$Se-homocholic acid-taurine ($^{75}$SeHCAT) in the enterohepatic circulation. A scintigraphic examination, with radio-labeled octreotide is indicated in suspected APUD cell neoplastic proliferation. In other diseases, specific imaging techniques such as computed tomography, or nuclear magnetic resonance endoscopic retrograde cholangiopancreatography and magnetic resonance cholangiopancreatography may have important diagnostic value.

Once infectious agents have been excluded and nutritional assessment performed, a stepwise approach to the child with chronic diarrhea may be applied. The main causes of chronic diarrhea should be investigated, based on the features of the diarrhea and the specific nutrient(s) that is (are) affected. The use of whole-exome sequencing is of benefit in children suspected of having mendelian-related causes of chronic diarrhea. A step-by-step diagnostic approach is important to minimize the unnecessary use of invasive procedures as well as the cost, while optimizing the yield of the diagnostic work-up (Table 341-6).

### Table 341-5 Noninvasive Tests for Intestinal Digestive–Absorptive Function and Inflammation

<table>
<thead>
<tr>
<th>TEST</th>
<th>NORMAL VALUES</th>
<th>IMPLICATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\alpha$-Antitripsin concentration</td>
<td>&lt;$0.9$ mg/g</td>
<td>Increased intestinal permeability/protein loss</td>
</tr>
<tr>
<td>Steatocrit</td>
<td>&lt;2.5% (older than 2 yr) fold increase over age-related values (younger than 2 yr)</td>
<td>Fat malabsorption</td>
</tr>
<tr>
<td>Fecal-reducing substances</td>
<td>Absent</td>
<td>Carbohydrate malabsorption</td>
</tr>
<tr>
<td>Elastase concentration</td>
<td>&gt;$200$ µg/g</td>
<td>Pancreatic function</td>
</tr>
<tr>
<td>Chymotrypsin concentration</td>
<td>&gt;7.5 units/g</td>
<td>Pancreatic function</td>
</tr>
<tr>
<td>Fecal occult blood</td>
<td>Absent</td>
<td>Blood loss in the stools/inflammation</td>
</tr>
<tr>
<td>Fecal calprotectin concentration</td>
<td>&lt;$100$ µg/g (in children to 4 yr of age)</td>
<td>Intestinal inflammation</td>
</tr>
<tr>
<td>Fecal leukocytes</td>
<td>&lt;$5$/microscopic field</td>
<td>Colonic inflammation</td>
</tr>
<tr>
<td>Nitric oxide in rectal dialysate</td>
<td>&lt;$5$ µM of $NO_3^-/NO_2^-$</td>
<td>Rectal inflammation</td>
</tr>
<tr>
<td>Dual sugar (cellobiose/mannitol) absorption test</td>
<td>Urine excretion ratio: 0.010 ± 0.018</td>
<td>Increased intestinal permeability</td>
</tr>
<tr>
<td>Xylose oral load</td>
<td>25 mg/dL</td>
<td>Reduced intestinal surface</td>
</tr>
</tbody>
</table>

### TREATMENT

Chronic diarrhea associated with impaired nutritional status should always be considered a serious disease, and therapy should be started promptly. Treatment includes general supportive measures, nutritional rehabilitation, elimination diet, and medications. The latter include therapies for specific etiologies as well as interventions aimed at countering fluid secretion and/or promoting restoration of disrupted intestinal epithelium. Because death in most instances is caused by dehydration, replacement of fluid and electrolyte losses is the most important early intervention.

Nutritional rehabilitation is often essential and is based on clinical and biochemical assessment. Potentially harmful nutrients must be identified and avoided. In moderate to severe malnutrition, caloric intake may be progressively increased to 50% or more above the recommended dietary allowances. The intestinal absorptive capacity should be monitored by digestive function tests. In children with steatorrhea, medium-chain triglycerides may be the main source of lipids. A lactose-free diet should be started in all children with chronic diarrhea and is recommended by the World Health Organization. Lactose is generally replaced by maltodextrin or a combination of complex carbohydrates. A sucrose-free formula is indicated in sucrase-isomaltase deficiency. Semielemental or elemental diets have the dual purpose of overcoming food intolerance, which may be the primary cause of chronic diarrhea, particularly in infancy and early childhood, and facilitating nutrient absorption. The sequence of elimination should begin from less to more restricted diets, that is, cow’s milk protein hydrolysate to amino-acid–based formulas, depending on the child’s situation. In severely compromised infants, it may be prudent to start with amino-acid–based feeding.

When oral nutrition is not feasible or fails, enteral or parenteral nutrition should be considered. Enteral nutrition may be performed via nasogastric or gastrostomy tube and is indicated in a child who is not able to be fed orally, either because of inability to tolerate nutrient requirements or because of extreme weakness. Continuous enteral nutrition is effective in children with a compromised absorptive capacity, such as short bowel syndrome where the remaining mucosal surface is intact. In extreme wasting, enteral nutrition may not be tolerated and parenteral nutrition is required.

Micronutrient and vitamin supplementation are part of nutritional rehabilitation, especially in malnourished children in developing countries. Zinc supplementation is important in both prevention and therapy of chronic diarrhea, since it promotes ion absorption, restores...
epithelial proliferation, and stimulates immune response. Nutritional rehabilitation has a general beneficial effect on the patient's general condition, intestinal function, and immune response.

Functional diarrhea in children may benefit from a diet based on the "4 F" principles (reduce fructose and fluids, increase fat and fiber). Probiotics have been used with some success as adjunctive therapy based on the evidence that changes in intestinal microflora might be beneficial in several other intestinal diseases.

Pharmacologic therapy includes antiinfectious drugs, immune suppressants, and drugs that may inhibit fluid loss and promote cell growth. If a bacterial agent is detected, specific antibiotics should be prescribed. Empiric antibiotic therapy may be used in children with either small bowel bacterial overgrowth or with suspected infectious diarrhea. Table 341-7 summarizes the treatment of postinfectious persistent diarrhea. Immune suppression should be considered in selected conditions such as autoimmune enteropathy.

Treatment may be also directed at modifying specific pathophysiologic processes. Secretion of ions may be reduced by proabsorptive agents, such as the enkephalinase inhibitor racecadotril. In diarrhea caused by neuroendocrine tumors, microvillus inclusion disease and enterotoxin-induced severe diarrhea, a trial of somatostatin analog octreotide may be considered. Zinc promotes both enterocyte growth and ion absorption and may be effective when intestinal atrophy and ion secretion are associated. However, when therapeutic attempts have failed, the only option to avoid intestinal failure may be parental nutrition or eventually intestinal transplantation.

*Bibliography is available at Expert Consult.*

### Table 341-7 | Treatment of Infectious Persistent Diarrhea

<table>
<thead>
<tr>
<th>FACTOR</th>
<th>INDICATIONS</th>
<th>DOSAGE</th>
<th>DURATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibiotics</td>
<td>Trimethoprim-sulfamethoxazole, Azithromycin</td>
<td>Salmonella spp., Shigella, Campylobacter</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ciprofloxacin, Ceftixarone, Erythromycin, Metronidazole</td>
<td>Giardia, Entamoeba</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>10-50 mg/kg/day in 2 divided doses–daily os</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1st day: 12 mg/kg/day once–daily os</td>
<td>7 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2nd-5th days: 6 mg/kg/day once–daily os</td>
<td>5 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>20-30 mg/kg/day in 2 divided doses–os or iv</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>50-100 mg/kg/day once–im or iv</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>50 mg/kg/day in 2-3 divided doses–os</td>
<td>7 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>20-30 mg/kg/day in 2-3 divided doses–os</td>
<td>7 days</td>
</tr>
<tr>
<td>Antiparasitic</td>
<td>Nitazoxanide, Albendazole</td>
<td>Amebiasis, Giardiasis, Cryptosporidiosis</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>and helminth infections</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>100 mg every 12 hr for children ages</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>12-47 mo</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>200 mg every 12 hr for children ages 4-11 yr</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>500 mg every 12 hr for children older than 11 yr</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>400 mg once</td>
<td></td>
</tr>
<tr>
<td>Probiotics</td>
<td>Lactobacillus GG</td>
<td>1-2 x 10^{11}–1 x 10^{11} CFU/day–os</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Saccharomyces boulardii</td>
<td>1 x 10^{10} germs live (500 mg)/day–os</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>For a minimum period of 7 days or until diarrhea stopped</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>For a minimum period of 7 days or till diarrhea stopped</td>
<td></td>
</tr>
<tr>
<td>Human serum immunoglobulin</td>
<td>Severe Rotavirus diarrhea</td>
<td>300 mg/kg single oral administration</td>
<td></td>
</tr>
<tr>
<td>Antisecretory</td>
<td>Racecadotril</td>
<td>Secretory diarrhea</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.5 mg/kg every 8 hr–os</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>For a minimum period of 7 days or till diarrhea stopped</td>
<td></td>
</tr>
<tr>
<td>Adsorbents</td>
<td>Diosmectite</td>
<td>3-6 g every 12-24 hr–os</td>
<td>5 days</td>
</tr>
</tbody>
</table>

*im, Intramuscular; iv, intravenous; os, by mouth.
Chapter 341  Chronic Diarrhea  1882.e1

Bibliography

341.1 Diarrhea from Neuroendocrine Tumors

Helen Spoudeas and David Branski

Rare tumors of the neuroendocrine cells of the gastroenteropancreatic axis and adrenal and extraadrenal sites derive from the APUD system. They are characterized by an excessive production of 1 or several peptides, which, when released into the circulation, exert their endocrine effects and can be measured by radioimmunologic methods (in the plasma or as their urinary metabolites) and hence act as tumor markers. In clinically functioning tumors, the hypersecretion causes a recognizable syndrome that can include watery diarrhea. Though rare, neuroendocrine tumor (NET) should be considered a potential cause in patients with a particularly severe or chronic course (resulting in electrolyte and fluid depletion), associated flushing, palpitations, or bronchospasm, or a positive family history of multiple endocrine neoplasia 1 or 2 syndromes (Table 341-8).

Depending on the tumor type, the peptide marker(s) in the plasma and/or the 24-hr urinary metabolite(s) measured (on 2 occasions), form the basis of the biochemical diagnosis, the prognosis (tumor load) and treatment monitoring. Baseline tests should include plasma chromogranin A and urinary 5-hydroxyindoloacetic acid, other specific biochemistry being guided by the suspected syndrome (see Table 341-8). Carcinoid tumors are gastroenteropancreatic NETs, typically of the midgut (rather than fore- or hindgut), which may cause flushing and bronchospasm in addition to diarrhea and which, because of their portal drainage, are the most prone to late presentation and malignancy. Localization of any NET is best achieved with a multimodality approach at a center of excellence. Thus whole-body CT, MRI, and somatostatin receptor scintigraphy may be required (because nearly all NETs express membrane receptors for small peptides, e.g., somatostatin), with gallium-68 positron emission tomography/CT recommended for detecting an unknown primary. Long-acting somatostatin analogs might also have a role in palliation.

Tumor resection is the treatment of choice but is potentially hazardous and can precipitate life-threatening adrenergic crises; it should only be undertaken by an endocrine surgeon with experience under carefully controlled medical and anesthetic conditions and in conjunction with an endocrinologist. Tumor histochemistry will confirm the NET type and classification of NETs should be based on the World Health Organization 2010 Union for International Cancer Control TNM criteria (7th edition). This diagnosis in a child should prompt a genetic referral to exclude a tumor predisposition syndrome in which the child is the index case and tumor registration. Management and follow-up is multidisciplinary and should be undertaken in an age-appropriate setting with access to adult specialists with expertise in these rare conditions.

<table>
<thead>
<tr>
<th>TUMOR AND CELL TYPE</th>
<th>SITE</th>
<th>MARKERS</th>
<th>SIGNS OF HORMONE HYPERSECRETION</th>
<th>THERAPY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carcinoid</td>
<td>Intestinal argentaffin cells, typically midgut, also foregut and hindgut, ectopic bronchial tree</td>
<td>Serotonin (5-HT), urine 5-HIAA (diagnostic) Also produce substance P, neuropeptide K, somatostatin, VIP Chromogranin A</td>
<td>Secretory diarrhea, crampy abdominal pain, flushing, wheezing, (and cardiac valve damage if foregut site)</td>
<td>Resection Somatostatin analog, (palliative) Genetic MEN-1</td>
</tr>
<tr>
<td>Gastrinoma, Zollinger-Ellison syndrome</td>
<td>Pancreas, small bowel, liver and spleen</td>
<td>Gastrin</td>
<td>Multiple peptic ulcers, secretory diarrhea</td>
<td>H2-blockers, PPI, tumor resection, (gastrectomy) Genetic MEN-1</td>
</tr>
<tr>
<td>Mastocytoma</td>
<td>Cutaneous, intestine, liver, spleen</td>
<td>Histamine, VIP</td>
<td>Pruritus, flushing, apnea if VIP, diarrhea</td>
<td>H1- and H2-blockers, cromolyn, steroids, resection if solitary</td>
</tr>
<tr>
<td>Medullary carcinoma</td>
<td>Thyroid C-cells</td>
<td>Calcitonin, VIP, prostaglandins</td>
<td>Secretory diarrhea</td>
<td>Radical thyroidectomy ± lymphadenectomy (genetic MEN-2A/B, familial MTC)</td>
</tr>
<tr>
<td>Ganglioneuroma, pheochromocytoma, ganglioneuroblastoma, neuroblastoma</td>
<td>Chromaffin cells; abdominal &gt; other sites; extraadrenal or adrenal</td>
<td>Metanephrines and catecholamines, VIP VMA, HMA in neuroblastoma</td>
<td>Hypertension, tachycardia, paroxysmal palpitations, sweating, anxiety, watery diarrhea*</td>
<td>Perioperative α-adrenergic (BP) and β-adrenergic blockade with volume support tumor resection Genetic MEN-2 (RET gene), VHL, NF-1, SDH</td>
</tr>
<tr>
<td>Somatostatinoma</td>
<td>Pancreas</td>
<td>Somatostatin</td>
<td>Secretory diarrhea, steatorrhea, choledolithiasis, diabetes</td>
<td>Resection Genetic MEN-1</td>
</tr>
<tr>
<td>VIPoma</td>
<td>Pancreas</td>
<td>VIP, prostaglandins</td>
<td>Secretory diarrhea, achlorhydria, hypokalemia</td>
<td>Somatostatin analogs, resection Genetic MEN-1</td>
</tr>
</tbody>
</table>

*Diarrhea has been reported only in adult patients with pheochromocytoma.
†Bold indicates major markers.
BP, blood pressure; H1, histamine receptor type 1; H2, histamine receptor type 2; HMA, homovanillic acid; MEN-1, multiple endocrine neoplasia type 1; MTC, medullary thyroid carcinoma; NF-1, neurofibromatosis type 1; PPI, proton pump inhibitor; SDH, succinate dehydrogenase; VHL, von Hippel-Lindau disease; VIP, vasoactive intestinal polypeptide; VMA, vanillylmandelic acid.

Adapted from Spoudeas HA, editor: Paediatric endocrine tumours. A multidisciplinary consensus statement of best practice from a working group convened under the auspices of the British Society of Paediatric Endocrinology and Diabetes (BSPED) and the United Kingdom Children’s Cancer Study Group (UKCCSG), Crawley, West Sussex, 2005, Novo Nordisk.
Recurrent abdominal pain in children was defined as at least 3 episodes of pain over at least 3 mo that interfered with function. In many situations the term recurrent abdominal pain was used synonymously with functional abdominal pain. Other terms, such as chronic abdominal pain, nonorganic abdominal pain, and psychogenic abdominal pain, that were also used for describing abdominal pain in children, led to clinical confusion. The American Academy of Pediatrics Subcommittee on Chronic Abdominal Pain and the North American Society for Pediatric Gastroenterology Hepatology and Nutrition Committee on Abdominal Pain suggested that the term recurrent abdominal pain no longer be used. Table 342-1 outlines the recommended clinical definitions for long-lasting intermittent or constant abdominal pain by the same committees.

Chronic abdominal pain can be organic or nonorganic, depending on whether a specific etiology is identified. Nonorganic abdominal pain or functional abdominal pain refers to pain without evidence of anatomic, inflammatory, metabolic, or neoplastic abnormalities. Functional gastrointestinal disorders (FGIDs) are a group of gastrointestinal (GI) disorders that include variable combinations of chronic or recurrent GI symptoms not explained by structural or biochemical abnormalities. The Rome Committee updates and modifies the information on FGIDs for clinical and research purposes. The Rome III process had 2 pediatric subcommittees based on age range: Neonate/Toddler (0-4 yr) and Child/Adolescent (4-18 yr). The Child/Adolescent committee categorized abdominal pain–related FGIDs under Category H2 (Table 342-2). Table 342-3 defines the Rome III criteria for the diagnosis of Childhood Functional Abdominal Pain (category H2d) and the Childhood Functional Abdominal Pain Syndrome (category H2d1).

The exact incidence and prevalence of chronic abdominal pain is not known. There are reports of chronic abdominal pain affecting 9-15% of children. There are also reports that 13% of middle school and 17% of high school children have weekly complaints of abdominal pain.

<table>
<thead>
<tr>
<th>Table 342-1</th>
<th>Recommended Clinical Definitions of Long-Standing Intermittent or Constant Abdominal Pain in Children</th>
</tr>
</thead>
<tbody>
<tr>
<td>DISORDER</td>
<td>DEFINITION</td>
</tr>
<tr>
<td>Chronic abdominal pain</td>
<td>Long-lasting intermittent or constant abdominal pain that is functional or organic (disease based)</td>
</tr>
<tr>
<td>Functional abdominal pain</td>
<td>Abdominal pain without demonstrable evidence of pathologic condition, such as anatomic metabolic, infectious, inflammatory or neoplastic disorder. Functional abdominal pain can manifest with symptoms typical of functional dyspepsia, irritable bowel syndrome, abdominal migraine or functional abdominal pain syndrome</td>
</tr>
<tr>
<td>Functional dyspepsia</td>
<td>Functional abdominal pain or discomfort in the upper abdomen</td>
</tr>
<tr>
<td>Irritable bowel syndrome</td>
<td>Functional abdominal pain associated with alteration in bowel movements</td>
</tr>
<tr>
<td>Abdominal migraine</td>
<td>Functional abdominal pain with features of migraine (paroxysmal abdominal pain associated with anorexia, nausea, vomiting or pallor as well as maternal history of migraine headaches)</td>
</tr>
<tr>
<td>Functional abdominal pain syndrome</td>
<td>Functional abdominal pain without the characteristics of dyspepsia, irritable bowel syndrome, or abdominal migraine</td>
</tr>
</tbody>
</table>


<table>
<thead>
<tr>
<th>Table 342-2</th>
<th>Childhood Functional GI Disorders: Child/Adolescent (Category H)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H1. Vomiting and aerophagia</td>
<td></td>
</tr>
<tr>
<td>H1a. Adolescent rumination syndrome</td>
<td></td>
</tr>
<tr>
<td>H1b. Cyclic vomiting syndrome</td>
<td></td>
</tr>
<tr>
<td>H1c. Aerophagia</td>
<td></td>
</tr>
<tr>
<td>H2. Abdominal pain—related functional gastrointestinal disorders</td>
<td></td>
</tr>
<tr>
<td>H2a. Functional dyspepsia</td>
<td></td>
</tr>
<tr>
<td>H2b. Irritable bowel syndrome</td>
<td></td>
</tr>
<tr>
<td>H2c. Abdominal migraine</td>
<td></td>
</tr>
<tr>
<td>H2d. Childhood functional abdominal pain</td>
<td></td>
</tr>
<tr>
<td>H2d1. Childhood functional abdominal pain syndrome</td>
<td></td>
</tr>
<tr>
<td>H3. Constipation and incontinence</td>
<td></td>
</tr>
<tr>
<td>H3a. Functional constipation</td>
<td></td>
</tr>
<tr>
<td>H3b. Nonretentive fecal incontinence</td>
<td></td>
</tr>
</tbody>
</table>

Adapted from Rome Foundation: Rome III disorders and criteria. www.romecriteria.org/criteria/.

<table>
<thead>
<tr>
<th>Table 342-3</th>
<th>Rome III Criteria for Childhood Functional Abdominal Pain H2d and Childhood Functional Abdominal Pain Syndrome H2d1</th>
</tr>
</thead>
<tbody>
<tr>
<td>H2d. CHILDHOOD FUNCTIONAL ABDOMINAL PAIN</td>
<td></td>
</tr>
<tr>
<td>Diagnostic criteria* must include all of the following:</td>
<td></td>
</tr>
<tr>
<td>• Episodic or continuous abdominal pain</td>
<td></td>
</tr>
<tr>
<td>• Insufficient criteria for other functional gastrointestinal disorders</td>
<td></td>
</tr>
<tr>
<td>• No evidence of an inflammatory, anatomic, metabolic, or neoplastic process that explains the subject’s symptoms</td>
<td></td>
</tr>
<tr>
<td>H2d1. CHILDHOOD FUNCTIONAL ABDOMINAL PAIN SYNDROME</td>
<td></td>
</tr>
<tr>
<td>Diagnostic criteria* must satisfy criteria for childhood functional abdominal pain and have at least 25% of the time one or more of the following:</td>
<td></td>
</tr>
<tr>
<td>• Some loss of daily function</td>
<td></td>
</tr>
<tr>
<td>• Additional somatic symptoms such as headache, limb pain, or difficulty sleeping</td>
<td></td>
</tr>
</tbody>
</table>

*Criteria fulfilled at least once per week for ≥2 mo prior to diagnosis. Adapted from Rome Foundation: Rome III disorders and criteria. http://www.romecriteria.org/criteria/.
PATHOPHYSIOLOGY

The symptoms of FGIDs may be the result of dysfunctions of the intestinal sensory and motor systems. The pathophysiology of functional abdominal pain is complex and not fully understood. Visceral hypersensitivity and motility disturbances are thought to be involved in functional abdominal pain. The traditional concept that motility disorders alone have an important role in functional pain has not been confirmed. It is believed that visceral hypersensitivity leading to abnormal bowel sensitivity to stimuli (physiologic, psychologic, noxious) might have a more dominant role in functional abdominal pain. Visceral hypersensitivity could be the result of abnormal interpretation of normal signals by the brain or aberrant signals sent to the brain or a combination. Intestinal pain receptors respond to mechanial and/or chemical stimuli. The visceral receptors can respond to both mechanical and chemical stimuli, but the mucosal receptors are primarily stimulated by chemical stimuli.

The viscera are innervated by dual set of nerves (vagal and splanchnic spinal nerves or pelvic and splanchnic spinal nerves). The spinal afferents carry impulses to the spinal cord. The dorsal horn of the spinal cord regulates conduction of impulses from peripheral nociceptive receptors to the spinal cord and brain, and the pain experience is further influenced by cognitive and emotional centers. Chronic peripheral nervous system pain can produce increased neural activity in higher central nervous system centers, leading to perpetuation of pain. Psychosocial stress can affect pain intensity and quality through these mechanisms. The child’s response to pain can be influenced by stress, personality type, and the reinforcement of illness behavior within the family. The autonomic and enteric nervous systems can overlie the visceral and peripheral nervous systems, respectively, in the abdomen. The autonomic nervous system can influence pain perception, and the enteric nervous system can influence pain perception and the initiation, perception, and perpetuation of pain.

A normal functioning enteric nervous system (ENS) is important for coordination of intestinal motility, secretion, and blood flow. Abnormalities of the ENS may be an underlying factor for functional abdominal pain. Inflammation of the intestine and its role in the pathogenesis of functional abdominal pain could be a result of the effects of the inflammatory mediators and cytokines (released by the various inflammatory cells) on the ENS. The dysregulation in the brain–gut interactions can also lead to functional abdominal pain. The role of certain triggers for pain, such as lactose, sorbitol, fructose, bile acids, or fatty acids, could be a result of the altered sensitivity or motor function, because some patients have relief when eliminating these from their diet. Altered intestinal permeability enabling passage of food antigens into the mucosa leading to prolonged stimulation of the intestinal mucosal immune system and the ENS is also a possible cause for functional abdominal pain.

EVALUATION AND DIAGNOSIS

While evaluating a patient with chronic abdominal pain, distinguishing organic pain and functional pain can be challenging. A wide range of potential organic causes of chronic abdominal pain (see Table 306-13) must be considered before establishing a diagnosis of functional pain (nonorganic). Frequently cited causes of chronic abdominal pain include constipation, esophagitis, gastritis, inflammatory bowel disease, and possibly giardiasis. There is little evidence that the frequency, severity, or location of the pain helps to distinguish between organic and nonorganic pain. It is controversial whether nighttime awakening because of pain is concerning for organic disorders or if it can also be seen with functional pain syndromes.

Children with chronic abdominal pain might have associated headaches, anorexia, nausea, vomiting, excessive gas, diarrhea or constipation, and joint pain, but this does not help distinguish between functional and organic disorder. Negative lifestyle events and high life stress levels also do not help to distinguish organic and nonorganic pain, despite several reports of higher levels of life stress in children with chronic abdominal pain. Daily stressors may increase the likelihood for pain episodes, but there is no evidence that psychologic issues distinguishes between organic and nonorganic abdominal pain. Nonetheless, it is important to investigate and manage the psychologic factors because there is evidence suggesting that children with chronic abdominal pain have more anxiety and depression symptoms. Whether this causes pain or is the result of pain is not known.

Children with functional pain do not have higher levels of conduct disorder or oppositional behavior compared to the controls but they can be more prone to emotional symptoms or psychiatric disorders later in life. Parents of patients with functional abdominal pain have more symptoms of somatization, anxiety, and depression. Both the family and the affected child (when the child gets to adult age) have a higher incidence of irritable bowel syndrome (IBS). A thorough history and physical examination will identify the alarm symptoms and signs (Tables 342-4 and 342-5). The presence of alarm symptoms and signs warrants further investigation. The absence of alarm symptoms and signs, a normal physical examination, and a normal stool Hemocult test is sufficient for an initial diagnosis of functional abdominal pain. The laboratory, radiologic, or endoscopic approach to children with chronic abdominal pain should be individualized, depending on the findings suggested by a detailed history and physical examination.

Laboratory studies may not be necessary if the history and physical examination lead to a diagnosis of functional abdominal pain. Nonetheless, medical tests can reassure the patient and family, and at times the physician, if there is significant functional disability and poor quality of life. A complete blood cell count, sedimentation rate, C-reactive protein, basic chemistry panel, celiac panel, stool culture, stool test for ova and parasites, and urinalysis are reasonable screening studies. The risk of celiac disease may be 4 times higher in these patients compared with the general population. Elevated stool calprotectin levels usually suggest an inflammatory etiology. If indicated, an ultrasound examination of the abdomen can give information about kidneys, gallbladder, and pancreas; with lower

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### Table 342-4

<table>
<thead>
<tr>
<th>Alarm Symptoms Usually Needing Further Investigations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain that wakes up the child from sleep</td>
</tr>
<tr>
<td>Persistent right upper or right lower quadrant pain</td>
</tr>
<tr>
<td>Significant vomiting (bilious vomiting, protracted vomiting, cyclical vomiting, or worrisome pattern to the physician)</td>
</tr>
<tr>
<td>Unexplained fever</td>
</tr>
<tr>
<td>Genitourinary tract symptoms</td>
</tr>
<tr>
<td>Dysphagia</td>
</tr>
<tr>
<td>Chronic severe diarrhea or nocturnal diarrhea</td>
</tr>
<tr>
<td>Gastrointestinal blood loss</td>
</tr>
<tr>
<td>Involuntary weight loss</td>
</tr>
<tr>
<td>Deceleration of linear growth</td>
</tr>
<tr>
<td>Delayed puberty</td>
</tr>
<tr>
<td>Family history of inflammatory bowel disease, celiac disease, and peptic ulcer disease</td>
</tr>
</tbody>
</table>

### Table 342-5

<table>
<thead>
<tr>
<th>Alarm Signs Usually Needing Further Investigations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Localized tenderness in the right upper quadrant</td>
</tr>
<tr>
<td>Localized tenderness in the right lower quadrant</td>
</tr>
<tr>
<td>Localized fullness or mass</td>
</tr>
<tr>
<td>Hepatomegaly</td>
</tr>
<tr>
<td>Splenomegaly</td>
</tr>
<tr>
<td>Jaundice</td>
</tr>
<tr>
<td>Costovertebral angle tenderness</td>
</tr>
<tr>
<td>Arthritis</td>
</tr>
<tr>
<td>Spinal tenderness</td>
</tr>
<tr>
<td>Perianal disease</td>
</tr>
<tr>
<td>Abnormal or unexplained physical findings</td>
</tr>
<tr>
<td>Hematochezia</td>
</tr>
<tr>
<td>Anemia</td>
</tr>
</tbody>
</table>
abdominal pain, a pelvic ultrasonogram may be indicated. An upper GI x-ray series is indicated if one suspects a disorder of the stomach or small intestine. *Helicobacter pylori* infection does not seem to be associated with chronic abdominal pain, but in patients with symptoms suggesting gastritis or ulcer, an *H. pylori* test (fecal *H. pylori* antigen) may be performed. Breath hydrogen testing is done for ruling out lactose or sucrose malabsorption. Lactose intolerance is so common that the finding may be coincidental, and the clinician must be cautious in attributing chronic abdominal pain to this condition.

Esophagogastroduodenoscopy is indicated with symptoms that suggest persistent upper GI pathology. In the absence of this suspicion, esophagogastroduodenoscopy is unlikely to identify an abnormality and is usually not necessary.

**TREATMENT**

Making a positive diagnosis of functional abdominal pain is important and can be done by the primary care pediatrician in most 4-18 yr old children with chronic abdominal pain if there are no alarm symptoms or signs, a normal physical examination, and a negative stool occult blood test. In practice, on many occasions children do not get a conclusive diagnosis of functional abdominal pain. This can lead to unwarranted referrals and increased anxiety to the patient and the family. Even if a diagnostic evaluation is initiated during the initial office visit, a discussion about functional abdominal pain as the most likely diagnosis during that visit will help the patient and family to understand the diagnosis better. Close following and counseling by one consistent healthcare provider is essential.

The most important component of the treatment is reassurance and education of the child and family. The child and family need to be reassured that no evidence of a serious underlying disorder is present. The family and the child with functional pain might worry about the inability to identify an organic cause and may be resistant to a diagnosis of nonorganic disease. Explanation in simple language that although the pain is real, there is no underlying serious disorder usually alleviates the anxiety in the patient and family. Children of families that do not accept a functional cause of the symptoms are more likely to have persistent somatic complaints and school absences. The parents should be instructed to avoid reinforcing the symptoms with secondary gain. If children have missed school or have been removed from routine activities because of the pain, it is important that they return to regular activities.

Treatment goals should be set for return to function and minimizing pain. Complete disappearance of pain would be an unreasonable goal to set. Cognitive-behavioral therapy is helpful in the short term for managing pain and functional disability (Table 342-6). Biofeedback, guided imagery, and relaxation techniques have been useful in some children with functional pain. Even though studies do not show consistent benefits from medications, time-limited use of medications is usually part of the multidisciplinary approach. The commonly used medications include acid suppressants for dyspepsia symptoms, antispasmodics, and low-dose amitriptyline. For chronic abdominal pain with IBS symptoms, antidiarrheals and nonstimulating laxatives are used. Peppermint oil for 2 wk improves IBS symptoms in children. There is no evidence that a lactose-restricted diet or fiber supplements decrease the frequency of attacks in chronic abdominal pain in children.

Proton pump inhibitors or visceral muscle relaxants (anticholinergics) are used empirically but are often unhelpful in the absence of specific indication.

**Irritable Bowel Syndrome**

IBS is characterized as a chronic FGID associated with abdominal pain or discomfort and altered bowel function without evidence of an inflammatory, anatomic, metabolic, or neoplastic process. Table 342-7 presents the Rome III diagnostic criteria for diagnosing IBS in children and adolescents.

Abdominal pain is episodic, cramping, or aching, usually in the lower abdomen, and often relieved by defecation. There may be abdominal discomfort, bloating, and flatulence. Diarrhea and constipation alone or in an alternating pattern must be present. The diarrhea is often watery and frequent and is associated with pain, the passage of mucus per rectum, and a feeling of incomplete emptying. The constipation is associated with a decreased stooling frequency and the passage of hard stools. Symptoms may be traced back to childhood or following an episode of presumed bacterial or viral gastroenteritis. It is important to rule out organic causes of abdominal pain and altered bowel patterns, especially celiac disease, even in the absence of the classic features of this disease.

Many dietary modifications have been suggested for relief of symptoms but not proven. Restriction of dietary fermentable oligosaccharides, disaccharides, monosaccharaides, and polyols in some studies have shown symptom relief.

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**Table 342-7** Rome III Criteria for Child/Adolescent Irritable Bowel Syndrome H2b

<table>
<thead>
<tr>
<th>Diagnostic criteria* must include all of the following:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Abdominal discomfort or pain associated with 2 or more of the following at least 25% of the time:</td>
</tr>
<tr>
<td>a. Improvement with defecation</td>
</tr>
<tr>
<td>b. Onset associated with a change in frequency of stool</td>
</tr>
<tr>
<td>c. Onset associated with a change in form (appearance) of stool</td>
</tr>
<tr>
<td>2. No evidence of an inflammatory, anatomic, metabolic, or neoplastic process that explains the subject’s symptoms</td>
</tr>
</tbody>
</table>

*Criteria fulfilled at least once per week for at least 6 mo prior to diagnosis.

*Discomfort* means an uncomfortable sensation not described as pain.

Adapted from Rome Foundation. Rome III disorders and criteria. [http://www.romecriteria.org/criteria/](http://www.romecriteria.org/criteria/)

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**Table 342-6** Effectiveness of Treatments for Abdominal Pain in Children

<table>
<thead>
<tr>
<th>THERAPY</th>
<th>DEFINITION OF DISORDER</th>
<th>EFFECTIVENESS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cognitive behavioral (family) therapy</td>
<td>Recurrent abdominal pain</td>
<td>Beneficial</td>
</tr>
<tr>
<td>Famotidine</td>
<td>Recurrent abdominal pain and dyspeptic symptoms</td>
<td>Inconclusive</td>
</tr>
<tr>
<td>Added dietary fiber</td>
<td>Recurrent abdominal pain</td>
<td>Unlikely to be beneficial</td>
</tr>
<tr>
<td>Lactose-free diet</td>
<td>Recurrent abdominal pain</td>
<td>Unlikely to be beneficial</td>
</tr>
<tr>
<td>Peppermint oil</td>
<td>Irritable bowel syndrome</td>
<td>Likely to be beneficial</td>
</tr>
<tr>
<td>Amitriptyline</td>
<td>Functional gastrointestinal disorders, irritable bowel syndrome</td>
<td>Inconsistent results</td>
</tr>
<tr>
<td>Lactobacillus GG</td>
<td>Irritable bowel syndrome using Rome III criteria</td>
<td>Unlikely to be beneficial</td>
</tr>
</tbody>
</table>

The effectiveness of analgesics, antispasmodics, sedatives, and antidepressants is currently unknown.

Probiotics are reported to be helpful in diarrhea predominant IBS, but larger trials are necessary to prove probiotics are beneficial. Management focuses on the dominant symptoms. Pain has been managed with cognitive-behavioral therapy, pain clinic referrals, peppermint, antispasmodic agents, and tricyclic antidepressant agents (amitriptyline). Diarrhea has been managed with loperamide, oral nonabsorbable antibiotics, and 5-HT3 antagonists (alosetron). Constipation is managed with fiber (psyllium), increased fluid intake, lactulose, 5-HT4 agonists (tegaserod), and selective C2 chloride channel–activating agents. In all medication trials, there is often a high response to placebo.

Bibliography is available at Expert Consult.
Chapter 342  Functional Abdominal Pain (Nonorganic Chronic Abdominal Pain)  1887.e1

Bibliography


Acute appendicitis remains the most common acute surgical condition in children and a major cause of childhood morbidity. While prompt appendectomy remains the mainstay of treatment, management has changed substantially in the past several decades with improved antibiotic regimens, advances in imaging techniques, percutaneous drainage procedures by interventional radiologists, initial nonoperative management in select cases, and the use of laparoscopy. Approximately 100,000 children are treated in children's hospitals for appendicitis each year. The incidence of appendicitis increases with age, from a rate of 1-2 per 10,000 children from birth to 4 yr of age, to a rate of 19-28 per 10,000 children younger than age 14 yr annually. Children have a lifetime risk of ~7% and appendicitis is diagnosed in 1-8% of children presenting to the emergency department for evaluation of abdominal pain. The misdiagnosis of appendicitis is second only to meningitis as a cause of medical malpractice suits in pediatric emergency care. Mortality is low (<1%), but morbidity remains high, mostly in association with complicated (perforated) appendicitis. Advances in surgical (laparoscopy) and imaging technology have significantly escalated treatment-related costs without demonstrable improvement in patient outcomes. In addition, there are marked variations in practice patterns and resource utilization in the evaluation and management of appendicitis. Children have a higher perforation rate than adults and up to 40% of children present with complicated disease.

**PATHOLOGY**

The clinical entity of acute appendiceal inflammation followed by perforation, abscess formation, and peritonitis is most likely a disease of multiple etiologies, the final common pathway of which involves invasion of the appendiceal wall by bacteria. One pathway to acute appendicitis begins with luminal obstruction; inspissated fecal material, lymphoid hyperplasia, ingested foreign body, parasites, and tumors have been implicated. Obstruction of the appendiceal lumen initiates a progressive cascade including increasing intraluminal pressures from bacterial proliferation and continued secretion of mucus, elevated intraluminal pressure, lymphatic and venous congestion and edema, impaired arterial perfusion, ischemia of the wall of the appendix, bacterial invasion of the appendiceal wall, and necrosis. This progression correlates with the clinical disease progression from simple appendicitis to gangrenous appendicitis and, thereafter, appendiceal perforation. Submucosal lymphoid follicles, which can obstruct the appendiceal lumen, are few at birth but multiply steadily during childhood, reaching a peak in number during the teen years, when acute appendicitis is most common, and declining after age 30 yr. Because of this prominence of lymphoid tissue, some have hypothesized that the appendix may have an immune function similar to that of the thymus or bursa of Fabricius. Fecaliths and appendicitis are more common in developed countries with refined, low-fiber diets than in developing countries with a high-fiber diet; no causal relationship has been established between lack of dietary fiber and appendicitis.

The finding that <50% of specimens from cases of acute appendicitis demonstrate luminal obstruction on radiographic, gross, or pathologic examination has prompted investigations of alternative etiologies. Enteric infection likely plays a role in many cases in association with mucosal ulceration and invasion of the appendiceal wall by bacteria. Bacteria such as *Versinia, Salmonella,* and *Shigella spp.*, and viruses such as infectious mononucleosis, mumps, coxsackievirus B, and adenovirus, are implicated. In addition, case reports demonstrate the occurrence of appendicitis from ingested foreign bodies, in association with carcinoid tumors of the appendix or *Ascaris* and following blunt abdominal trauma. Children with cystic fibrosis have an increased incidence of appendicitis; the cause is believed to be the abnormal thickened mucus. Appendicitis in neonates is rare and warrants diagnostic evaluation for cystic fibrosis and Hirschsprung disease.

A primary focus in the management of acute appendicitis is avoidance of sepsis and the infectious complications leading to increased morbidity; mostly seen in association with perforation. Bacteria can be cultured from the serosal surface of the appendix before microscopic or gross perforation and bacterial invasion of the mesenteric veins can result in portal vein or superior mesenteric vein sepsis (pyelephlebitis), thrombosis, and liver abscess. Subsequent to perforation, the microbiologic fecal contamination may be localized to the right lower quadrant (RLQ) or pelvis by the omentum and adjacent loops of bowel, resulting in a localized abscess or inflammatory mass (phlegmon), or, alternatively, the fecal contamination can spread throughout the peritoneal cavity, causing diffuse peritonitis. Young children typically have a poorly developed omentum and are often unable to control the local infection. Perforation and abscess formation with appendicitis can lead to fistula formation in adjacent organs, scrotal cellulitis and abscess through a patent processus vaginalis (congenital indirect inguinal hernia), or small bowel obstruction.

**CLINICAL FEATURES**

Appendicitis is most common in older children, with peak incidence between the ages of 12 and 18 yr; it is rare in children younger than 5 yr of age (<5% of cases) and extremely rare (<1% of cases) in children younger than 3 yr of age. It affects boys slightly more often than girls and whites more often than blacks in the United States. There is a seasonal peak incidence in autumn and spring. There appears to be a familial predisposition in some cases, particularly in children in whom appendicitis develops before age 6 yr. Perforation in appendicitis is more common in children compared to adults, particularly in young children; with perforation rates as high as 82% for children younger than 5 yr and approaching 100% in infants. There is an increased incidence of perforated appendicitis in children of minority race and children with Medicaid health insurance.

Appendicitis in children has an immensely broad spectrum of clinical presentation. The signs and symptoms can be classic or often atypical and quite variable depending on the timing of presentation, the patient's age, the location of the appendix, and individual variability in the evolution of the disease process. Children early in the disease process can appear well and demonstrate minimal symptoms, subtle findings on physical examination, and normal laboratory studies; those with perforation and advanced peritonitis often demonstrate severe illness with bowel obstruction, renal failure, and septic shock.

While the classic presentation of acute appendicitis is well described, this represents <50% of cases; therefore, the majority of cases of appendicitis have an “atypical” presentation. The illness typically begins insidiously with a brief (several hours) period of generalized malaise and anorexia; the child does not appear ill and the family is not likely to seek consultation assuming the child has “stomach flu” or a viral syndrome. Unfortunately, if the diagnosis is appendicitis, the illness escalates rapidly with progressive abdominal pain followed by vomiting, and appendiceal perforation is likely to occur within 48 hr of the
onset of illness. The opportunity for diagnosis before perforation in acute appendicitis in children is generally brief (~36–48 hr).

Abdominal pain is consistently the primary and often the first symptom; beginning shortly (hours) after the onset of illness. As with other visceral organs, there are no somatic pain fibers within the appendix; therefore, early appendiceal inflammation results in pain which is vague, poorly localized, unrelated to activity or position, often colicky, and periumbilical in location as a result of visceral inflammation from a distended appendix. Progression of the inflammatory process in the next 12–24 hr leads to involvement of the adjacent parietal peritoneal surfaces, resulting in somatic pain localized to the RLQ. It is important to note the position of the appendix can vary greatly.

In 50% of the population it is located in a retrocecal position; likely resulting in a delayed presentation. In others it is located over the pelvic brim, occasionally descending low down in the pelvis. The position of the appendix is a critical factor affecting interpretation of presenting signs and symptoms and accurate diagnosis. The pain becomes steady and more severe and is exacerbated by movement. The child often describes marked discomfort with the “bumpy” car ride to the hospital, moves cautiously, and has difficulty getting onto the examining room stretcher. Nausea and vomiting occur in more than half the patients, and usually follow the onset of abdominal pain by several hours. Anorexia is a classic and consistent finding in acute appendicitis, but occasionally, affected patients are hungry. Diarrhea and urinary symptoms are also common, particularly in cases of perforated appendicitis when there is likely inflammation near the rectum and possible abscess in the pelvis. As it progresses, appendicitis is often associated with adynamic ileus; leading to the complaint of constipation and possible misdiagnosis. Because enteric infections can cause appendicitis, diarrhea may be the initial manifestation and gastroenteritis may be the assumed diagnosis. In contrast to gastroenteritis, the abdominal pain in appendicitis is constant (not cramping or relieved by defecation), the emesis may become bile stained and persistent, and the clinical course worsens steadily rather than demonstrating a waxing and waning pattern. Fever is common and typically low-grade unless perforation has occurred. Most patients demonstrate at least mild tachycardia.

The temporal progression of symptoms from vague, mild pain, malaise, and anorexia to severe localized pain, fever, and vomiting typically occurs rapidly, in 24–48 hr in the majority of cases. If the diagnosis is delayed beyond 36–48 hr, the perforation rate exceeds 65%. A period after perforation of lessened abdominal pain and acute symptoms has been described, presumably with the elimination of pressure within the appendix. If the omentum or adjacent intestine is able to wall off the infectious process, the evolution of illness is less predictable and delay in presentation is likely. If perforation leads to diffuse peritonitis, the child generally has escalating diffuse abdominal pain and rapid development of toxicity evidenced by dehydration and signs of sepsis including hypotension, oliguria, acidosis, and high-grade fever. When several days have elapsed in the progression of appendicitis, patients often develop signs and symptoms of developing small bowel obstruction. If the appendix is retrocecal, appendicitis predictably evolves more slowly and patients are likely to relate 4–5 days of illness preceding evaluation. The pain is typically more lateral and posterior and can mimic the symptoms associated with septic arthritis of the hip or a psoas muscle abscess. Occasionally patients will complain of urinary symptoms, presumably related to inflammation adjacent to the ureter and/or bladder. Painful voiding may not be from dysuria but pressure transmitted to an inflamed peritoneum.

**PHYSICAL EXAMINATION**

Although the hallmark of diagnosing acute appendicitis remains a careful and thorough history and physical examination, all clinicians know the arcane nature of acute appendicitis, the consistent or typical clinical features are not present in all patients, and the diagnosis can be a humbling experience even for the most experienced clinicians. A primary focus of the initial assessment is attention to the temporal evolution of the illness in relation to specific presenting signs and symptoms. In many children, appendicitis can be confidently diagnosed based on history and physical examination alone, and the children can thus be spared the treatment delay, expense, and possible radiation exposure associated with imaging studies.

Physical examination begins with inspection of the child's demeanor as well as the appearance of the abdomen. Because appendicitis most often has an insidious onset, children rarely present <12 hr from the onset of illness, and the children who do present early are likely to have minimal findings. Children with early appendicitis (18–36 hr) typically appear mildly ill and move tentatively, hunched forward and, often with a slight limp favoring the right side. Supine, they often lie quietly on their right side with their knees pulled up to relax the abdominal muscles, and when asked to lie flat or sit up, they move cautiously and might use a hand to protect the RLQ.

Early in appendicitis, the abdomen is typically flat; abdominal distension suggests more advanced disease characteristic of perforation or developing small bowel obstruction. Auscultation can reveal normal or hyperactive bowel sounds in early appendicitis, which are replaced by hypoactive bowel sounds as the disease progresses to perforation. The judicious use of morphine analgesia to relieve abdominal pain does not change diagnostic accuracy or interfere with surgical decision making, and patients should receive adequate pain control.

Localized abdominal tenderness is the single most reliable finding in the diagnosis of acute appendicitis. McBurney described the classic point of localized tenderness in acute appendicitis, which is the junction of the lateral and middle thirds of the line joining the right anterior–superior iliac spine and the umbilicus, but the tenderness can also localize to any of the aberrant locations of the appendix. Localized tenderness is a later and less-consistent finding when the appendix is retrocecal in position (>50% of cases). In cases of an appendix localized entirely in the pelvis, the tenderness on abdominal examination may be minimal and best appreciated on rectal examination.

A gentle touch on the child's arm at the beginning of the examination with the reassurance that the abdominal examination will be similarly gentle can help to establish trust and increase the chance for a reliable and reproducible examination. The examination is best initiated in the left lower abdomen, so that the immediate part of the exam is not uncomfortable, and conducted in a counterclockwise direction moving gently to the left upper abdomen, right upper abdomen, and, lastly, the right lower abdomen. This should alleviate anxiety, allow relaxation of the abdominal musculature, and enhance trust. The examiner makes several “circles” of the abdomen with sequentially more pressure. A soft, compressible, nontender abdominal wall is reassuring. In appendicitis, any abdominal wall movement, including coughing (Duphny sign), may elicit pain. A consistent finding in acute appendicitis is guarding and rigidity of the overlying rectus muscle. This rigidity may be voluntary, to protect the area of tenderness from the examiner’s hand, or involuntary, secondary to peritonitis causing spasm of the overlying muscle.

Examination findings must be interpreted relative to the temporal evolution of the illness. Abdominal tenderness may be vague or even absent early in the course of appendicitis and is often diffuse after rupture. Rebound tenderness and referred tenderness (Rovsing sign) are also consistent findings in acute appendicitis but not always present. Rebound tenderness is elicited by deep palpation of the abdomen followed by the sudden release of the examining hand. This is often very painful to the child and has demonstrated poor correlation with peritonitis, so it should be avoided. Gentle finger percussion is a better test for peritoneal irritation. Similarly, digital rectal examination is uncomfortable and unlikely to contribute to the evaluation of appendicitis in most cases of appendicitis in children. Psoas and obturator internus signs are pain with passive stretch of these muscles. The psoas sign is elicited with active right thigh flexion or passive extension of the hip and typically positive in cases of a retrocecal appendix. The obturator sign is demonstrated by adductor pain after internal rotation of the flexed thigh and typically positive in cases of a pelvic appendix. Physical examination may demonstrate a mass in the RLQ representing an
inflammatory phlegmon around the appendix or a localized abscess (fluid collection).

**DIAGNOSTIC STUDIES**

**Laboratory Findings**

A variety of laboratory tests have been used in the evaluation of children with suspected appendicitis. Individually, none are very sensitive or specific for appendicitis, but collectively they can affect the clinician’s level of suspicion and decision-making to proceed with pediatric surgery consultation, discharge, or imaging studies. Findings should be interpreted with attention to the temporal evolution of the illness.

A complete blood count with differential and urinalysis are commonly obtained. The leukocyte count in early appendicitis may be normal or slightly elevated; however, it is only mildly elevated with a left shift (11,000-16,000/mm³) as the illness progresses in the initial 24-48 hr. Whereas a normal white blood cell (WBC) count never completely eliminates appendicitis, a count <8,000/mm³ in a patient with a history of illness longer than 48 hr should be viewed as highly suspicious for an alternative diagnosis. The leukocyte count may be markedly elevated (>20,000/mm³) in perforated appendicitis and rarely in nonperforated cases; a markedly elevated WBC count, other than in cases of advanced, perforated appendicitis, should raise suspicion of an alternative diagnosis.

Urinalysis often demonstrates a few white or red blood cells, as a result of the proximity of the inflamed appendix to the ureter or bladder, but it should be free of bacteria. The urine is often concentrated and contains ketones from diminished oral intake and vomiting. Gross hematuria is uncommon and suggests primary renal pathology or specific for appendicitis, but collectively they can affect the clinical decision-making to proceed with pediatric surgery consultation, discharge, or imaging studies. Findings should be interpreted with attention to the temporal evolution of the illness.

Electrolytes and liver chemistries are generally normal unless there has been a delay in diagnosis, leading to severe dehydration and/or sepsis. Amylase and liver enzymes are only helpful to exclude alternative diagnoses such as pancreatitis and cholecystitis and are not obtained if appendicitis is the strongly suspected diagnosis. Electrolytes are most helpful to assess level of illness and direct fluid resuscitation, but rarely aid accurate diagnosis.

C-reactive protein increases in proportion to the degree of appendiceal inflammation but is nonspecific and not widely used. Serum amyloid A protein is consistently elevated in patients with acute appendicitis with a sensitivity and specificity of 86% and 83%, respectively.

**Table 343-1**

<table>
<thead>
<tr>
<th>FEATURE</th>
<th>SCORE</th>
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<tr>
<td>Anorexia</td>
<td>1</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>1</td>
</tr>
<tr>
<td>Cough/percussion/hopping tenderness</td>
<td>2</td>
</tr>
<tr>
<td>Right lower quadrant tenderness</td>
<td>2</td>
</tr>
<tr>
<td>Migration of pain</td>
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</tr>
<tr>
<td>Leukocytosis &gt;10,000 (10⁹/L)</td>
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</tr>
<tr>
<td>Polymorphonuclear-neutrophilia &gt;7,500 (10⁹/L)</td>
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<tr>
<td>Total</td>
<td>10</td>
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**Radiologic Studies**

Following a thorough initial evaluation; history, physical examination, and review of vital signs and laboratory studies, if the diagnosis is uncertain, advanced radiographic studies can improve diagnostic accuracy.

**Plain Radiographs**

Plain abdominal radiographs may be helpful in select cases of abdominal pain/suspected appendicitis. Plain abdominal x-rays can demonstrate several findings in acute appendicitis including sentinel loops of bowel and localized ileus, scoliosis from psoas muscle spasm, a colonic air-fluid level above the right iliac fossa (colon “cutoff” sign), a RLQ soft-tissue mass, or a calcified appendicolith (5-10% of cases), but they are normal in 50% of patients, have a low sensitivity, and are not generally recommended (Fig. 343-1). Plain films are most helpful in evaluating complicated cases in which small bowel obstruction or free air is suspected.

**Ultrasound**

Ultrasound is usually utilized for diagnostic accuracy in the evaluation of acute appendicitis and has demonstrated >90% sensitivity and specificity in pediatric centers experienced with the technique. Graded abdominal compression is used to displace the cecum and ascending colon and identify the appendix, which has a typical target appearance (Fig. 343-2). The ultrasound criteria for appendicitis include wall thickness ≥6 mm, luminal distention, lack of compressibility, a complex mass in the RLQ, or an appendicolith. The visualized appendix usually...
Disadvantages of CT scan include; greater cost; radiation exposure; possible need for intravenous, oral, or rectal contrast; and possible need for sedation. Children have an increased sensitivity to radiation and a longer life ahead to potentially develop a radiation-induced malignancy. A single CT scan has been reported to confirm a 1 in 1,000 lifetime mortality risk, and the risk has been reported as high as 1 in 550 in children younger than age 5 yr. Oral contrast is problematic if it coincides with the site of localized pain and tenderness. Findings that suggest advanced appendicitis on ultrasound include asymmetric wall thickening, abscess formation, associated free intraperitoneal fluid, surrounding tissue edema, and decreased local tenderness to compression. The main limitation of ultrasound is an inability to visualize the appendix, which is reported in up to 20% of cases. A normal appendix must be visualized to exclude appendicitis by ultrasound. Certain conditions predictably decrease the sensitivity and reliability of ultrasound for appendicitis, including obesity, bowel distention, and pain, which interferes with the exam. Major advantages of ultrasound include its easy availability, rapid method, low cost, and freedom from need for patient preparation and ionizing radiation. Ultrasound can be particularly helpful in adolescent girls, a group with a high negative appendectomy rate (normal appendix found at surgery), because of its ability to evaluate for ovarian pathology without ionizing radiation. A diagnostic or normal ultrasound exam eliminates the need for CT and should be considered the first exam in a center experienced with the technique.

**CT Scan**

CT scan had been the gold standard imaging study for evaluating children with suspected appendicitis, but carries the significant negative effects of radiation exposure and increased costs. It should be used only in carefully selected patients and always observing the reduced radiation dosage recommendations for children. CT examination can be performed in many ways, including standard CT scan, helical CT scan, with or without oral and intravenous contrast, examination of both the abdomen and pelvis or pelvis alone, focused appendiceal CT scan, and focused appendiceal CT scan with rectal contrast. All of these techniques have demonstrated >95% sensitivity and specificity for acute appendicitis. Findings on CT scan consistent with appendicitis include a distended (dilated >7 mm) thick-walled appendix, inflammatory streaking of surrounding mesenteric fat, and a pericecal phlegmon or abscess (Figs. 343-3 and 343-4). In addition, appendicoliths are more readily demonstrated on CT scan (40-50%) than on plain radiographs (5-15%). CT scan may be most useful in advanced appendicitis to identify and guide percutaneous drainage of fluid collections and identification of an inflammatory mass, which might prompt a plan for initial nonoperative management. The use of CT scan to “rule out” acute appendicitis and avoid the need (and expenditures) of in-hospital admission is suspect as in early appendicitis CT findings are predictably subtle and in more advanced cases CT scan should be unnecessary as an accurate diagnosis should be able to be made on careful history and physical examination.

**Figure 343-2 Ultrasound examination of patients with appendicitis.** A, Transverse ultrasound scan of the appendix demonstrates the characteristic “target sign.” In this case, the innermost portion is sonolucent, compatible with fluid or pus. B, Longitudinal view of another patient demonstrates the alternating hyperechoic and hypoechoic layers with an outermost hypoechoic layer, suggesting periappendiceal fluid. C, Longitudinal ultrasound scan of the right lower quadrant demonstrates a dilated, noncompressible appendix. The bright echo within the appendix represents an appendicolith with acoustic shadowing (arrow). (From Kuhn JP, Slovis TL, Haller JO: Caffrey’s pediatric diagnostic imaging, vol 2, ed 10, Philadelphia, 2004, Mosby, p. 1684.)

**Figure 343-3 A, Phlegmon (open arrow) is noted around the enlarged appendix (solid arrow) in perforated appendicitis. B, Extraluminal air is shown adjacent to the wall-enhanced appendix (arrow) in perforated appendicitis. (From Yeung KW, Chang MS, Hsiao CP: Evaluation of perforated and nonperforated appendicitis with CT, Clin Imaging. 28(6):422–427, 2004.)**
appendicitis is confirmed, because of the risk for aspiration at induction of anesthesia. Because the finding of fat stranding in surrounding tissues is a key component of CT evaluation for appendicitis, CT is less reliable in thin children with minimal body fat. For this reason, rectal contrast can increase diagnostic accuracy in this group. CT imaging is also helpful in demonstrating nonappendiceal causes of abdominal pain.

Following initial evaluation, if the diagnosis of acute appendicitis is suspected but uncertain, it is advisable to obtain pediatric surgical consultation before proceeding with a CT scan. An alternative approach to diminish the use of CT scans is the emerging use of observational consultation before proceeding with a CT scan. An alternative approach is often more challenging. If the diagnosis is appendicitis, perforation has likely occurred and the child's presentation should evidence signs and symptoms of localized abscess/phlegmon in the RLQ or diffuse peritonitis. At this point in the illness, the WBC count should be elevated (>12,000/mm³) with a left shift; a WBC count <7,000/mm³ with a lymphocytosis is distinctly unusual in advanced appendicitis and more typical of gastroenteritis. A slightly slower progression of illness is also typical when the appendix is in a retrocecal position and symptoms of dysuria will be present, and the tenderness is located more in the flank or costovertebral angle. Rarely, appendicitis may recur in the stump of a previous appendectomy. Children younger than 3 yr of age and adolescent girls have historically proven to be at particularly high risk for an incorrect diagnosis.

Most important is differentiation of the patients with gastroenteritis, which is the most common misdiagnosis in the child with appendicitis. The time course of illness (hours, days, weeks) leading to presentation is a critical component of the history. The classic patient with acute appendicitis describes abdominal pain as the preeminent symptom. In general, symptoms of systemic illness such as headache, chills, and myalgias indicate that a patient does not have appendicitis. Acute appendicitis most often begins insidiously as generalized malaise or anorexia, but there is early (within hours) onset of abdominal pain and the illness typically escalates rapidly in the initial 24-48 hr. Most patients with acute appendicitis have 1-3 episodes of vomiting in the initial 24-48 hr of illness; multiple episodes of vomiting are unusual in early appendicitis. In contrast, when gastroenteritis is the diagnosis, diarrhea and vomiting are more likely to be predominant symptoms early in the illness, and abdominal pains may seem associated with the frequent episodes of diarrhea and vomiting. In patients with an acute presentation (<72 hr of illness), vomiting preceding pain, large-volume diarrhea, large amounts of nonbilious vomiting, and high fever suggest gastroenteritis. In addition, patients with appendicitis typically have normal or hypovolemic bowel sounds, whereas gastroenteritis typically produces persistently hyperactive bowel sounds. From the onset of illness, the child with appendicitis typically has a steadily deteriorating clinical course, whereas the child with gastroenteritis may have an undulating course, at times feeling better and other times feeling worse.

In the classic child with acute appendicitis who presents within 48 hr of the onset of illness, the WBC count can be low, normal, or elevated but is only rarely elevated >20,000/mm³. WBC counts in this range should prompt consideration of alternative diagnoses.

A child who presents with a history of illness of longer than 3-4 days is often more challenging. If the diagnosis is appendicitis, perforation has likely occurred and the child's presentation should evidence signs and symptoms of localized abscess/phlegmon in the RLQ or diffuse peritonitis. At this point in the illness, the WBC count should be elevated (>12,000/mm³) with a left shift; a WBC count <7,000/mm³ with a lymphocytosis is distinctly unusual in advanced appendicitis and more typical of gastroenteritis. A slightly slower progression of illness is also typical when the appendix is in a retrocecal position and symptoms and anterior abdominal wall tenderness typically are slower to evolve.

An abnormal hemogram combined with purpuric skin lesions, arthritis, and nephritis suggests a diagnosis of Henoch-Schönlein purpura or hemolytic-uremic syndrome. Torsion of an undescended testis and epididymitis are common but should be discovered on physical examination. Meckel diverticulitis is an infrequent condition, but the clinical presentation closely mimics appendicitis and the diagnosis is usually made at surgery. Primary spontaneous peritonitis is classically seen in prepubertal girls is often mistaken for appendicitis.

It should be recognized that “missed” appendicitis is the most common cause of small bowel obstruction in children without history of prior abdominal surgery. Atypical presentations of appendicitis are expected in association with other conditions such as pregnancy, Crohn disease, steroid treatment, and immunosuppressive therapy.

Figure 343-4  A, Precontrast-enhanced CT reveals an appendicolith (arrow) in perforated appendicitis. B, Postcontrast-enhanced CT (1 cm below the level in A) reveals intraluminal air in the appendix (curved arrow) associated with ileal wall enhancement in perforated appendicitis. (From Yeung KW, Chang MS, Hsiao CP: Evaluation of perforated and nonperforated appendicitis with CT, Clin Imaging 28(6):422–427, 2004.)

**MRI/White Blood Cell Scan**

MRI is at least equivalent to CT in diagnostic accuracy for appendicitis and does not involve ionizing radiation. The use of MRI in the evaluation of appendicitis is limited because it is less available, more costly, often requires sedation, and does not offer equivalent access for drainage of fluid collections. MRI may prove most useful in adolescent girls when advanced imaging is needed. Radionuclide-labeled WBC scans have also been used in some centers in evaluating atypical cases of possible appendicitis in children and demonstrated a high sensitivity (97%) but only modest specificity (80%).

**DIFFERENTIAL DIAGNOSIS**

The list of illnesses that can mimic acute appendicitis is extensive because many gastrointestinal, gynecologic, and inflammatory disorders can manifest with similar illness history, signs, and symptoms. Differential diagnosis, even limited to common conditions, includes gastroenteritis, mesenteric adenitis, Meckel diverticulitis, inflammatory bowel disease, diabetes mellitus, sickle cell disease, streptococcal pharyngitis, lower lobe pneumonia, cholecystitis, pancreatitis, urinary tract infection, infectious enteritis, and, in girls, ovarian torsion, ectopic pregnancy, ruptured ovarian cysts, and pelvic inflammatory disease (including tuboovarian abscess). Intestinal tract lymphoma, tumors of the appendix (carcinoid in children), and ovarian tumors are rare but can also masquerade as acute appendicitis. In patients with pyelonephritis, the fever and WBC count are likely much higher, symptoms of dysuria will be present, and the tenderness is located more in the flank or costovertebral angle. Rarely, appendicitis may recur in the stump of a previous appendectomy.
Appendicitis in association with Crohn disease often has a protracted presentation with an atypical pattern of recurring but localized abdominal pain.

The diagnosis of appendicitis in adolescent girls is especially challenging, and some series report negative appendectomy rates as high as 30–40%. Ovarian cysts are often acutely painful as a result of rupture, rapid enlargement, or hemorrhage. Rupture of an ovarian follicle associated with ovulation often causes mid-cycle lateralizing pain (mittel- schmerz), but there is no progression of symptoms and systemic illness is absent. Ovarian tumors and torsion can also mimic acute appendicitis, although ovarian torsion is typically characterized by the acute onset of severe pain and is associated with more dramatic nausea and vomiting than is normally seen in early appendicitis. In pelvic inflammatory disease, the pain is typically suprapubic, bilateral, and of longer duration. The need for accurate urgent diagnosis in girls is influenced by concern that perforated appendicitis can predispose the patient to future ectopic pregnancy or tubal infertility, although data have not consistently demonstrated increased incidence of infertility after perforated appendicitis. For these reasons, adjunct diagnostic studies (ultrasound, CT, or diagnostic laparoscopy) should be used more liberally in this group of patients to keep negative appendectomy rates low.

**DIAGNOSTIC APPROACH**

A diagnosis of acute appendicitis is made in only 50-70% of children at the time of initial assessment; negative appendectomy rates remain high (10-20%) and perforation rates (30-40%) have not changed in the past few decades.

Traditionally, early surgery in equivocal cases was the standard; aimed to minimize perforation rates and complications. Negative laparotomy rates of 10-20% were common and were deemed acceptable to keep perforation rates low. Many authors have criticized these high negative laparotomy rates, citing the risks and expense of unnecessary surgery and anesthesia. In a national database, overall rupture rates for appendicitis varied from 20-76%, with a median of 36%. The median overall negative laparotomy rate (normal appendix at surgery) was 2.6%, significantly lower than traditionally reported rates of 10-20%.

The lack of consensus in management approach is reflected by the fact that the use of diagnostic imaging in cases of suspected appendicitis varied from 18-89%.

Some clinicians remain steadfast to the primacy of a careful history and physical examination and rarely order advanced imaging studies. The initial assessment, along with the history and physical examination, may include a complete blood count with differential, urinalysis, and plain films (chest and abdominal series). If the initial assessment leads to a high level of suspicion for appendicitis, pediatric surgical consultation should be the next step, with the likelihood of prompt appendectomy without further studies. If the initial evaluation suggests a nonsurgical diagnosis and a low concern for appendicitis, the child may be discharged with family education regarding the natural history and progression of acute appendicitis and advice to return for repeat evaluation if the child is not improving on liquids and a bland diet in the next 24 hr. This approach has demonstrated high sensitivity and specificity (>90%) at certain institutions, but collective data from many centers have not been able to reproduce this degree of accuracy.

Previous reports recommending CT scans in all equivocal cases to minimize perforation rates and morbidity are not supported in the current climate to reduce the use of CT scan and ionizing radiation. It seems likely that if imaging studies are obtained in all patients with equivocal presentations and a brief duration of illness (<24 hr), the false-negative rate of the imaging studies will increase. Maximum benefit and effectiveness of advanced imaging is obtained when it is used selectively in children for whom the diagnosis is equivocal after careful history and physical examination by an experienced clinician and who are not too early in the temporal evolution of the illness.

In equivocal cases, some centers proceed with a plan of active observation. Many reports substantiate improved diagnostic accuracy by observation and serial examination over a period of 12-24 hr, simplifying the eventual decision to proceed with appendectomy, discharge the patient, or proceed with advanced imaging studies, and report no correlation between surgical morbidity and timing of surgery. The use of observation units, where the child may be observed with intravenous fluids, serial vital signs, and planned repeat physical examination in 6-12 hr, is a strategy gaining increased popularity. At the end of a period of observation, the clinician should decide to discharge the patient based on improved clinical status, proceed to appendectomy, or proceed to further imaging evaluation. Advanced imaging in this equivocal group will be more reliable further into the disease process and hopefully can minimize the negative laparotomy rate without increasing the perforation rate (missed or delayed diagnosis). Less than 2% of children’s appendices perforate while under observation.

A thoughtful approach in equivocal cases of appendicitis is to begin with ultrasound if it is available and the hospital has experience with ultrasound for possible appendicitis. In 1 study, ultrasound decreased the need for CT scan in 22% of patients. If ultrasound imaging is inconclusive, the next diagnostic step could be pediatric surgical consultation, a brief period of observation followed by clinical reevaluation and CT scan if the diagnosis remains equivocal. The period of observation (12-24 hr) can occur at home provided the patient is physiologically well; a hospital-based observational unit has the advantage of being able to provide intravenous fluids. CT scan may be used as the first-line test in obese patients, in cases of probable advanced or perforated appendicitis, or when there is gaseous distention of the bowel. Practice guidelines have decreased both length of stay and costs without increasing complications. One such guideline employing clinical judgment and selective imaging attained a positive and negative predictive value for appendicitis of 94% and 99%, respectively.

**TREATMENT**

Once the diagnosis of appendicitis is confirmed or highly suspected, the standard treatment for acute appendicitis is most often prompt appendectomy. Some reports suggest initial nonoperative management (antibiotics and drainage of fluid collections) as an alternative option in late presentations, depending on the patient’s general condition and the state of the appendix. In adults with simple appendicitis, broad-spectrum antibiotics alone have resulted in resolution of symptoms. Nonetheless, there is a 20% chance of recurrence within 1 year of conservative therapy, and of those 20% will present with perforation or a gangrenous appendix. One small nonrandomized trial of nonoperative therapy for uncomplicated appendicitis in children reported a success rate of ~90%. To be considered uncomplicated, patients had pain ≤48 hours, ultrasonographic or CT documentation of a nonruptured appendix, as well as an appendiceal diameter ≤1.1 cm without phlegmon, abscess, or fecalith. Management included a minimum of 24 hr of intravenous antibiotics (piperacillin-tazobactam or ciprofloxacin with metronidazole) followed by amoxicillin-clavulanate or ciprofloxacin with metronidazole to complete a 10-day total antibiotic course.

Emergency (middle of the night) surgery is rarely indicated, and most patients require preoperative supportive measures to stabilize vital signs and to ensure the safety of the procedure, anesthesia, and improve outcomes. In addition, often, unexpected pathology (appendiceal tumors, intestinal lymphoma, congenital renal anomalies, inflammatory bowel disease) is discovered at operation, and intraoperative consultation and frozen section may be needed. There is no correlation between timing of surgery and perforation rates or postoperative morbidity when the operation proceeds within 24-48 hr of diagnosis. In addition, appendectomy can be a challenging operation, with potential for major complications including injury to adjacent intestine, the iliac vessels, or the right ureter. The operation should proceed semielectively within 12-24 hr of diagnosis. Children with appendicitis are typically at least mildly dehydrated and require preoperative fluid resuscitation to correct hypovolemia and electrolyte abnormalities before anesthesia. Fever, if present, should be treated. Pain management begins even before a definitive diagnosis is made, and consultation of a pain service, if available, is appropriate once a decision is made to proceed to surgery. In the majority of cases, preoperative management can be accomplished during the period of diagnostic evaluation and prompt appendectomy can be performed.
In patients in whom perforated appendicitis is identified at the time of diagnosis, the operation is even less urgent and proper preoperative management is more critical. When the illness is protracted owing to a delay in diagnosis or presentation, patients can demonstrate significant physiologic derangements including severe dehydration, hypotension, acidosis, and renal failure. These patients require a longer period of stabilization with fluid resuscitation and antibiotics, including, in occasional cases, admission to an intensive care unit before proceeding with more definitive management. Based on the patient’s status, findings on CT scan, and availability of experienced radiologists, the initial plan may be percutaneous drainage of fluid collections by interventional radiology and continued fluid resuscitation and antibiotics. An inflammatory mass (phlegmon) without an identifiable fluid component might initially respond to nonoperative management with fluids and antibiotics. Placement of 1 or more drainage catheters under imaging (CT or ultrasound) guidance has been successful in more than 80% of patients. Most pediatric surgeons recommend delayed appendectomy (during the same hospitalization) or interval appendectomy (4-6 wk after the initial presentation), to prevent recurrent appendicitis (>20%); this is an area of some controversy.

If diffuse peritonitis exists, most surgeons proceed promptly with appendectomy after a brief period of intravenous fluids and broad-spectrum antibiotics. Others continue nonoperative management provided the patient demonstrates clinical improvement by physiologic criteria including hemodynamic stability, urine output, control of fever, and declining leukocyte count. If the patient demonstrates clinical recovery by resolution of fever, sepsis, and return of bowel function, generally a 2 wk course of oral antibiotics is completed and a decision is made regarding interval appendectomy in 6-8 wk. A child who fails to improve within 24-72 hr needs an urgent appendectomy to control sepsis. Emergency appendectomy should only be performed in the occasional circumstance when physiologic resuscitation requires urgent control of advanced peritoneal sepsis not amenable to interventional drainage or this is not available.

**Antibiotics**

Antibiotics substantially lower the incidence of postoperative wound infections and intraabdominal abscesses in perforated appendicitis, but their role is less well defined in simple appendicitis. The antibiotic regimen should be directed against the typical bacterial flora found in the appendix, including anaerobic organisms (Bacteroides, Clostridia, and Peptostreptococcus spp.) and Gram-negative aerobic bacteria (Escherichia coli, Pseudomonas aeruginosa, Enterobacter, and Klebsiella spp.). Gram-positive organisms are less commonly found in the colon, and the need to provide antibiotic coverage for them (primarily enterococcus) is controversial. Many antibiotic combinations have demonstrated equivalent efficacy in controlled trials in terms of wound infection rate, resolution of fever, length of stay, and incidence of complications.

For simple nonperforated appendicitis, one preoperative dose of a single broad-spectrum agent (cefotixin) or equivalent is sufficient. The practice in perforated or gangrenous appendicitis, most surgeons prefer combination regimens such as Cefazolin (pipercillin/tazobactam), ticarcillin/clavulanate, or ceftriaxone/metronidazole. The traditional “triple” antibiotic regimen (ampicillin, gentamicin, and clindamycin or metronidazole) is still effective, but adds cost and has the concern for ototoxicity. Antibiotic coverage is continued postoperatively for 3-5 days. Oral antibiotics are equally as effective as intravenous, and therefore the patient can be switched to an oral regimen and discharged once bowel function returns. This transition to oral antibiotics has significantly affected length of stay and cost in the management of perforated appendicitis.

**Interval Appendectomy**

Ruptured appendicitis complicated by a walled-off inflammatory mass or abscess can be treated without immediate appendectomy. This strategy is intended to avoid a predictable higher surgical complication rate and is often useful in children, in whom the overall incidence of perforation approaches 50%. In this group of patients, debate exists over the need for interval appendectomy if the child recovers well without “up front” appendectomy. The risk of developing recurrent appendicitis if the appendix is not removed is unknown, and published reports vary between 10% and 80% (most are closer to 10%). Most cases of recurrent appendicitis develop within 2 yr of the initial illness. Some authors believe interval appendectomy is unnecessary because of the low risk for recurrent appendicitis. Others support interval appendectomy to avoid recurrent appendicitis and to confirm the original diagnosis, citing an incidence of unexpected pathology in 30% of interval appendectomy specimens. The vast majority of pediatric surgeons perform interval appendectomy routinely (4-6 wk interval) after initial nonoperative management of perforated appendicitis.

**Surgical Technique**

Diagnostic laparoscopy and laparoscopic appendectomy (minimally invasive technique) for both simple and perforated appendicitis are the preferred approaches in most pediatric centers; the open surgery is still performed in selected cases. Laparoscopic appendectomy has significant advantages in administrative factors (cost, resource utilization, length of stay), and slight improvement in clinical outcome measures (wound infection rate, intraabdominal abscess, anastomotic requirements, return to full activity), but have failed to establish an evidence-based preference between laparoscopic and open appendectomy in children. In nonperforated appendicitis, laparoscopic appendectomy appears to have lower narcotic analgesic requirements, decreased wound morbidity, and improved cosmesis, but operative times seem slightly higher and costs are almost doubled compared to the open procedure. Length of hospitalization is similar for both approaches.

The role of laparoscopy in perforated appendicitis is less-well defined. There are no convincing data to recommend one approach in all patients. Most pediatric surgeons use both approaches selectively. The laparoscopic approach is used most often for obese patients, when alternative diagnoses are suspected, and in adolescent girls to better evaluate for ovarian pathology and pelvic inflammatory disease while avoiding the ionizing radiation associated with CT imaging. Injection of local anesthetic (bupivacaine) into the wound reduces postoperative pain.

**Complications**

Morbidity rates for appendicitis vary widely in large series from 10-45%. The principal determinant of complications is the severity of the appendicitis. In nonperforated appendicitis, an overall complication rate of 3-7% is expected. With perforation, the complication rate rises to 15-30%. The most common complications are wound infections (3-10%) and intraabdominal abscesses; both are more common after perforation. Perforation and abscess formation can also lead to fistula formation in adjacent organs. Perforation rates are consistently >80% in children younger than 5 yr of age. Delay in return to full activity and function is also predictable in perforated appendicitis. Patients with advanced appendicitis can progress to sepsis and multi-system organ failure, but generally these patients respond promptly to antibiotics, fluids, and other supportive measures preoperatively. Other potential complications include postoperative ileus, diffuse peritonitis, portal vein pylephlebitis (rare), and adhesive small bowel obstruction. Readmission rates are significantly higher in perforated appendicitis (>20%) and this has become an important marker in recent quality metrics. Mortality with appendicitis is rare (<0.5%) and seen mostly in neonates and immunocompromised patients.

**INCIDENTAL APPENDICOLITHS**

The question of the “ incidental” appendicolith is an intriguing one for pediatric practitioners. These are patients who do not have appendicitis but are found to have an appendicolith with imaging. In adults, incidental appendicoliths identified by CT scans vary in incidence from <1% to as high as 10%. An appendicolith is defined as a calcification within the appendiceal lumen. They have a characteristic dense and laminated appearance when compared to other lower abdominal calcifications, including phleboliths (venous calcifications) and, in
girls, ovarian calcifications, most commonly seen in ovarian tumors. They can be appreciated on plain film, ultrasound, and CT scan; CT scan is the most reliable. Occasionally an appendicolith is noted during laparoscopy while visualizing a noninflamed appendix.

When an appendicolith is noted in the evaluation of a child with abdominal pain and suspected appendicitis, the finding of the appendicolith confirms the diagnosis; surgical consultation and prompt appendectomy is indicated. Appendicoliths may be noted in the evaluation of patients who have no signs of appendicitis; such as imaging obtained after trauma or for nonspecific abdominal complaints. The concern in this setting is that the appendicolith may increase the eventual development of acute appendicitis. In addition, there is the concern that appendicitis that develops in association with an appendicolith may have a rapidly escalating course and early perforation. Some physicians believe that an appendicolith may be associated with recurrent RLQ/iliac fossa pain.

Incidental appendicoliths may be transient and in most short-term follow-up studies have a low risk of subsequent acute appendicitis. The risk of subsequent appendicitis may be higher in those presenting with abdominal pain or those younger than 19 yr of age. The lifetime risk for the development of appendicitis in patients with an incidental appendicolith is approximately 5%.

Radiographically detected incidental appendicoliths are usually managed with observation, planned follow up, and patient education for signs of an acute appendicitis, while those detected during laparoscopy to rule out acute appendicitis (when the appendix is normal in appearance) may or may not undergo appendectomy. After discussing the risks and benefits with the family, and persistence of the appendicolith, some conclude that an elective appendectomy may be indicated.

*Bibliography is available at Expert Consult.*
In understanding the spectrum of anorectal anomalies, it is necessary to consider the importance of the sphincter complex, a mass of muscle fibers surrounding the anorectum (Fig. 344-1). This complex is the combination of the puborectalis, levator ani, external and internal sphincters, and the superficial external sphincter muscles, all meeting at the rectum. Anorectal malformations are defined by the relationship of the rectum to this complex and include varying degrees of stenosis to complete atresia. The incidence is 1 per 3,000 live births. Significant long-term concerns focus on bowel control and urinary and sexual functions.

EMBRYOLOGY
The hindgut forms early as the part of the primitive gut tube that extends into the tail fold in the 2nd wk of gestation. At about day 13, it develops a ventral diverticulum, the allantois or primitive bladder. The junction of allantois and hindgut become the cloaca, into which the genital, urinary, and intestinal tubes empty. This is covered by a cloacal membrane. The urorectal septum descends to divide this common channel by forming lateral ridges, which grow in and fuse by the middle of the 7th wk. Opening of the posterior portion of the membrane (the anal membrane) occurs in the 8th wk. Failures in any part of these processes can lead to the clinical spectrum of anogenital anomalies.

Imperforate anus can be divided into low lesions, where the rectum has descended through the sphincter complex, and high lesions, where it has not. Most patients with imperforate anus have a fistula. There is a spectrum of malformation in boys and girls. In boys, low lesions usually manifest with meconium staining somewhere on the perineum along the median raphe (Fig. 344-2A). Low lesions in girls also manifest as a spectrum from an anus that is only slightly anterior on the perineal body to a fourchette fistula that opens on the moist mucosa of the introitus distal to the hymen (Fig. 344-3A). A high imperforate anus in a boy has no apparent cutaneous opening or fistula, but it usually has a fistula to the urinary tract, either the urethra or the bladder (Fig. 344-2B). Although there is occasionally a rectovaginal fistula, in girls, high lesions are usually cloacal anomalies in which the rectum, vagina, and urethra all empty into a common channel or cloacal stem of varying length (Fig. 344-3B). The interesting category of boys with imperforate anus and no fistula occurs mainly in children with trisomy 21.

ASSOCIATED ANOMALIES
There are many anomalies associated with anorectal malformations (Table 344-1). The most common are anomalies of the kidneys and urinary tract in conjunction with abnormalities of the sacrum. This complex is often referred to as the caudal regression syndrome. Boys with a rectovesical fistula and patients with a persistent cloaca have a 90% risk of urologic defects. Other common associated anomalies are cardiac anomalies and esophageal atresia with or without tracheoesophageal fistula. These can cluster in any combination in a patient. When combined, they are often accompanied by abnormalities of the radial aspect of the upper extremity and are termed the VATERR sequence.

**Table 344-1**

<table>
<thead>
<tr>
<th><strong>GENITOURINARY</strong></th>
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<tbody>
<tr>
<td>Vesicoureteric reflux</td>
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<td>Renal agenesis</td>
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<td>Renal dysplasia</td>
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<td>Ureteral duplication</td>
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<td>Cryptorchidism</td>
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<td>Hypospadias</td>
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<td>Bicornuate uterus</td>
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<td>Vaginal septums</td>
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<tr>
<th><strong>VERTEBRAL</strong></th>
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<tr>
<td>Spinal dysraphism</td>
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<td>Tethered chord</td>
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<td>Presacral masses</td>
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<td>Meningocele</td>
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<td>Lipoma</td>
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<td>Dermoid</td>
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<td>Teratoma</td>
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<tr>
<th><strong>CARDIOVASCULAR</strong></th>
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<tbody>
<tr>
<td>Tetralogy of Fallot</td>
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<tr>
<td>Ventricular septal defect</td>
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<tr>
<td>Transposition of the great vessels</td>
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<td>Hypoplastic left-heart syndrome</td>
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<tr>
<th><strong>GASTROINTESTINAL</strong></th>
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<tr>
<td>Tracheoesophageal fistula</td>
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<td>Duodenal atresia</td>
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<tr>
<td>Malrotation</td>
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<td>Hirschsprung disease</td>
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<tr>
<th><strong>CENTRAL NERVOUS SYSTEM</strong></th>
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<tbody>
<tr>
<td>Spina bifida</td>
<td></td>
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<tr>
<td>Tethered cord</td>
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</table>
**Figure 344-1** Normal anorectal anatomy in relation to pelvic structures. **A**, Male. **B**, Female. (From Peña A: Atlas of surgical management of anorectal malformations, New York, 1989, Springer-Verlag, p. 3.)

**Figure 344-2** Imperforate anus in males. **A**, Low lesions. **B**, High lesions. (From Peña A: Atlas of surgical management of anorectal malformations, New York, 1989, Springer-Verlag, pp. 7, 26.)

**Figure 344-3** Imperforate anus in females. **A**, Vestibular fistula. **B**, Cloaca. (From Peña A: Atlas of surgical management of anorectal malformations, New York, 1989, Springer-Verlag, pp. 50, 60.)
Rectal Atresia

Rectal atresia is a rare defect occurring in only 1% of anorectal anomalies. It has the same characteristics in both sexes. The unique feature of this defect is that affected patients have a normal anal canal and a normal anus. The defect is often discovered while rectal temperature is being taken. An obstruction is present approximately 2 cm above the skin level. These patients need a protective colostomy. The functional prognosis is excellent because they have a normal sphincteric mechanism (and normal sensation), which resides in the anal canal.

APPROACH TO THE PATIENT

Evaluation includes identifying associated anomalies (see Table 344-1). Careful inspection of the perineum is important to determine the presence or absence of a fistula. If the fistula can be seen there, it is a low lesion. The invertogram or upside-down x-ray is of little value, but a prone crosstable lateral plain x-ray at 24 hr of life (to allow time for bowel distention from swallowed air) with a radiopaque marker on the perineum can demonstrate a low lesion by showing the renal gas bubble <1 cm from the perineal skin. A plain x-ray of the entire sacrum, including both iliac wings, is important to identify sacral anomalies and the adequacy of the sacrum. An abdominal-pelvic ultrasound and voiding cystourethrograph must be performed. The clinician should also pass a nasogastric tube to identify esophageal atresia and should obtain an echocardiogram. In boys with a high lesion, the voiding cystourethrograph often identifies the rectourinary fistula. In girls with a high lesion, more invasive evaluation, including vaginogram and endoscopy, is often necessary for careful detailing of the cloacal anomaly.

Good clinical evaluation and a urinalysis provide enough data in 80-90% of male patients to determine the need for a colostomy. Voluntary sphincteric muscles surround the most distal part of the bowel in cases of perineal and rectourethral fistulas, and the intraluminal bowel pressure must be sufficiently high to overcome the tone of those muscles before meconium can be seen in the urine or on the perineum. The presence of meconium in the urine and a flat bottom are considered indications for the creation of a colostomy. Clinical findings consistent with the diagnosis of a perineal fistula represent an indication for an anoplasty without a protective colostomy. Ultrasound is valuable not only for the evaluation of the urinary tract, but it can also be used to investigate spinal anomalies in the newborn and to determine how close to the perineum the rectum has descended.

More than 90% of the time, the diagnosis in females can be established on perineal inspection. The presence of a single perineal orifice is a clue. A palpable pelvic mass (hydrocolpos) reinforces this diagnosis. A vestibular fistula is diagnosed by careful separation of the labia, exposing the vestibule. The rectal orifice is located immediately in front of the hymen within the female genitalia and in the vestibule. A perineal fistula is easy to diagnose. The rectal orifice is located somewhere between the female genitalia and the center of the sphincter and is surrounded by skin. Less than 10% of these patients fail to pass meconium through the genitalia or perineum after 24 hr of observation. Those patients can require a prone crosstable lateral film.

OPERATIVE REPAIR

Sometimes a perineal fistula, if it opens in good position, can be treated by simple dilation. Hegar dilators are employed, starting with a No. 5 or 6 and letting the baby go home when the mother can use a No. 8. Twice-daily dilatations are done at home, increasing the size every few weeks until a No. 14 is achieved. By 1 yr of age, the stool is usually well formed and further dilation is not necessary. By the time No. 14 is reached, the examiner can usually insert a little finger. If the anal ring is soft and pliable, dilation can be reduced in frequency or discontinued.

Occasionally, there is no visible fistula, but the rectum can be seen to be filled with meconium bulging on the perineum, or a covered anus is otherwise suspected. If confirmed by plain x-ray or ultrasound of
the perineum that the rectum is <1 cm from the skin, the clinician can do a minor perineal procedure to perforate the skin and then proceed with dilation or do a simple perineal anoplasty.

When the fistula orifice is very close to the introitus or scrotum, it is often appropriate to move it back surgically. This also requires postoperative dilation to prevent stricturing formation. This procedure can be done any time from the newborn period to 1 yr. It is preferable to wait until dilatations have been done for several wk and the child is bigger. The anorectum is a little easier to dissect at this time. The posterior sagittal approach of Peña is used, making an incision around the fistula and then in the midline to the site of the posterior wall of the new location. The dissection is continued in the midline, using a muscle stimulator to be sure there is adequate muscle on both sides. The fistula must be dissected cephalad for several centimeters to allow posterior positioning without tension. If appropriate, some of the distal fistula is resected before the anastomosis to the perineal skin.

In children with a high lesion, a double-barrel colostomy is performed. This effectively separates the fecal stream from the urinary tract. It also allows the performance of an augmented pressure colostogram before repair to identify the exact position of the distal rectum and the fistula. The definitive repair or posterior sagittal anorectoplasty (PSARP) is performed at about 1 yr of age. A midline incision is made, often splitting the coccyx and even the sacrum. Using a muscle stimulator, the surgeon stays strictly in the midline and divides the sphincter complex and identifies the rectum. The rectum is then opened in the midline and the fistula is identified from within the rectum. This allows a division of the fistula without injury to the urinary tract. The rectum is then dissected proximally until enough length is gained to suture it to an appropriate perineal position. The muscles of the sphincter complex are then sutured around (and especially behind) the rectum.

Other operative approaches (such as an anterior approach) are used, but the most popular procedure is by laparoscopy. This operation allows division of the fistula under direct visualization and identification of the sphincter complex by transillumination of the perineum. Other imaging techniques in the management of anorectal malformations include 3D endorectal ultrasound, intraoperative MRI and colonoscopy-assisted PSARPs, which may help perform a technically “better” operation. None of these other procedures or innovations has demonstrated improved outcomes.

A similar procedure can be done for female high anomalies with variations to deal with separating the vagina and rectum from within the cloacal stem. When the stem is longer than 3 cm, this is an especially difficult and complex procedure.

Usually, the colostomy can be closed 6 wks or more after the PSARP. Two weeks after any anal procedure, twice-daily dilatations are performed by the family. By doing frequent dilatations, each one is not so painful and there is less tissue trauma, inflammation, and scarring.

**OUTCOME**
The ability to achieve rectal continence depends on both motor and sensory elements. There must be adequate muscle in the sphincter complex and proper positioning of the rectum within the complex. There must also be intact innervation of the complex and of sensory elements as well as the presence of these sensory elements in the anorectum. Patients with low lesions are more likely to achieve true continence. They are also, however, more prone to constipation, which leads to overflow incontinence. It is very important that all these patients are followed closely, and that the constipation and anal dilation are well managed until toilet training is successful. Tables 344-2 and 344-3 outline the results of continence and constipation in relation to the malformation encountered.

Children with high lesions, especially boys with rectoprostatic urethral fistulas and girls with cloacal anomalies, have a poorer chance of being continent, but they can usually achieve a socially acceptable defecation (without a colostomy) pattern with a bowel management program. Often, the bowel management program consists of a daily enema to keep the colon empty and the patient clean until the next enema. If this is successful, an antegrade continence enema (ACE) procedure, sometimes called the Malone or MACE procedure, can improve the patient’s quality of life. These procedures provide access to the right colon either by bringing the appendix out the umbilicus in a nonrefluxing fashion or by putting a plastic button in the right lower quadrant to access the cecum. The patient can then sit on the toilet and administer the enema through the ACE, thus flushing out the entire colon. Antegrade regimens can produce successful 24 hr cleanliness rates of up to 95%. Of special interest is the clinical finding that most patients improve their control with growth. Patients who wore diapers or pull-ups to primary school are often in regular underwear by high school. Some groups have taken advantage of this evidence of psychological influences to initiate behavior modification early with good results.

### 344.2 Anal Fissure

**Begum Akay and Michael D. Klein**

Anal fissure is a laceration of the anal mucocutaneous junction. It is an acquired lesion of unknown etiology. While likely secondary to the forceful passage of a hard stool, it is mainly seen in infants younger

<table>
<thead>
<tr>
<th>Table 344-2</th>
<th>Results of Surgical Treatment of Anorectal Malformations: Total Continence*</th>
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<tbody>
<tr>
<td><strong>TYPE</strong></td>
<td><strong>PERCENTAGE</strong></td>
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<td>LOW</td>
<td></td>
</tr>
<tr>
<td>Perineal fistula</td>
<td>90</td>
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<td>Rectal atresia/stenosis</td>
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<tr>
<td>Vestibular fistula</td>
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<tr>
<td>HIGH</td>
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</tr>
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<td>Imperforate with no fistula</td>
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<tr>
<td>Bulbar urethral fistula</td>
<td>50</td>
</tr>
<tr>
<td>Short cloaca</td>
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</tr>
<tr>
<td>Prostatic fistula</td>
<td>31</td>
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<tr>
<td>Long cloaca</td>
<td>29</td>
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<tr>
<td>Bladder neck fistula</td>
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*Voluntary bowel movements, no soiling.


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<thead>
<tr>
<th>Table 344-3</th>
<th>Constipation and Type of Anogenital Malformation</th>
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<tbody>
<tr>
<td><strong>TYPE</strong></td>
<td><strong>PERCENTAGE</strong></td>
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<tr>
<td>Vestibular fistula</td>
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<tr>
<td>Bulbar urethral fistula</td>
<td>64</td>
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<tr>
<td>Rectal atresia/stenosis</td>
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<tr>
<td>Imperforate with no fistula</td>
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<td>Perineal fistula</td>
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<td>Long cloaca</td>
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<td>Prostatic fistula</td>
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<td>Short cloaca</td>
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<tr>
<td>Bladder neck fistula</td>
<td>16</td>
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than 1 yr of age when the stool is frequently quite soft. Fissures may be the consequence and not the cause of constipation.

**CLINICAL MANIFESTATIONS**

A history of constipation is often described, with a recent painful bowel movement corresponding to the fissure formation after passing of hard stool. The patient then voluntarily retains stool to avoid another painful bowel movement, exacerbating the constipation, resulting in harder stools. Complaints of pain on defecation and bright red blood on the surface of the stool are often elicited.

The diagnosis is established by inspection of the perineal area. The infant's hips are held in acute flexion, the buttocks are separated to expand the folds of the perianal skin, and the fissure becomes evident as a minor laceration. Often a small skin appendage is noted peripheral to the lesion. This “skin tag” actually represents epithelialized granulomatous tissue, formed in response to chronic inflammation. Findings on rectal examination can include hard stool in the ampulla and rectal spasm.

**TREATMENT**

The parents must be counseled as to the origin of the laceration and the mechanism of the cycle of constipation. The goal is to ensure that the patient has soft stools to avoid overstretching the anus. The healing process can take several weeks or even several months. A single episode of impaction with passing of hard stool can exacerbate the problem. Treatment requires that the primary cause of the constipation be identified. The use of dietary and behavioral modification and a stool softener is indicated. Parents should titrate the dose of the stool softener based on the patient’s response to treatment. Stool softening is best done by increasing water intake or using an oral polyethylene glycolate such as MiraLAX or GlycoLax. Surgical intervention, including stretching of the anus, “internal” anal sphincterotomy, or excision of the fissure, is not indicated or supported by scientific evidence.

Chronic anal fissures in older patients are associated with constipation, prior rectal surgery, Crohn disease, and chronic diarrhea. They are managed initially like fissures in infants, with stool softeners with the addition of sitz baths. Topical 0.2% glyceryl trinitrate reduces anal spasm and heals fissures, but it is often associated with headaches. Calcium channel blockers, such as 2% diltiazem ointment and 0.5% nifedipine cream, are more effective and cause fewer headaches than glyceryl trinitrate. Injection of botulinum toxin from 1.25-25 units is also effective and probably replicates chemically the action of internal sphincterotomy which is the most effective treatment in adults, although seldom used in children.

Perianal abscess, like all skin and soft-tissue infections, have become much more common since the year 2000 (a 4-fold increase in patients admitted to our hospital, and a 3-fold increase in patients presenting to the emergency room). These usually manifest in infancy and are of unknown etiology. Fistula appears to secondary to abscess rather than a cause. Links to congenitally abnormal crypts of Morgagni have been proposed, suggesting that deeper crypts (3-10 mm rather than the normal 1-2 mm) lead to trapped debris and cryptitis (Fig. 344-4).

Conditions associated with the risk of an anal fistula include Crohn disease, tuberculosis, pilonidal disease, hidradenitis, HIV, trauma, foreign bodies, dermal cysts, sacrococcygeal teratoma, actinomycesis, lymphgranuloma venereum and radiotherapy.

The most common organisms isolated from perianal abscesses are mixed aerobic (Escherichia coli, Klebsiella pneumoniae, Staphylococcus aureus) and anaerobic (Bacteroides spp, Clostridium, Veillonella) flora. Ten percent to 15% yield pure growth of E. coli, S. aureus, or Bacteroides fragilis. There is a strong male predominance in those affected who are younger than 2 yr of age. This imbalance corrects in older patients, where the etiology shifts to associated conditions such as inflammatory bowel disease, leukemia, or immunocompromised states.

**CLINICAL MANIFESTATIONS**

In younger patients, symptoms are usually mild and can consist of low-grade fever, mild rectal pain, and an area of perianal cellulitis. Often these spontaneously drain and resolve without treatment. In older patients with underlying predisposing conditions, the clinical course may be more serious. A compromised immune system can mask fever and allow rapid progression to toxicity and sepsis. Abscesses in these patients may be deeper in the ischiorectal fossa or even supralevator in contrast to those in younger patients, which are usually adjacent to the involved crypt.

Progression to fistula in patients with perianal abscesses occurs in up to 85% of cases and usually manifests with drainage from the perineal skin or multiple recurrences. Similar to abscess formation, fistulas have a strong male predominance. Histologic evaluation of fistula tracts typically reveals an epithelial lining of stratified squamous cells associated with chronic inflammation. It might also reveal an alternative etiology such as the granulomas of Crohn disease or even evidence of tuberculosis.
TREATMENT

Treatment is rarely indicated in infants with no predisposing disease because the condition is often self-limited. Even in cases of fistulization, conservative management (observation) is advocated because the fistula often disappears spontaneously. Antibiotics are not useful in these patients. When dictated by patient discomfort, abscesses may be drained under local anesthesia. Fistulas requiring surgical intervention may be treated by fistulotomy (unroofing or opening), fistulectomy (excision of the tract leaving it open to heal secondarily), or placement of a seton (heavy suture threaded through the fistula, brought out the anus and tied tightly to itself). In patients with inflammatory bowel disease topical tacrolimus has been effective.

Older children with predisposing diseases might also do well with minimal intervention. If there is little discomfort and no fever or other sign of systemic illness, local hygiene and antibiotics may be best. The danger of surgical intervention in an immunocompromised patient is the creation of an even larger, nonhealing wound. There certainly are such patients with serious systemic symptoms who require more aggressive intervention along with treatment of the predisposing condition. Broad-spectrum antibiotic coverage must be administered and wide excision and drainage are mandatory in cases involving sepsis and expanding cellulitis.

Fistulas in older patients are mainly associated with Crohn disease, a history of pull-through surgery for the treatment of Hirschsprung disease, or, in rare cases, tuberculosis. Those fistulas are often resistant to therapy and require treatment of the predisposing condition.

Complications of treatment include recurrence and, rarely, incontinence.

344.4 Hemorrhoids

Begum Akay and Michael D. Klein

Hemorrhoidal disease does occur in children and adolescents, often related to a diet deficient in fiber and poor hydration. In younger children, the presence of hemorrhoids should also raise the suspicion of portal hypertension. A third of patients with hemorrhoids require treatment.

CLINICAL MANIFESTATIONS

Presentation depends on the location of the hemorrhoids. External hemorrhoids occur below the dentate line (see Figs. 344-4 and 344-5) and are associated with extreme pain and itching, often due to acute thrombosis. Internal hemorrhoids are located above the dentate line and manifest primarily with bleeding, prolapse, and occasional incarceration.

TREATMENT

In most cases, conservative management with dietary modification, decreased straining, and avoidance of prolonged time spent sitting on the toilet results in resolution of the condition. Discomfort may be treated with topical analgesics or anti-inflammatories such as Anusol (pramoxine) and Anusol-HC (hydrocortisone) and sitz baths. The natural course of thrombosed hemorrhoid involves increasing pain, which peaks at 48-72 hr, with gradual remission as the thrombus organizes and involutes over the next 1-2 wk. In cases where the patient with external hemorrhoids presents with excruciating pain soon after the onset of symptoms, thrombectomy may be indicated. This is best accomplished with local infiltration of bupivacaine 0.25% with epinephrine 1:200,000, followed by incision of the vein or skin tag and extraction of the clot. This provides immediate relief; recurrence is rare and further follow-up is unnecessary.

Internal hemorrhoids can become painful when prolapse leads to incarceration and necrosis. Pain usually resolves with reduction of hemorrhoidal tissue. Surgical treatment is reserved for patients failing conservative management. Techniques described in adults include excision, rubber banding, stapling, and excision using the LigaSure device. Given the infrequency of hemorrhoidal disease in children, and the need for general anesthesia to treat it, we have been quite satisfied with simple excision ligating the vein proximal and using the Bovie for hemostasis.

Complications are rare (<5%) and include recurrence, bleeding, infection, nonhealing wounds, and fistula formation.

344.5 Rectal Mucosal Prolapse

Begum Akay and Michael D. Klein

Rectal mucosal prolapse is the exteriorization of the rectal mucosa through the anus. In the unusual occurrence when all of the layers of the rectal wall are included, it is called procidentia or rectoceles. Most cases of rectal tissue protruding through the anus are prolapse and not polyps, hemorrhoids, intussusception, or other tissue.

Most cases of prolapse are idiopathic. The onset is often between 1 and 5 yr of age. It usually occurs when the child begins standing and then resolves by approximately 3-5 yr of age when the sacrum has taken its more adult shape and the anal lumen is oriented posteriorly. Thus, the entire weight of the abdominal viscera is not pushing down on the rectum as it is earlier in development.

Other predisposing factors include intestinal parasites (particularly in endemic areas), malnutrition, diarrhea, ulcerative colitis, pertussis, Ehlers-Danlos syndrome, meningocele (more often associated with procidentia owing to the lack of perineal muscle support), cystic fibrosis, and chronic constipation. Patients treated surgically for imperforate anus can also have varying degrees of rectal mucosal prolapse. This is particularly common in patients with poor sphincteric development.

CLINICAL MANIFESTATIONS

Rectal mucosal prolapse usually occurs during defecation, especially during toilet training. Reduction of the prolapse may be spontaneous or accomplished manually by the patient or parent. In severe cases, the prolapsed mucosa becomes congested and edematous, making it more difficult to reduce. Rectal prolapse is usually painless or produces mild discomfort. If the rectum remains prolapsed after defecation, it can be traumatized by friction with undergarments, with resultant bleeding, wetness, and potentially, ulceration. The appearance of the prolapse varies from bright red to dark red and resembles a beehive. It can be as long as 10-12 cm. See Chapter 345 for a distinction from a prolapsed polyp.
TREATMENT

Initial evaluation should include tests to rule out any predisposing conditions, especially cystic fibrosis and sacral root lesions. Reduction of protrusion is aided by pressure with warm compresses. An easy method of reduction is to cover the finger with a piece of toilet paper, introduce it into the lumen of the mass, and gently push it into the patient’s rectum. The finger is then immediately withdrawn. The toilet paper adheres to the mucosal membrane, permitting release of the finger. The paper, when softened, is later expelled.

Conservative treatment consists of careful manual reduction of the prolapse after defecation, attempts to avoid excessive pushing during bowel movements (with patient’s feet off the floor), use of laxatives and stool softeners to prevent constipation, avoidance of inflammatory conditions of the rectum, and treatment of intestinal parasitosis when present. If all this fails, surgical treatment may be indicated. Existing surgical options are associated with some morbidity, and therefore medical treatment should always be attempted first.

Sclerosing injections have been associated with complications such as neurogenic bladder. We have found linear cauteryization effective and with few complications other than recurrence. In the operating room, the prolapse is recreated by traction on the mucosa. Linear burns are made through nearly the full thickness of the mucosa using electrocautery. One can usually make 8 linear burns on the outside and 4 on the inside of the prolapsed mucosa. In the immediate postoperative period, prolapse can still occur, but in the next several weeks, the burned areas contract and keep the mucosa within the anal canal. The Delorme mucosal sleeve resection addresses mucosal prolapse via a transanal approach by incising, prolapsing, and amputating the redundant mucosa. The resulting mucosal defect is then approximated with absorbable suture.

For patients with procidentia or full-thickness prolapse or intussusception of the rectosigmoid (usually from myelodysplasia or other sacral root lesions) other, more invasive options exist. Those most commonly in use by pediatric surgeons today include the following: A modification of the Thiersch procedure involves placing a subcutaneous suture to narrow the anal opening. Complications include obstruction, fecal impaction, and fistula formation. Laparoscopic rectopexy is effective and can be performed as an outpatient. The Altemeier perineal rectosigmoidectomy is a transanal, full-thickness resection of redundant bowel with a primary anastomosis to the anus.

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Bibliography


Tumors of the digestive tract in children are mostly polypoid. They are also commonly syndromic tumors and tumors with known genetic identification (Table 345-1). They usually manifest as painless rectal bleeding, but they can serve as lead points for intussusception. Most intestinal tumors can be generally classified into 2 groups: hamartomatous or adenomatous.

**HAMARTOMATOUS TUMORS**

Hamartomas are benign tumors composed of tissues that are normally found in an organ but that are not organized normally. Juvenile, retention, or inflammatory polyps are hamartomatous polyps, which represent the most common intestinal tumors of childhood, occurring in 1-2% of children. Patients generally present in the 1st decade, most often at ages 2-5 yr, and rarely at younger than 1 year. Polyps may be found anywhere in the gastrointestinal (GI) tract, most commonly in the colon or rectum; they are often solitary but may be multiple.

Histologically, juvenile polyps are composed of hamartomatous collections of mucus-filled glandular and stromal elements with inflammatory infiltrate, covered with a thin layer of epithelium. These polyps are often bulky, vascular, and prone to bleed as their growth exceeds their blood supply with resultant mucosal ulceration, or autoamputation with bleeding from a residual central artery.
Patients often present with painless rectal bleeding after defecation. Bleeding is generally scant and intermittent; rarely iron deficiency anemia is the chief presenting symptom. Extensive bleeding can occur but is generally self-limited, requiring supportive care until the bleeding stops spontaneously after autoamputation. Occasionally endoscopic polypectomy is required for control of bleeding. Abdominal pain or cramps are uncommon unless associated with intussusception. Patients can present with prolapse, with a dark, edematous, pedunculated mass protruding from the rectum. Mucus discharge and pruritus are associated with prolapse.

Patients presenting with rectal bleeding require thorough work-up; differential diagnosis includes anal fissure, other intestinal polypsis syndromes, Meckel diverticulum, inflammatory bowel disease, intestinal infections, Henoch-Schönlein purpura, or coagulopathy.

Diagnosis and therapy are best accomplished via endoscopy. Polyps may be visualized via air-contrast barium enema, but this provides no therapeutic advantage and is uncomfortable and usually performed without sedation or anesthesia. Colonoscopy affords opportunity for biopsy, polypectomy by snare cautery, and visualization of synchronous lesions; up to 50% of children have 1 or more additional polyps, and approximately 20% may have more than 5 polyps. Retrieved polyps should be sent for histologic evaluation for definitive diagnosis.

### Juvenile Polyposis Syndrome

Patients with juvenile polyposis syndrome (JPS) present with multiple juvenile polyps, ≥5 but typically 50-200. Polyps may be isolated to the colon or distributed throughout the GI tract. There is often a family history (20-50%) with an autosomal dominant pattern of variable penetrance. Alterations in transforming growth factor-β pathways have been identified in some JPS patients and families; mutations in SMAD4 or BMPR1A are found in 50-60% of patients with JPS. Genetic testing is available for both of these mutations. Clinical diagnosis of JPS is established by presence of 1 of the following: ≥3-10 polyps on colonoscopy; polyps outside the colon; or any number of polyps in a patient with a family history of JPS.

Histologically, these polyps are identical to solitary juvenile polyps; however, the GI malignancy risk is greatly increased (10-50%). Most malignancy is colorectal, although gastric, upper GI, and pancreatic tumors have been described. The risk of malignancy is greater in patients with >3 polyps and a positive family history. These patients...
should therefore undergo routine esophagogastroduodenoscopy, colonoscopy, and upper GI contrast studies. Serial polypectomy or polyp biopsy should be undertaken if possible. If dysplasia or malignant degeneration is found, a total colectomy is indicated.

Juvenile polyposis of infancy is characterized by early polyph formation (younger than 2 yr of age) and may be associated with protein-losing enteropathy, hypoprothrombinemia, anemia, failure to thrive, and intussusception. Early endoscopic or surgical intervention may be needed.

**Peutz-Jeghers Syndrome**

Peutz-Jeghers syndrome (PJS) is a rare autosomal dominant disorder (incidence: ~1:120,000 total population) characterized by mucocutanous pigmentation and extensive GI hamartomatous polyposis. Macular pigmented lesions may be dark brown to dark blue and are found primarily around the lips and oral mucosa, although these lesions may also be found on the hands, feet, or perineum. Lesions can fade by puberty or adulthood.

Polyps are primarily found in the small intestine (in order of prevalence: jejunum, ileum, duodenum) but may also be colonic or gastric. Histologically, polyps are defined by normal epithelium surrounding bundles of smooth muscle arranged in a branching or frondlike pattern. Symptoms arising from GI polyps in PJS are similar to those of other polyposis syndromes, namely bleeding and abdominal cramping from obstruction or recurrent intussusception. Patients can require repeated laparotomies and intestinal resections.

The diagnosis of PJS is made clinically in patients with histologically proven hamartomatous polyps if 2 of 3 conditions are met: positive family history with an autosomal dominant inheritance pattern, mucocutaneous hyperpigmentation, and small bowel polyposis. Genetic testing can reveal mutations in LKB1/STK11; (19p13.3), a serine-threonine kinase that acts as a tumor suppressor gene. Up to 94% of patients with clinical characteristics of PJS have a mutation at this locus. Only 50% of patients with PJS have an affected family member, suggesting a high rate of spontaneous mutations.

Patients with PJS have increased risk of GI and extraintestinal malignancies. Lifetime cancer risk has been reported from 47-93%. Colorectal, breast, and reproductive tumors are most common. GI surveillance should begin in childhood (by age 8 yr or when symptoms occur) with upper and lower endoscopy. The small bowel may be evaluated radiographically, with enteroscopy, or with wireless capsule endoscopy. Polyps larger than 1.5 cm should be removed. Screening for breast, gynecologic, and testicular cancers should be routine after age 18 yr.

**PTEN Hamartoma Tumor Syndromes**

Mutations in the tumor-suppressor gene protein tyrosine phosphatase and tensin homolog (PTEN) are associated with several rare autosomal dominant syndromes, including Cowden syndrome and Bannayan-Riley-Ruvalcaba syndrome. These patients present with multiple hamartomas in skin (99%), brain, breast, thyroid, endometrium, and GI tract (60%). Patients are at increased risk for breast and thyroid malignancies; the risk of GI cancer does not appear to be elevated.

**ADENOMATOUS TUMORS**

**Adenomatous Polyposis Coli-Associated Polyposis Syndromes**

Familial adenomatous polyposis (FAP) is the most common genetic polyposis syndrome (incidence 1:5,000 to 1:17,000 persons) and is characterized by numerous adenomatous polyps throughout the colon, as well as extraintestinal manifestations. FAP and related syndromes (attenuated FAP; Gardner and Turcot syndromes) are linked to mutations in the adenomatous polyposis coli (APC) gene, a tumor suppressor mapped to 5q21. APC regulates degradation of β-catenin, a protein with roles in regulation of the cytoskeleton, tissue architecture organization, cell migration and adherence, and numerous other functions. Intracellular accumulation of β-catenin may be responsible for colonic epithelial cell proliferation and adenoma formation. More than 400 APC mutations have been described, and up to 30% of patients present with no family history (spontaneous mutations).

Polyps generally develop late in the 1st decade of life or in adolescence (mean age of presentation is 16 yr). At the time of diagnosis, 5 or more adenomatous polyps are present in the colon and rectum. By young adulthood the number typically increases to hundreds or even thousands. Adenomatous polyps (or adenomas) are precancerous lesions within the surface epithelium of the intestine, displaying various degrees of dysplasia. Without intervention, the risk of developing colon cancer is 100% by the 5th decade of life (average age of cancer diagnosis is 40 yr). Other GI adenomas can develop, particularly in the stomach and duodenum (50-90%). The risk of periampullary or duodenal carcinoma is significantly elevated (4-12% lifetime risk). Young patients with FAP are also at increased risk for developing hepatoblastoma (1.6% before age 5 yr).

Extraintestinal manifestations of FAP may be present from birth or develop in early childhood. Lesions include congenital hypertrophy of retinal pigment epithelium, desmoid tumors, epidermoid cysts, osteomas, fibromas, and lipomas. Many of these benign soft-tissue tumors appear before intestinal polyps develop. Expression of extraintestinal findings can depend on location of mutation on the APC gene.

Other syndromes associated with APC mutations include Gardner syndrome, classically characterized by multiple colorectal polyps, desmoid tumors, and soft-tissue tumors including fibromas, osteomas (typically mandibular), epidermoid cysts, and lipomas. Once thought to be a distinct clinical entity, Gardner syndrome shares many characteristics with FAP. Up to 20% of FAP patients present with the classic extraintestinal manifestations once associated with Gardner syndrome. Some (but not all) cases of Turcot syndrome are also related to APC. These patients present with colorectal polyposis and primary brain tumors (medulloblastoma). Attenuated FAP is characterized by a significantly increased risk of colorectal cancer but fewer polyps than classic FAP (average: 30 polyps). The average age of cancer diagnosis in this form of FAP is 50-55 yr. Upper GI tumors and extraintestinal manifestations may be present but are less common.

The clinical presentation of FAP is variable. Polyps are generally asymptomatic initially (and might remain so). If symptoms develop, they can include rectal bleeding (possibly with secondary anemia), cramping, and diarrhea. The presence of symptoms at presentation does not correlate with malignant changes. Diagnosis should be suspected from family history, and ensuing sigmoidoscopy or colonscopy is confirmatory. Histologic examination of biopsied polyps reveals adenomatous architecture (as opposed to inflammatory or hamartomatous polyps found in other polyposis syndromes) with varying degrees of dysplasia. Genetic testing for APC mutations is clinically available, and index patients should be tested. If a mutation is identified, affected family members should be screened and appropriate genetic counseling should be provided. If the index patient does not demonstrate a defined mutation, family members may undergo genetic testing, which might identify novel APC mutations. Children with identified APC mutations must undergo careful surveillance, with sigmoidoscopy every 1-2 yr. Once polyps are identified, colonoscopy should be performed annually. Patients should also have upper endoscopy after development of colon polyps to monitor for gastric and especially duodenal lesions.

Treatment of FAP requires prophylactic proctocolectomy to prevent cancer. Ileoanal pull-through procedures restore bowel continuity, with acceptable functional outcomes. Resection should be done once polyposis has become extensive (>20-30) or by the mid-teens. Nonsteroidal antiinflammatory agents, such as sulindac, and cyclooxygenase-2 inhibitors, such as celecoxib, might inhibit polypl progression. No guidelines have been established, however, and their efficacy in preventing malignant transformation of existing polyps is unknown.

**Carcinoma**

Primary carcinomas of the small bowel or colon are extremely rare in children. Development of adenocarcinoma in adolescence or early
adulthood may be associated with a genetic predisposition or syndrome such as FAP, hereditary nonpolyposis colon carcinoma, PJS, or inflammatory bowel disorders such as Crohn disease or ulcerative colitis.

Colorectal carcinoma, though rare (reported incidence of 1 case per 1,000,000 persons younger than 19 yr of age), is the most common primary GI carcinoma in children. Many cases are spontaneous (i.e., not associated with a genetic predisposition or syndrome). Histologically, tumors tend to be poorly differentiated and pathologically aggressive. Patients may be asymptomatic, or they present with nonspecific signs and symptoms such as abdominal pain, constipation, and vomiting. Delay in diagnosis is common. Many patients present with advanced-stage disease, with microscopic or gross metastases at the time of diagnosis. Surgical resection is the primary treatment modality, although with delayed presentation and advanced-stage disease, complete resection may not be possible. Chemotherapy and radiation have a limited role in patients with metastatic disease.

**OTHER GASTROINTESTINAL TUMORS**

**Lymphoma**

Lymphoma is the most common GI malignancy in the pediatric population. Approximately 30% of children with non-Hodgkin lymphoma present with abdominal tumors. Immune-compromised patients have an increased incidence of lymphoma. Predisposing conditions include HIV/AIDS, agammaglobulinemia, long-standing celiac disease, and bone marrow or solid-organ transplantation. Lymphoma can occur anywhere in the GI tract, but it most commonly occurs in distal small bowel and ileocecal region. Presenting symptoms include crampy abdominal pain, vomiting, obstruction, bleeding, or palpable mass. Lymphoma should be considered in patients older than 3 yr of age who present with intussusception.

**Nodular Lymphoid Hyperplasia**

Lymphoid follicles in the lamina propria and submucosa of the gut normally aggregate in Peyer patches, most prominently in the distal ileum. These follicles can become hyperplastic, forming nodules that protrude into the lumen of the bowel. Some suggested etiologies are infectious (classically *Giardia*), allergic, or immunologic. Nodular lymphoid hyperplasia has been described in infants with enterocolitis secondary to dietary protein sensitivity. This phenomenon has also been described in patients with inflammatory bowel disease and Castleman disease. Patients may be asymptomatic or may present with abdominal pain, rectal bleeding, diarrhea, or intussusception. Nodular lymphoid hyperplasia usually resolves spontaneously and rarely requires therapy; in cases with severe pain or bleeding, corticosteroids may be effective.

**Carcinoid Tumor**

Carcinoids are neuroendocrine tumors of enterochromaffin cells, which can occur throughout the GI tract, but in children they are typically found in the appendix. This is often an incidental diagnosis at the time of appendectomy. Complete resection of small tumors (<1 cm) with clear surgical margins is curative. Appendiceal tumors >2 cm mandate further bowel resection. Carcinoid tumors outside the appendix (small intestine, rectum, stomach) are more likely to metastasize. Metastatic carcinoid tumor within the liver can give rise to the carcinoid syndrome. Serotonin, 5-hydroxytryptophan, or histamine are elaborated by the tumor, and elevated serum levels cause cramps, diarrhea, vasomotor disturbances (flushing), bronchoconstriction, and right-heart failure. The diagnosis is confirmed by elevated urinary 5-hydroxyindolacetic acid. Symptomatic relief of carcinoid symptoms may be achieved with administration of somatostatin analogs (octreotide).

**Leiomyoma**

Leiomyomas are rare benign tumors that can arise anywhere in the GI tract, although most often in the stomach, jejunum, or distal ileum. Age of presentation is variable, from the newborn period through adolescence. Patients may be asymptomatic or can present with an abdominal mass, obstruction, intussusception, volvulus, or pain and bleeding from central necrosis of the tumor. Surgical resection is the treatment of choice. Pathologically, these tumors may be difficult to distinguish from malignant leiomyosarcomas. Smooth muscle tumors occur with increased incidence in children with HIV or those requiring immunosuppression after transplantation.

**Gastrointestinal Stromal Cell Tumors**

Gastrointestinal stromal cell tumors (GISTs) are intestinal mesenchymal tumors that probably arise from interstitial cells of Cajal or their precursors. Historically, these may have been diagnosed as tumors of smooth muscle or neural cell origin. The World Health Organization recognized GIST in 1990 as a distinct neoplasm. Typically GISTs arise in adults, after the 3rd decade of life. Cases have also been reported in the pediatric population, generally in adolescents. In the pediatric population tumors are most commonly found in the stomach, though they can occur anywhere in the GI tract or even the mesentery or omentum. Patients may be asymptomatic or can present with an abdominal mass, lower GI bleeding, or obstruction. Treatment consists of surgical en bloc resection of local disease. Recurrence rates are high and early postoperative surveillance is recommended. GISTs occurring in adults are typically associated with mutation in the *KIT* oncogene. This mutation is less commonly found in pediatric GISTs (~15%). Adjuvant therapy for *KIT* lesions is imatinib or sunitinib, tyrosine kinase inhibitors that are available as oral therapy. Patients with persistent disease or metastases might benefit from treatment.

**Vascular Tumors**

Vascular malformations and hemangiomas are rare in children. The usual presentation is painless rectal bleeding, which may be chronic or acute, with massive or even fatal hemorrhage. There are usually no associated symptoms, although intussusception has been described. Half of patients have associated cutaneous hemangiomas or telangiectasias. These lesions may be associated with blue rubber bleb nevus syndrome or hereditary hemorrhagic telangiectasia. About half of these lesions are in the colon and can be identified on colonoscopy. During acute bleeding episodes, bleeding can be localized via nuclear medicine bleeding scans, mesenteric angiography, or endoscopy. Colonic bleeding may be controlled by endoscopic means. Surgical intervention is required only occasionally for isolated lesions.

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Inguinal hernias are one of the most common conditions seen in pediatric practice and the most common surgical procedure performed in pediatric surgical practice. The frequency of this condition in concert with its potential morbidity of ischemic injury to the intestine, testis, or ovary makes proper diagnosis and management an important part of daily practice for pediatric practitioners and pediatric surgeons. The overwhelming majority of inguinal hernias in infants and children are congenital indirect hernias (99%) as a consequence of a patent processus vaginalis (PV); a developmental structure important in testicular descent. The incidence of inguinal hernia in children is up to 10 times higher in boys than in girls. Two other types of inguinal hernia are direct (acquired) hernia (0.5-1.0%) and femoral hernia (<0.5%). Approximately 50% of inguinal hernias manifest clinically in the 1st yr of life, most in the 1st 6 mo. Premature infants have an incidence of
inguinal hernia approaching 30%. The risk of incarceration and possible strangulation of an inguinal hernia is also greatest in the 1st yr of life (30-40%) and mandates prompt identification and operative repair to minimize morbidity and complications.

EMBRYOLOGY AND PATHOGENESIS

Indirect inguinal hernias in infants and children are congenital and result from an arrest of embryologic development; failure of obliteration of the PV rather than a weakness in the inguinal musculature. The pertinent developmental anatomy of indirect inguinal hernia relates to development of the gonads and descent of the testis through the internal ring and into the scrotum late in gestation. The testes descend from the urogenital ridge in the retroperitoneum to the area of the internal ring by about 28 wk of gestation. The final descent of the testes into the scrotum occurs late in gestation between weeks 28 and 36. The testis is preceded in descent to the scrotum by the gubernaculum and the PV. The PV, an outpouring of peritoneum in the lower abdomen, is present in the developing fetus at 12 wk gestation that develops lateral to the deep inferior epigastric vessels and descends anteriorly along the spermatic cord within the cremasteric fascia through the internal inguinal ring. The testes accompanies the PV as it exits the abdomen and descends into the scrotum. The gubernaculum testis forms from the mesonephros (developing kidney), attaches to the lower pole of the testis, and directs the testis through the internal ring, inguinal canal and into the scrotum. The testis passes through the inguinal canal in a few days but takes about 4 wk to migrate from the external ring to the scrotum. The cord-like structures of the gubernaculum occasionally pass to ectopic locations (perineum or femoral region), resulting in ectopic testes.

In the last few weeks of gestation or shortly after birth, the layers of the PV normally fuse together and obliterate the patency from the peritoneal cavity through the inguinal canal to the testis. The PV, an outpouring of peritoneum in the lower abdomen, is present in the developing fetus at 12 wk gestation that develops lateral to the deep inferior epigastric vessels and descends anteriorly along the spermatic cord within the cremasteric fascia through the internal inguinal ring. The testes accompanies the PV as it exits the abdomen and descends into the scrotum. The gubernaculum testis forms from the mesonephros (developing kidney), attaches to the lower pole of the testis, and directs the testis through the internal ring, inguinal canal and into the scrotum. The testis passes through the inguinal canal in a few days but takes about 4 wk to migrate from the external ring to the scrotum. The cord-like structures of the gubernaculum occasionally pass to ectopic locations (perineum or femoral region), resulting in ectopic testes.

In the last few weeks of gestation or shortly after birth, the layers of the PV normally fuse together and obliterate the patency from the peritoneal cavity through the inguinal canal to the testis. The PV also obliterates just above the testis, and the portion of the PV that encloses the testis becomes the tunica vaginalis. In girls, the PV obliterates earlier, at approximately 7 mo of gestation, and may explain why girls demonstrate a much lower incidence of inguinal hernia. Failure of the PV to close permits fluid or abdominal viscera to escape the peritoneal cavity into the extraabdominal inguinal canal and accounts for a variety of inguinal–scrotal abnormalities seen in infancy and childhood. The ovaries descend into the pelvis from the urogenital ridge but do not exit from the abdominal cavity. The cranial portion of the gubernaculum in girls differentiates into the ovarian ligament, and the inferior aspect of the gubernaculum becomes the round ligament, which passes through the internal ring and attaches to the labia majora. The PV in girls extends into the labia majora through the inguinal canal and is also known as the canal of Nuck. Involution of the left-sided PV precedes that of the right; which is consistent with the increased incidence of indirect inguinal hernias on the right side (60%).

Androgenic hormones, adequate end-organ receptors, and mechanical factors such as increased intra-abdominal pressure influence complete descent of the testis through the inguinal canal. The testes and spermatic cord structures (spermatic vessels and vas deferens) are located in the retroperitoneum but are affected by increases in intraabdominal pressure as a consequence of their intimate attachment to the descending PV. The genitofemoral nerve also has an important role: It innervates the cremaster muscle, which develops within the gubernaculum, and experimental division or injury to both nerves in the fetus prevents testicular descent. Failure of regression of smooth muscle (present to provide the force for testicular descent) might have a role in the development of indirect inguinal hernias. Several studies have investigated genes involved in the control of testicular descent for their role in closure of the patent PV, for example, hepatocyte growth factor and calcitonin gene-related peptide. Unlike in adult hernias, there does not appear to be any change in collagen synthesis associated with inguinal hernias in children (Fig. 346-1).

A direct inguinal hernia originates medial to the deep inferior epigastric vessels and is external to the cremasteric fascia; the hernia sac directly through the posterior wall of the inguinal canal. A femoral hernia originates medial to the femoral vein and descends inferior to the inguinal ligament along the femoral canal.

GENETICS

There is some genetic risk incurred for siblings of patients with inguinal hernias; the sisters of affected girls are at the highest risk, with a relative risk of 17.8. In general, the risk of brothers of a sibling is approximately 4-5, as is the risk of a sister of an affected brother. Both a multifactorial threshold model and autosomal dominance with incomplete penetrance and sex influence have been suggested as an explanation for this pattern of inheritance.

PATHOLOGY

Failure of closure of the PV leads to a number of common inguinal–scrotal conditions in infants and children including: inguinal hernia, scrotal hydrocele (communicating and noncommunicating), and hydrocele of the spermatic cord. Closure of the PV is often incomplete at birth and continues postnatally; the rate of patency is inversely proportional to the age of the child. It has been estimated that the patency rate of the PV is as high as 80% at birth and decreases to ≈50% during the 1st yr of life, and that ≈60% of boys have a persistent patency of the PV at 2 yr of age. Patency of the PV after birth is an opening from the abdominal cavity to the inguinal region and therefore a potential hernia, but not all patients will develop a clinical hernia. An inguinal hernia occurs clinically when intraabdominal contents escape

![Diagram of hernia and hydroceles.](https://example.com/diagram.png)
Predisposing Factors for Hernias

<table>
<thead>
<tr>
<th>Table 346-1</th>
<th>Predisposing Factors for Hernias</th>
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<td>Prematurity</td>
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<td>Urogenital</td>
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<td>• Cryptorchidism</td>
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<td>• Exstrophy of the bladder or cloaca</td>
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<td>• Ambiguous genitalia</td>
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<td>• Hypospadias/epispadias</td>
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<td>Increased peritoneal fluid</td>
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<td>• Ascites</td>
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<td>• Ventrículoperitoneal shunt</td>
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<td>• Peritoneal dialysis catheter</td>
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<td>Increased intraabdominal pressure</td>
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<td>• Repair of abdominal wall defects</td>
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<td>• Severe ascites (chylous)</td>
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<td>• Meconium peritonitis</td>
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<td>Chronic respiratory disease</td>
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<td>• Cystic fibrosis</td>
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<td>Connective tissue disorders</td>
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<td>• Ehlers-Danlos syndrome</td>
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the abdominal cavity and enter the inguinal region through the patency. Based on their location in the inguinal canal (lateral to the inferior epigastric vessels), these are indirect inguinal hernias but are rarely associated with a muscular weakness or defect, as is typical of an adult hernia. Depending on the extent of patency of the PV, the hernia may be confined to the inguinal region or pass down into the scrotum. Complete failure of obliteration of the PV, mostly seen in infants, predisposes to a complete inguinal hernia characterized by a protrusion of abdominal contents into the inguinal canal and possibly extending into the scrotum. Obliteration of the PV distally (around the testis) with patency proximally results in the classic indirect inguinal hernia with the protrusion in the inguinal canal.

A hydrocele is when only fluid enters the patent PV; the swelling may exist only in the scrotum (scrotal hydrocele), only along the spermatic cord in the inguinal region (hydrocele of the spermatic cord), or extend from the scrotum through the inguinal canal and even into the abdomen (abdominal–scrotal hydrocele). A hydrocele is termed a communicating hydrocele if it demonstrates fluctuation in size, often increasing in size after activity and, at other times, being smaller when the fluid decompresses into the peritoneal cavity. Occasionally, hydroceles develop in older children following trauma, inflammation, or tumors affecting the testis. Although reasons for failure of closure of the PV are unknown, it is more common in cases of testicular nondescent (cryptorchidism) and prematurity. In addition, persistent patency of the PV is twice as common on the right side, presumably related to later descent of the right testis and interference with obliteration of the PV from the developing inferior vena cava and external iliac vein.

Table 346-1 lists the risk factors identified as contributing to the development of clinical inguinal hernia and that relate to conditions that predispose to failure of obliteration of the PV. Incidence of inguinal hernia in patients with cystic fibrosis is approximately 15%, believed to be related to an altered embryogenesis of the wolffian duct structures, which leads to an absent vas deferens in males with this condition. There is also an increased incidence of inguinal hernia in patients with testicular feminization syndrome and other disorders of sexual development. The rate of recurrence after repair of an inguinal hernia in patients with a connective tissue disorder approaches 50%, and often the diagnosis of connective tissue disorders in children results from investigation after development of a recurrent inguinal hernia.

INCIDENCE

The incidence of congenital indirect inguinal hernia in full-term newborn infants is estimated at 3.5-5.0%. The incidence of hernia in preterm and low birthweight infants is considerably higher, ranging from 9-11%, and approaches 30% in very-low birthweight infants (<1,000 g) and preterm infants (<28 wk of gestation). Inguinal hernia is much more common in boys than girls, with a male:female ratio of approximately 8:1. Approximately 60% of inguinal hernias occur on the right side, 30% are on the left side, and 10% are bilateral. The incidence of bilateral hernias is higher in girls and appears to be 20-40%. An increased incidence of congenital inguinal hernia has been documented in twins and in family members of patients with inguinal hernia. There is a history of another inguinal hernia in the family in 11.5% of patients.

CLINICAL PRESENTATION

An inguinal hernia typically appears as a bulge or mass in the inguinal region. In boys, the mass potentially extends through the inguinal area into the scrotum; in girls the mass typically occurs in the upper portion of the labia majora. The bulge or mass is most visible at times of irritability or increased intraabdominal pressure (crying, straining, coughing). It may be present at birth or might not appear until weeks, months, or years later. The bulge is most often first noted by the parents or on routine examination by the primary care physician. The classic history from the parents is of intermittent groin, labial, or scrotal swelling that spontaneously reduces but that is gradually enlarging or is more persistent and is becoming more difficult to reduce. The hallmark signs of an inguinal hernia on physical examination are a smooth, firm mass that emerges through the external inguinal ring lateral to the pubic tubercle and enlarges with increased intraabdominal pressure. When the child relaxes, the hernia typically reduces spontaneously or can be reduced by gentle pressure, first posteriorly to free it from the external ring and then upward toward the peritoneal cavity. In boys, the hernia sac contains intestines; female infants often have an ovary and fallopian tube in the hernia sac.

Methods used to demonstrate the hernia on examination vary depending on the age of the child. A quiet infant can be made to strain the abdominal muscles by stretching the infant out supine on the bed with legs extended and arms held straight above the head. Most infants struggle to get free, thus increasing the intraabdominal pressure and pushing out the hernia. Older patients can be asked to perform the Valsalva maneuver by blowing up a balloon or coughing. The older child should be examined while standing and examination after voiding also can be helpful. With increased intraabdominal pressure, the protruding mass is obvious on inspection of the inguinal region or can be palpated by an examining finger invaginating the scrotum to palpate at the external ring. Another test is the “silk glove sign,” which describes the feeling of the layers of the hernia sac as they slide over the spermatic cord structures with rolling of the spermatic cord beneath the index finger at the pubic tubercle. A femoral hernia appears as a protrusion on the medial aspect of the thigh, below the inguinal region and does not enter the scrotum or labia. In the absence of a bulge, the finding of increased thickness of the inguinal canal structures on palpation also suggests the diagnosis of an inguinal hernia. It is important on examination to note the position of the testes because retractile testes are common in infants and young boys and can mimic an inguinal hernia with a bulge in the region of the external ring. Because in the female patient approximately 20-25% of inguinal hernias are sliding hernias (the contents of the hernia sac are adherent within the sac and therefore not reducible), a fallopian tube or ovary can be palpated in the inguinal canal as a firm, slightly mobile, non-tender mass in the labia or inguinal canal.

As the majority of young child hernias reduce spontaneously, the physical examination in the office can be equivocal. Infants and children with a strong history suggestive of inguinal hernia and an equivocal clinical examination may be offered ultrasound or referral to a pediatric surgeon. In recent years, diagnostic laparoscopy has been increasingly used to evaluate for suspected inguinal hernia; particularly in infants where the risk of incarceration and potential injury to the intestines or testis is high. In an older child with low risk of
incarceration, the parents can be educated and asked to observe for the bulge and take a digital image at home.

**EVALUATION OF ACUTE INGUINAL–SCROTAL SWELLING**

Commonly in pediatric practice, an inguinal–scrotal mass appears suddenly in an infant or child and is associated with discomfort. The differential diagnosis includes incarcerated inguinal hernia, acute hydrocele, torsion of an descended testis, and suppurative inguinal lymphadenitis. Differentiating between the incarcerated inguinal hernia and the acute hydrocele is probably the most difficult. The infant or child with an incarcerated inguinal hernia is likely to have associated findings suggesting intestinal obstruction, such as colicky abdominal pain, abdominal distention, vomiting, and cessation of stool, and might appear ill. The infant with an acute hydrocele might have discomfort but is consolable and tolerates feedings without signs or symptoms suggesting intestinal obstruction. When the diagnosis is incarcerated inguinal hernia, plain radiographs typically demonstrate distended intestines with multiple air–fluid levels.

On examination of the child with the acute hydrocele, the clinician may note that the mass is somewhat mobile. In addition, in the area between the suspected hydrocele mass and the internal ring, the cord structures can appear only slightly thickened. With the incarcerated hernia, there is a lack of mobility of the groin mass and marked swelling or mass extending from the scrotal mass through the inguinal area and up to and including the internal ring. An experienced clinician can selectively use a bimanual examination to help differentiate groin abnormalities. The examiner palpates the internal ring per rectum, with the other hand placing gentle pressure on the inguinal region over the internal ring. In cases of an indirect inguinal hernia, an intrabdominal organ can be palpated extending through the internal ring.

Another method used in evaluation is transillumination. It must be noted that transillumination can be misleading because the thin wall of the infant’s intestine can approximate that of the hydrocele wall and both might transilluminate. This is also the reason aspiration to determine the contents of a groin mass is discouraged. Ultrasonography can help distinguish between a hernia, a hydrocele, and lymphadenopathy. An expeditious diagnosis is important to avoid the potential complications of an incarcerated hernia, which can develop rapidly. Diagnostic laparoscopy has emerged as an effective and reliable tool in this setting by pediatric surgeons but requires general anesthesia.

The occurrence of suppurative adenopathy in the inguinal region can be confused with an incarcerated inguinal hernia. Examination of the watershed area of the inguinal lymph node might reveal a superficial infected or crusted lesion. In addition, the swelling associated with inguinal lymphadenopathy is typically located more inferior and lateral than the mass of an inguinal hernia, and there may be other associated enlarged nodes in the area. Torsion of an undescended testes can manifest as a painful erythematous mass in the groin. The absence of a gonad in the scrotum in the ipsilateral side should clinic this diagnosis.

**Incarcerated Hernia**

Incarceration is a common consequence of untreated inguinal hernia in infants and presents as a nonreducible mass in the inguinal canal, scrotum, or labia. Contained structures can include small bowel, appendix, omentum, colon, or, rarely, Meckel diverticulum. In girls, the ovary, fallopian tube, or both are commonly incarcerated. Rarely, the uterus in infants can also be pulled into the hernia sac. A strangulated hernia is one that is tightly constricted in its passage through the inguinal canal and, as a result, the hernia contents have become ischemic or gangrenous.

Although incarceration may be tolerated in adults for years, most nonreducible inguinal hernias in children, unless treated, rapidly progress to strangulation with potential infarction of the hernia contents or intestinal obstruction. Initially, pressure on the herniated viscera leads to impaired lymphatic and venous drainage. This leads, in turn, to swelling of the herniated viscera, which further increases the compression in the inguinal canal, ultimately resulting in total occlusion of the arterial supply to the trapped viscera. Progressive ischemic changes take place, culminating in gangrene and/or perforation of the herniated viscera. The testis is at risk of ischemia because of compression of the testicular blood vessels by the strangulated hernia. In girls, herniation of the ovary places it at risk of strangulation and torsion. The incidence of incarceration of an inguinal hernia is between 12% and 17% throughout childhood; two-thirds of incarcerated hernias occur in the 1st yr of life. The greatest risk is in infants younger than 6 mo of age, with reported incidences of incarceration between 25% and 30%. The incidence of incarceration is slightly less in premature infants, although the reasons are unclear.

The symptoms of an incarcerated hernia are irritability, feeding intolerance, and abdominal distention in the infant; pain in the older child. Within a few hours, the infant becomes inconsolable; lack of flatus or stool signals complete intestinal obstruction. A somewhat tense, nonfluctuant mass is present in the inguinal region and can extend down into the scrotum or labia. The mass is well defined, firm, and does not reduce. With the onset of ischemic changes, the pain intensifies, and the vomiting becomes bilious or feculent. Blood may be noted in the stools. The mass is typically tender, and there is often edema and erythema of the overlying skin. The testes may be normal, demonstrate a reactive hydrocele, or may be swollen and hard on the affected side because of venous congestion resulting from compression of the spermatic veins and lymphatic channels at the inguinal ring by the tightly strangulated hernia mass. Abdominal radiographs demonstrate features of partial or complete intestinal obstruction, and gas within the incarcerated bowel segments may be seen below the inguinal ligament or within the scrotum.

**Ambiguous Genitalia**

Infants with disorders of sexual development commonly present with inguinal hernias, often containing a gonad, and require special consideration. In female infants with inguinal hernias, particularly if the presentation is bilateral inguinal masses, testicular feminization syndrome should be suspected (>50% of patients with testicular feminization have an inguinal hernia) (see Chapter 588). Conversely, the true incidence of testicular feminization in all female infants with inguinal hernias is difficult to determine but is approximately 1%. In phenotypic females, if the diagnosis of testicular feminization is suspected preoperatively, the child should be screened with a buccal smear for Barr bodies and appropriate genetic evaluation before proceeding with the hernia repair. The diagnosis of testicular feminization is occasionally made at the time of operation by identifying an abnormal gonad (testis) within the hernia sac or absence of the uterus on laparoscope or rectal exam. In the normal female infant, the uterus is easily palpated as a distinct midline structure beneath the symphysis pubis on rectal examination. Preoperative diagnosis of testicular feminization syndrome or other disorders of sexual development such as mixed gonadal dysgenesis and selected pseudehermaphrodites enables the family to receive genetic counseling, and gonadectomy can be accomplished at the time of the hernia repair.

**MANAGEMENT**

The presence of an inguinal hernia in the pediatric age group constitutes the indication for operative repair. An inguinal hernia does not resolve spontaneously, and early repair eliminates the risk of incarceration and the associated potential complications, particularly in the 1st 6-12 mo of life. The timing of operative repair depends on several factors, including age, general condition of the patient, and comorbid conditions. In infants (younger than 1 yr old) with an inguinal hernia, repair should proceed promptly (within 2-3 wk) because as many as 70% of incarcerated inguinal hernias requiring emergency operation occur in infants younger than 11 mo. In addition, the incidence of complications associated with elective hernia repair (intestinal injury, testicular atrophy, recurrent hernia, wound infection) are low (∼1%), but rise to as high as 18-20% when repair is performed at the time of
incarceration. The incidence of testicular atrophy after incarceration in infants younger than 3 mo of age has been reported as high as 30%. Therefore, an approach emphasizing prompt elective repair in infants is warranted. In children older than 1 yr, the risk of incarceration is less and the repair can be scheduled with less urgency. For the routine reducible hernia, the operation should be carried out electively shortly after diagnosis. Elective inguinal hernia repair can be safely performed in an outpatient setting with an expectation for full recovery within 48 hr. The operation should be performed at a facility with the ability to admit the patient to an inpatient unit as needed. Certain conditions can dictate postponement of repair, such as marked prematurity, intercurrent pneumonia (especially respiratory syncytial virus), other infections, or severe congenital heart disease. In cases of prematurity (1,800-2,000 g), repair is typically performed before discharge from the neonatal ICU.

The operation is most often performed under general anesthesia, but it can be performed under spinal anesthesia in selected high-risk infants in whom avoidance of intubation is preferable (because of, e.g., chronic lung disease or bronchopulmonary dysplasia). A regional caudal block or local inguinal nerve block using local anesthetic is useful to diminish perioperative pain and increase patient comfort. These techniques, along with the use of rapid-acting general anesthetics, allow the majority of infants to be discharged home within hours of operation. Prophylactic antibiotics are not routinely used except for associated conditions, such as congenital heart disease or the presence of a ventriculoperitoneal shunt. Preterm infants mandate special consideration because of their higher risk for apnea and bradycardia following general anesthesia (see Chapter 61). Infants younger than 44 wk postconceptional age and full-term infants younger than 3 mo of age and with comorbid conditions should be observed overnight with appropriate apnea and cardiorespiratory monitors.

An incarcerated, irreducible hernia without evidence of strangulation in a clinically stable patient should initially be managed nonoperatively. Unless there is clear peritonitis or bowel compromise, incarcerated hernias can usually be reduced manually using a technique called taxis. Manual reduction is performed first with traction caudal and posteriorly to free the mass from the external inguinal ring, and then upward to reduce the contents back into the peritoneal cavity. The attempt should not be continued if the infant is crying and resisting the pressure on the hernia. The use of cautious sedation or analgesia with experienced monitoring before attempting reduction can be helpful; this reduces intraabdominal pressure and relieves the pressure on the neck of the hernia sac at the inguinal ring. Care must be taken to avoid respiratory depression, especially common in the premature infant. Other techniques advocated to assist in the nonoperative reduction of an incarcerated inguinal hernia include elevation of the lower torso and legs. Ice packs should be avoided in infants because of the risk of hypothermia but may be used for brief periods in the older child. If reduction is successful but difficult, the patient should be observed (several hours) to ensure that feedings are tolerated and there is no concern that necrotic intestine was reduced; fortunately, this is an uncommon occurrence. Because of the high risk for early recurrent incarceration, surgical repair is performed 24-48 hr later, by which time there is less edema, handling of the sac is easier, and the risk of complications is reduced.

A common presentation in female patients is an irreducible ovary in the inguinal hernia in an otherwise asymptomatic patient. The inguinal mass is soft and nontender to gentle exam, and there is no swelling or edema; thus, there are no findings suggesting strangulation. This represents a “sliding” hernia with the fallopian tube and ovary fused to the wall of the hernia sac. Overzealous attempts to reduce the hernia are unwarranted and potentially harmful to the tube and ovary. The risk that incarceration of the ovary in this setting will lead to strangulation is not known. Most pediatric surgeons recommend elective repair of the hernia within 24-48 hr. For any patient who presents with a prolonged history of incarceration, signs of peritoneal irritation, or small bowel obstruction, surgery and operative reduction and repair of the hernia should be urgently performed.

**Operative Management**

When the hernia cannot be reduced or signs of strangulation are present, immediate operation is indicated to prevent further damage to the contents of the hernia sac or testis. If there are signs of intestinal obstruction or strangulation, urgent, initial management includes nasogastric intubation, intravenous fluids, and administration of broad-spectrum antibiotics. When fluid and electrolyte imbalance has been corrected and the child’s condition is satisfactory, exploration is undertaken. The operation consists of opening of the inguinal canal, reduction of the contents of the hernia sac, separation of the hernia sac from the spermatic cord vessels and vas deferens in the inguinal canal, and high ligation of the hernia sac at the internal ring. Resection of nonviable structures within the hernia sac or of an infarcted testis may be indicated based on the experience and judgment of the surgeon. Although often the testis might appear ischemic, most testes recover after the incarceration is relieved and should not be removed.

The elective operative repair of a congenital indirect inguinal hernia is straightforward and consists of high ligation of the hernia sac (PV) at the level of the internal ring, thus preventing protrusion of abdominal contents into the inguinal canal. In boys, this requires careful separation of the sac from the spermatic cord structures and avoidance of injury to these vital structures. An associated hydrocele, present approximately 20% of the time, is released anteriorly to avoid injury to the spermatic cord structures located posteriorly. In girls, surgical repair is simpler because the hernia sac and round ligament can be ligated without concern for injury to the ovary and its blood supply, which generally remain within the abdomen. If the ovary and fallopian tube are within the sac and not reducible, the sac is ligated distal to these structures and the internal ring is closed after reducing the sac and its contents to the abdominal cavity.

**Laparoscopic Inguinal Hernia Repair**

Although the classic open inguinal hernia repair is most commonly performed, laparoscopic repair is increasingly used by pediatric surgeons experienced in the technique. Like the open technique, the laparoscopic technique is fundamentally a high ligation of the indirect inguinal hernia sac. In the open surgical technique, a small inguinal skin crease incision is employed, the inguinal canal is opened and careful identification and separation of the hernia sac from the vas deferens and the testicular blood supply is performed, followed by high ligation of the sac at the level of the internal ring (entrance point to the peritoneal cavity). In female infants, opening of the sac to visualize the ovary and fallopian tube may help avoid injury to these structures during suture ligation of the sac and also rule out testicular feminization syndrome. In laparoscopic inguinal hernia repair, the hernia sac, anterior to the vas deferens and the testicular blood vessels, is suture-ligated at the internal ring without inguinal exploration or handling of the spermatic cord structures. Proponents of the laparoscopic approach cite ease of examining the contralateral internal ring, decreased manipulation of the vas deferens and spermatic vessels, decreased operative time, and an ability to identify unsuspected direct or femoral hernias. In a prospective, randomized study, the laparoscopic approach was associated with decreased pain, parental perception of faster recovery, and parental perception of better wound cosmesis; however, complications and recurrence rates have been slightly higher for the laparoscopic approach and the approach has yet to gain wide acceptance. Laparoscopic procedures in infants should always be performed expeditiously and with low insufflations pressure to avoid the risk of cardiorespiratory compromise. Postoperative pain in both techniques is managed with oral acetaminophen for 24-48 hr; older children may require a brief period of postoperative narcotics.

**Contralateral Inguinal Exploration**

Controversy exists regarding when to proceed with contralateral groin exploration in infants and children with a unilateral indirect inguinal hernia. The only purpose of contralateral exploration is to avoid the occurrence of a hernia on that side at a later date. The advantages of contralateral exploration include avoidance of parental anxiety and
possibly a second anesthesia, the cost of additional surgery, and the risk of contralateral incarceration. The disadvantages of exploration include potential injury to the spermatic cord vessels, vas deferens, and testis; increased operative and anesthesia time; and the fact that, in many infants, it is an unnecessary procedure. The relevant issues in the debate revolve around the frequency of occurrence of contralateral hernias after one-sided hernia repair and the relation of this to age, gender, and side of the clinically apparent hernia. Most large series noted a chance of developing a contralateral hernia following inguinal hernia repair as 30-40% in children younger than 2 yr of age; leading most pediatric surgeons to recommend routine contralateral exploration in this age group. Unfortunately, infants and young children have delicate spermatic cord structures and when boys were studied 8-20 yr after inguinal hernia repair, 5.8% of them had decreased testicular size on the side of the repair and 1% had testicular atrophy. In girls, because of the higher incidence of bilateral inguinal hernias and elimination of concern for injury to the spermatic cord or testis, routine contralateral exploration is recommended up to age 5 or 6 yr. Laparoscopy enables assessment of the contralateral side without risk of injury to the spermatic cord structures or testis. This procedure can be performed through an umbilical incision or by passing a 30-degree or 70-degree oblique scope through the open hernia sac just before ligation of the hernia sac on the involved side. If patency of the contralateral side is demonstrated, the surgeon can proceed with bilateral hernia repair, and if the contralateral side is properly obliterated, exploration and potential complications are avoided. The downside of this approach include the risks associated with laparoscopy, and that laparoscopy cannot differentiate between a patent PV and a true hernia (Figs. 346-2 and 346-3). Infants and children with risk factors for development of an inguinal hernia or with medical conditions that increase the risk of infants, it is an unnecessary procedure. The relevant issues in the debate revolve around the frequency of occurrence of contralateral hernias after one-sided hernia repair and the relation of this to age, gender, and side of the clinically apparent hernia. Most large series noted a chance of developing a contralateral hernia following inguinal hernia repair as 30-40% in children younger than 2 yr of age; leading most pediatric surgeons to recommend routine contralateral exploration in this age group. Unfortunately, infants and young children have delicate spermatic cord structures and when boys were studied 8-20 yr after inguinal hernia repair, 5.8% of them had decreased testicular size on the side of the repair and 1% had testicular atrophy. In girls, because of the higher incidence of bilateral inguinal hernias and elimination of concern for injury to the spermatic cord or testis, routine contralateral exploration is recommended up to age 5 or 6 yr. Laparoscopy enables assessment of the contralateral side without risk of injury to the spermatic cord structures or testis. This procedure can be performed through an umbilical incision or by passing a 30-degree or 70-degree oblique scope through the open hernia sac just before ligation of the hernia sac on the involved side. If patency of the contralateral side is demonstrated, the surgeon can proceed with bilateral hernia repair, and if the contralateral side is properly obliterated, exploration and potential complications are avoided. The downside of this approach include the risks associated with laparoscopy, and that laparoscopy cannot differentiate between a patent PV and a true hernia (Figs. 346-2 and 346-3). Infants and children with risk factors for development of an inguinal hernia or with medical conditions that increase the risk of general anesthesia should be approached with a low threshold for routine contralateral exploration.

**DIRECT INGUINAL HERNIA**

Direct inguinal hernias are rare in children; approximately 0.5-1%. Direct hernias appear as groin masses that extend toward the femoral vessels with exertion or straining. The etiology is from a muscular defect or weakness in the floor of the inguinal canal medial to the epigastric vessels. Thus, direct inguinal hernias in children are generally considered an acquired defect. In one-third of cases, the patient has a history of a prior indirect hernia repair on the side of the direct hernia, which suggests a possible injury to the floor muscles of the inguinal canal at the time of the first herniorrhaphy. Patients with **connective tissue disorders** such as Ehlers-Danlos syndrome or Marfan syndrome and mucopolysaccharidosis such as Hunter-Hurler syndrome are at increased risk for the development of direct inguinal hernias either independently or after indirect inguinal hernia repair.

Operative repair of a direct inguinal hernia involves strengthening of the floor of the inguinal canal, and many standard techniques have been described, similar to repair techniques used in adults. The repair can be performed through a single limited incision and, therefore, laparoscopic repair does not offer significant advantage. Recurrence after repair, in contrast to that in adults, is extraordinarily rare. Because typically the area of muscular weakness is small and pediatric tissues have greater elasticity, primary repair is usually possible. Prosthetic material for direct hernia repair or other approaches, such as preperitoneal repair, are rarely required in the pediatric age group. The older child with a direct inguinal hernia and a connective tissue disorder may be the exception, and a laparoscopic approach and prosthetic material in such a case can be useful for repair.

**FEMORAL HERNIA**

Femoral hernias are also rare in children (<1% of groin hernias in children). They are more common in girls than boys, with a ratio of 2:1. They are extremely rare in infancy and occur typically in older children. Femoral hernias represent a protrusion through the femoral canal. The bulge of a femoral hernia is located below the inguinal ligament and typically projects toward the medial aspect of the proximal thigh. Femoral hernias are more often missed clinically than direct hernias on physical examination or at the time of indirect hernia repair. Repair of a femoral hernia involves closure of the defect at the femoral canal, generally suturing the inguinal ligament to the pectineal ligament/fascia.

**COMPLICATIONS**

Complications after elective inguinal hernia repair are uncommon (<1.5%) but significantly higher in association with incarceration (≈10%). The major risk of elective inguinal hernia repair in infants and children relates to the need for general anesthesia. Surgical complications can be related to technical factors (recurrence, iatrogenic cryptorchidism, inadvertent injury to the vas deferens or spermatic vessels), or to the underlying process, such as bowel ischemia, gonadal infarction, and testicular atrophy following incarceration.

**Wound Infection**

Wound infection occurs in <1% of elective inguinal hernia repairs in infants and children, but the incidence increases to 5-7% in association with incarceration and emergent repair. The patient typically develops fever and irritability 3-5 days after the surgery, and the wound demonstrates warmth, erythema, and fluctuance. Management consists of opening and draining the wound, a short course of antibiotics, and a
Injury to the Vas Deferens and Male Fertility

Similar to the gonadal vessels, the vas deferens can be injured as a consequence of compression from an incarcerated hernia or during operative repair. This injury is almost certainly underreported because there appears to be an association between infertile males with testicular atrophy and abnormal sperm count and a previous hernia repair. A relationship has also been reported between infertile males with spermatic autoagglutinating antibodies and previous inguinal hernia repair. The proposed etiology is that operative injury to the vas deferens during inguinal hernia repair might result in obstruction of the vas with diversion of spermatozoa to the testicular lymphatics, and this breach of the blood–testis barrier produces an antigenic challenge, resulting in formation of spermatic autoagglutinating antibodies.

Bibliography is available at Expert Consult.
Chapter 346  Inguinal Hernias

Bibliography


The human pancreas develops from the ventral and dorsal domains of the primitive duodenal endoderm beginning at about the 5th wk of gestation (Fig. 347-1). The larger dorsal anlage, which develops into the tail, body, and part of the head of the pancreas, grows directly from the duodenum. The smaller ventral anlage develops as 1 or 2 buds from the primitive liver and eventually forms the major portion of the head of the pancreas. At about the 17th wk of gestation, the dorsal and ventral anlagen fuse as the buds develop and the gut rotates. The ventral duct forms the proximal portion of the major pancreatic duct of Wirsung, which opens into the ampulla of Vater. The dorsal duct forms the distal portion of the duct of Wirsung and the accessory duct of Santorini, which empties independently in approximately 5% of people. Variations in fusion might account for pancreatic developmental anomalies. Pancreatic agenesis has been associated with a base pair deletion in the ipf1 HOX gene, PDX1, and possibly in the PTF1A and FS123TER genes. Other genes involved in pancreatic organogenesis include the IHH, SHH or sonic hedgehog gene, SMAD2, and transforming growth factor-1β genes.

The pancreas lies transversely in the upper abdomen between the duodenum and the spleen in the retroperitoneum (Fig. 347-2). The head, which rests on the vena cava and renal vein, is adherent to the C loop of the duodenum and surrounds the distal common bile duct. The tail of the pancreas reaches to the left splenic hilum and passes above the left kidney. The lesser sac separates the tail of the pancreas from the stomach.

By the 13th wk of gestation, exocrine and endocrine cells can be identified. Primitive acini containing immature zymogen granules are found by the 16th wk. Mature zymogen granules containing amylase,
Part XVIII ♦ The Digestive System

Complete or partial pancreatic agenesis is a rare condition. Complete agenesis is associated with severe neonatal diabetes and usually death at an early age (see Chapter 589). Partial or dorsal pancreatic agenesis is often asymptomatic but may be associated with diabetes, congenital heart disease, polypsplenia, and recurrent pancreatitis. Pancreatic agenesis is also associated with malabsorption.

An annular pancreas results from incomplete rotation of the left (ventral) pancreatic anlage, which may be a result of recessive mutations in the IHH or SHH genes. Patients usually present in infancy with symptoms of complete or partial bowel obstruction or in the 4th or 5th decade. There is often a history of maternal polyhydramnios. Other congenital anomalies, such as Down syndrome, tracheoesophageal fistula, intestinal atresia, imperforate anus, malrotation and cardiorenal abnormalities, and pancreatitis, may be associated with annular pancreas. Some children present with chronic vomiting, pancreatitis, or biliary colic. The treatment of choice is duodenojejunosotomy. Division of the pancreatic ring is not attempted, because a duodenal diaphragm or duodenal stenosis often accompanies annular pancreas.

Ectopic pancreatic rests in the stomach or small intestine occur in approximately 3% of the population. Most cases (70%) are found in the upper intestinal tract. Recognized on barium contrast studies by their typical umbilicated appearance, they are rarely of clinical importance. On endoscopy, they are irregular, yellow nodules 2-4 mm in diameter. A pancreatic rest may rarely be the lead point of an intussusception, produce hemorrhage, or cause bowel obstruction.

Pancreas divisum, which occurs in 5-15% of the population, is the most common pancreatic developmental anomaly. As the result of failure of the dorsal and ventral pancreatic anlagen to fuse, the tail, body, and part of the head of the pancreas drain through the small accessory duct of Santorini rather than the main duct of Wirsung. Some investigators believe that this anomaly may be associated with recurrent pancreatitis when there is relative obstruction of the outflow of the ventral pancreas. Diagnosis is made by endoscopic retrograde cholangiopancreatography or by magnetic resonance cholangiopancreatography. It was recently shown that pancreatitis in patients with pancreas divisum is associated with mutations in the CFT gene. Sphincterotomy is no longer recommended in these patients unless other anomalies are present.

Choleodochal cysts are dilations of the biliary tract and usually cause biliary tract symptoms, such as jaundice, pain, and fever. On occasion, the presentation may be pancreatitis. The diagnosis is usually made with ultrasonography, CT or biliary scanning, or magnetic resonance cholangiopancreatography. Similarly, a choledochocele, an intraduodenal choledochal cyst may manifest with pancreatitis. The diagnosis can be difficult and require magnetic resonance cholangiopancreatography, endoscopic retrograde cholangiopancreatography, or endoscopic ultrasound.

A number of rare conditions, such as Ivemark and Johanson-Blizzard syndromes include pancreatic dysgenesis or dysfunction among their features. Many of these syndromes include renal and hepatic dysgenesis along with the pancreatic anomalies.

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Bibliography
Bibliography
The acinus is the functional unit of the exocrine pancreas. Acinar cells are arrayed in a semicircle around a lumen. Ducts that drain the acini are lined by centroacinar and ductular cells. This arrangement allows the secretions of the various cell types to mix.

The acinar cell synthesizes, stores, and secretes more than 20 enzymes, which are stored in zymogen granules, some in inactive forms. The relative concentration of the various enzymes in pancreatic juice is affected and perhaps controlled by the diet, probably by regulating the synthesis of specific messenger RNA. The main enzymes involved in digestion include amylase, which splits starch into maltose, isomaltose, maltotriose; dextrins; and trypsin and chymotrypsin, endopeptidases secreted by the pancreas as inactive proenzymes. Trypsinogen is activated in the gut lumen by enterokinase, a brush-border enzyme. Trypsin can then activate trypsinogen, chymotrypsinogen, and procarboxypeptidase into their respective active forms. Pancreatic lipase requires colipase, a coenzyme also found in pancreatic fluid, for activity. Lipase liberates fatty acids from the 1 and 3 positions of triglycerides, leaving a monoglyceride.

The stimuli for exocrine pancreatic secretion are neural and hormonal. Acetylcholine mediates the cephalic phase; cholecystokinin (CCK) mediates the intestinal phase. CCK is released from the duodenal mucosa by luminal amino acids and fatty acids. Feedback regulation of pancreatic secretion is mediated by pancreatic proteases in the duodenum. Secretion of CCK is inhibited by the digestion of a trypsin-sensitive, CCK-releasing peptide released in the lumen of the small intestine or by a monitor peptide released in pancreatic fluid.

Centroacinar and duct cells secrete water and bicarbonate. Bicarbonate secretion is under feedback control and is regulated by duodenal intraluminal pH. The stimulus for bicarbonate production is secretin in concert with CCK. Secretin cells are abundant in the duodenum.

Although normal pancreatic function is required for digestion, malabsorption occurs only after considerable reduction in pancreatic function; lipase and colipase secretion must be decreased by 90-98% before fat malabsorption occurs.

Although amylase and lipase are present in the pancreas early in gestation, secretion of both amylase and lipase is low in the infant. Adult levels of these enzymes are not reached in the duodenum until late in the 1st yr of life. Digestion of the starch found in many infant formulas depends in part on the low levels of salivary amylase that reach the duodenum. This explains the diarrhea that may be seen in infants who are fed formulas high in glucose polymers or starch. Neonatal secretion of trypsinogen and chymotrypsinogen is at approximately 70% of the level found in the 1 yr old infant. The low levels of amylase and lipase in duodenal contents of infants may be partially compensated by salivary amylase and lingual lipase. This explains the relative starch and fat intolerance of premature infants.

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the standard screening test for pancreatic insufficiency, has a sensitivity and specificity > 90%. A fecal elastase > 100 µg/g of stool has a 99% predictive value in ruling out pancreatic insufficiency based on an abnormal 72 hr fecal fat. Falsely abnormal results can occur in many enteropathies, such as celiac disease, and when the stool is very loose. The activity of other pancreatic enzymes in stool is now rarely measured.

**DIRECT TESTING**
Classically, a triple-lumen tube was used to isolate the pancreatic secretions in the duodenum. Measurement of bicarbonate concentration and enzyme activity (*trypsin, chymotrypsin, lipase, and amylase*) is performed on the aspirated secretions. Because this test is cumbersome and time consuming it is infrequently used except in the research setting. Although the most commonly used direct test is collection of pancreatic juice at endoscopy after stimulation with secretin and/or cholecystokinin there is controversy over this approach.

A 72 hr stool collection for quantitative analysis of fat content is the gold standard for the diagnosis of malabsorption. The collection is usually performed at home, and the parent is asked to keep a careful dietary record, from which fat intake is calculated. A preweighed, sealable plastic container is used, which the parent keeps in the freezer. Freezing helps to preserve the specimen and reduce odor. Infants are dressed in disposable diapers with the plastic side facing the skin so that the complete sample can be transferred to the container. Normal fat absorption is >93% of intake. The presence of fat malabsorption does not differentiate between pancreatic dysfunction and enteropathies, such as celiac disease. Qualitative examination of the stool for microscopic fat globules can give false-positive and false-negative results.

Pancreatic function can also be measured by a breath test using $^{13}$C-triolein as the substrate. This test has not gained widespread acceptance because it is relatively insensitive in detecting mild cases of pancreatic insufficiency, and detection of $^{13}$CO$_2$ requires a mass spectrophotometer that is not generally available.

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Bibliography
Chapter 349

Disorders of the Exocrine Pancreas
Steven L. Werlin and Michael Wilschanski

DISORDERS ASSOCIATED WITH PANCREATIC INSUFFICIENCY

Other than cystic fibrosis, conditions that cause pancreatic insufficiency are very rare in children. They include Shwachman-Diamond syndrome, Johanson-Blizzard syndrome, isolated enzyme deficiencies, enterokinase deficiency (see Chapter 338), chronic pancreatitis, and protein-calorie malnutrition (see Chapters 46 and 338).

CYSTIC FIBROSIS

(See Chapter 403.)

Cystic fibrosis (CF) is the most common lethal genetic disease in white children. By the end of the 1st yr of life, 85-90% of children with CF have pancreatic insufficiency, which, if untreated, will lead to malnutrition. Treatment of the associated pancreatic insufficiency leads to improvement in absorption, better growth, and more normal stools.
Pancreatic function can be monitored in children with CF with serial measurements of fecal elastase. Ten percent to 15% of CF patients are pancreatic sufficient and their presentation tends to be later in life, including recurrent pancreatitis, male infertility, and chronic bronchiectasis. CF is part of the newborn screen in every state in the United States and in most countries in the Western world.

**SHWACHMAN-DIAMOND SYNDROME**  
(See Chapter 131.)
Shwachman-Diamond syndrome (SDS) is an autosomal recessive syndrome (1 per 20,000 births) caused by a mutation of the Shwachman-Bodian-Diamond (SBDS) gene on chromosome 7, which causes ribosomal dysfunction in 90-95% of patients. Signs and symptoms of SDS include pancreatic insufficiency; neutropenia, which may be cyclic, neutrophil chemotaxis defects, metaphyseal dysostosis, failure to thrive, and short stature. Some patients with SDS have liver or kidney involvement, dental disease, or learning difficulty. SDS is a common cause of congenital neutropenia.

Patients typically present in infancy with poor growth and steatorrhea. These children can be readily differentiated from those with CF by their normal sweat chloride levels, lack of mutations in the CF gene, characteristic metaphyseal lesions, and fatty pancreas characterized by a hypodense appearance on CT and MRI scans.

Despite adequate pancreatic replacement therapy and correction of malabsorption, poor growth commonly continues. Pancreatic insufficiency is often transient, and steatorrhea frequently spontaneously improves with age. Recurrent pyogenic infections (otitis media, pneumonia, osteomyelitis, dermatitis, sepsis) are frequent and are a common cause of death. Thrombocytopenia is found in 70% of patients and anemia in 50%. Development of a myelodysplastic syndrome can occur, with transformation to acute myeloid leukemia in 24%. The pancreatic acini are replaced by fat with little fibrosis. Islet cells and ducts are normal. Bone marrow transplant is the treatment of choice in patients who develop acute myeloid leukemia.

**PEARSON SYNDROME**
Pearson syndrome is caused by a mitochondrial DNA mutation affecting oxidative phosphorylation that manifests in infants with severe macrocytic anemia and variable thrombocytopenia. The bone marrow demonstrates vacuoles in erythroid and myeloid precursors as well as ringed sideroblasts. In addition to its role in severe bone marrow failure, pancreatic insufficiency contributes to growth failure. Mitochondrial DNA mutations are transmitted through maternal inheritance to both sexes or are sporadic.

**JOHANSON-BLIZZARD SYNDROME**
The features of the Johanson-Blizzard syndrome include exocrine pancreatic deficiency, aplasia or hypoplasia of the alae nasi, congenital deafness, hypothyroidism, developmental delay, short stature, ectodermal scalp defects, absence of permanent teeth, urogenital malformations, and imperforate anus. This syndrome is caused by a mutation in the UBR1 gene found on chromosome 15. The UBR1 protein acts as a ubiquitin ligase.

**ISOLATED ENZYME DEFICIENCIES**
Isolated deficiencies of trypsinogen, enterokinase, lipase, and colipase have been reported. Although enterokinase is a brush-border enzyme, deficiency causes pancreatic insufficiency because enterokinase is required to activate trypsinogen to trypsin in the duodenum. Deficiencies of trypsinogen or enterokinase manifest with failure to thrive, hypoproteinemia, and edema. Isolated amylase deficiency is typically developmental and resolves by age 2-3 yr.

**OTHER SYNDROMES ASSOCIATED WITH PANCREATIC INSUFFICIENCY**
Pancreatic agenesis, congenital pancreatic hypoplasia, and congenital rubella are rare causes of pancreatic insufficiency. Pancreatic insufficiency has also been reported in duodenal atresia and stenosis and may also be seen in an infant with familial or nonfamilial hyperinsulinemic hypoglycemia, who requires 95-100% pancreatectomy to control hypoglycemia. Pancreatic insufficiency, which may be found in children with celiac disease and undernutrition, recovers with nutritional rehabilitation.

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Bibliography
Chapter 350
Treatment of Pancreatic Insufficiency
Steven L. Werlin and Michael Wilschanski

The most important therapy of pancreatic insufficiency is pancreatic enzyme replacement therapy (PERT). The enzymes are enterically coated to protect the enzymes from degradation by gastric acid and from autodigestion in the small intestine. It is common for patients to change from one product to another using a 1:1 lipase ratio and then titrating for maximum efficacy.

The North American Cystic Fibrosis Foundation has published dosing guidelines based on age and fat ingestion (Table 350-1). Because these products contain excess protease compared with lipase, the dosage is estimated from the lipase requirement. The final dosage of PERT for children is often established by trial and error. An adequate dose is one that is followed by resumption of normal growth and the return of the stools to normal fat content, which, when desired, can be verified by a 72-hr fecal fat collection and normalization of stool consistency color. Because there is no elastase in enzyme preparations, fecal elastase can not be used to monitor appropriateness of PERT dosage. Enzyme replacement should be divided and given at the beginning of and during the meal. Enzymes should not be chewed, crushed, or dissolved in food, which would allow gastric acid to penetrate the enteric coating and destroy the enzymes. Enzymes must also be given with snacks, which contain fat. Increasing enzyme supplements beyond the recommended dose does not improve absorption, might retard growth, and can cause fibrosing colonopathy (see below).

A major issue has been the ingestion of enzymes by infants. The importance of correct enzyme ingestion in infants and children is obvious but there may be difficulty in feeding the infant microspheres, however small they may be. Enterically coated microspheres can be

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<tr>
<th>Table 350-1</th>
<th>Pancreatic Enzyme Replacement Therapy</th>
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<tr>
<td>Infants (up to 12 mo)</td>
<td>2000-4000 units lipase/120 mL breast milk or formula</td>
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<tr>
<td>12 mo-4 yr</td>
<td>1000 units lipase/kg/meal initially, then titrate per response</td>
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<tr>
<td>Children older than 4 yr and adults</td>
<td>500 units lipase/kg/meal initially, up to maximum of 2500 units lipase/kg/meal or 10,000 units lipase/kg/day or 4,000 units lipase/g fat ingested per day</td>
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<tr>
<td>PLUS: one half the standard meal dose to be given with snacks</td>
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mixed with apple sauce for oral use or crushed for use in tube feeding. Patients treated with this approach achieve growth and weight gain, proving their efficacy.

Treatment of exocrine pancreatic insufficiency by oral enzyme replacement usually corrects protein malabsorption, but steatorrhea is difficult to completely correct. Factors contributing to fat malabsorption include inadequate dosage, incorrect timing of doses in relation to food consumption or gastric emptying, lipase inactivation by gastric acid, and the observation that chymotrypsin in the enzyme preparation digests and thus inactivates lipase.

When adequate fat absorption is not achieved, gastric acid neutralization with an H2-receptor antagonist or, more commonly, a proton pump inhibitor, decreases enzyme inactivation by gastric acid and thus improves delivery of lipase into the intestine. Enteric coating also protects lipase from acid inactivation.

Untoward effects secondary to PERT include allergic reactions, increased uric acid levels, and kidney stones. Fibrosing colonopathy, consisting of colonic fibrosis and strictures, can occur 7-12 mo after overdose of PERT.

Fat-soluble vitamin supplements are required by pancreatic insufficiency patients because of the ongoing mild to moderate fat malabsorption that occurs despite PERT.

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Bibliography


Acute pancreatitis, the most common pancreatic disorder in children, is increasing in incidence and at least 30-50 cases are now seen in major pediatric centers per year. In children, blunt abdominal injuries, multisystem disease such as the hemolytic uremic syndrome and inflammatory bowel disease, biliary stones or microlithiasis (sludging), and drug toxicity are the most common etiologies. Although many drugs and toxins can induce acute pancreatitis in susceptible persons, in children, valproic acid, L-asparaginase, 6-mercaptopurine, and azathioprine are the most common causes of drug-induced pancreatitis. Other cases follow organ transplantation or are caused by infections, metabolic disorders, or mutations in susceptibility genes (see Chapter 351.2). Fewer than 5% of cases are idiopathic (Table 351-1).

After an initial insult, such as ductal disruption or obstruction, there is premature activation of trypsinogen to trypsin within the acinar cell. Trypsin then activates other pancreatic proenzymes, leading to autodigestion, further enzyme activation, and release of active proteases. Lysosomal hydrolases colocalize with pancreatic proenzymes within the acinar cell. Pancreatitis (similar in concept to cholestasis) with continued synthesis of enzymes occurs. Lecithin is unstable and can be activated by minute quantities of trypsin. Other cases follow organ transplantation or are caused by infections, metabolic disorders, or mutations in susceptibility genes (see Chapter 351.2). Fewer than 5% of cases are idiopathic (Table 351-1).

Histopathologically, interstitial edema appears early. Later, as the episode of pancreatitis progresses, localized and confluent necrosis, blood vessel disruption leading to hemorrhage, and an inflammatory response in the peritoneum can develop.

Criteria for the diagnosis of pancreatitis in children are defined as 2 of 3 of the following: abdominal pain; serum amylase and/or lipase activity at least 3 times greater than the upper limit of normal; and imaging findings characteristic of, or compatible with, acute pancreatitis.

**CLINICAL MANIFESTATIONS**

**Mild Acute Pancreatitis**

The patient with acute pancreatitis has severe abdominal pain, persistent vomiting, and possibly fever. The pain is epigastric or in either upper quadrant, steady, often resulting in the child’s assuming an antalgic position with hips and knees flexed, sitting upright, or lying on the side. The child is very uncomfortable and irritable and appears acutely ill. The abdomen may be distended and tender and a mass may be palpable. The pain can increase in intensity for 24–48 hr, during which time vomiting may increase and the patient can require hospitalization for dehydration and might need fluid and electrolyte therapy. The prognosis for complete recovery in the acute uncomplicated case is excellent.

**Severe Acute Pancreatitis**

Severe acute pancreatitis is rare in children. In this life-threatening condition, the patient is acutely ill with severe nausea, vomiting, and abdominal pain. Shock, high fever, jaundice, ascites, hypocalcemia, and pleural effusions can occur. A bluish discoloration may be seen around the umbilicus (Cullen sign) or in the flanks (Grey Turner sign). The pancreas is necrotic and can be transformed into an inflammatory hemorrhagic mass. The mortality rate, which is approximately 20%, is related to the systemic inflammatory response syndrome with multiple organ dysfunction, shock, renal failure, acute respiratory distress syndrome, disseminated intravascular coagulation, massive gastrointestinal bleeding, and systemic or intraabdominal infection. The percentage of necrosis seen on CT scan and failure of pancreatic tissue to enhance on CT scan (suggesting necrosis) predicts the severity of the disease.

**DIAGNOSIS**

Acute pancreatitis is usually diagnosed by measurement of serum lipase and amylase activities. Serum lipase is now considered the test of choice for acute pancreatitis as it is more specific than amylase for acute inflammatory pancreatic disease and should be determined when pancreatitis is suspected. The serum lipase rises by 4-8 hr, peaks at 24-48 hr, and remains elevated 8-14 days longer than serum amylase. Serum lipase can be elevated in nonpancreatic diseases. The serum amylase level is typically elevated for up to 4 days. A variety of other conditions can also cause hyperamylasemia without pancreatitis (Table 351-2). Elevation of salivary amylase can mislead the clinician to diagnose pancreatitis in a child with abdominal pain. The laboratory can separate amylase isoenzymes into pancreatic and salivary fractions. Initially, serum amylase levels are normal in 10-15% of patients.

Other laboratory abnormalities that may be present in acute pancreatitis include hemoconcentration, coagulopathy, leukocytosis, hyperglycemia, glucosuria, hypocalcemia, elevated γ-glutamyl transpeptidase, and hyperbilirubinemia.

X-ray of the chest and abdomen might demonstrate nonspecific findings. The chest x-ray might demonstrate atelectasis, basilar infiltrates, elevation of the hemidiaphragm, left- (rarely right-) sided pleural effusions, pericardial effusion, and pulmonary edema. Abdominal x-rays might demonstrate a sentinel loop, dilation of the transverse colon (cutoff sign), ileus, pancreatic calcification (if recurrent), blurring of the left psoas margin, a pseudocyst, diffuse abdominal haziness (ascites), and peripancreatic extraluminal gas bubbles.
Table 351-1  Etiology of Acute and Recurrent Pancreatitis in Children

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<td>Azathioprine</td>
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<td>Cholelithiasis, microlithiasis, and choledocholithiasis (stones or sludge)</td>
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<td>Burns</td>
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<td>Child abuse</td>
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<td>Hypothermia</td>
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<td>Surgical trauma</td>
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<td>Total-body cast</td>
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CT scanning has a major role in the diagnosis and follow-up of children with pancreatitis. Findings can include pancreatic enlargement, hypoechoic, sonolucent edematous pancreas, pancreatic masses, fluid collections, and abscesses (Fig. 351-1); 20% or more of children with acute pancreatitis initially have normal imaging studies. In adults, CT findings are the basis of a widely accepted prognostic system. Ultrasonography is more sensitive than CT scanning for the diagnosis of biliary stones. Magnetic resonance cholangiopancreatography and endoscopic retrograde cholangiopancreatography are essential in the investigation of recurrent pancreatitis, nonresolving pancreatitis, and disease associated with gallbladder pathology. Endoscopic ultrasonography also helps visualize the pancreaticobiliary system.

TREATMENT
The aims of medical management are to relieve pain and restore metabolic homeostasis. Analgesia should be given in adequate doses. Fluid, electrolyte, and mineral balance should be restored and maintained. Nasogastric suction is useful in patients who are vomiting. While vomiting, the patient should be maintained with nothing by mouth. Recovery is usually complete within 4-5 days. Refeeding can commence when vomiting has resolved. Early refeeding by nasogastric tube or on demand decreases the complication rate and length of stay.

In severe pancreatitis, antibiotics are used to treat infected necrosis but prophylactic antibiotics are not recommended. Gastric acid is suppressed. Endoscopic therapy can be of benefit when pancreatitis is caused by anatomic abnormalities, such as strictures or stones. Enteral
Chapter 351 ♦ Pancreatitis

Pancreatitis

is rarely required but may include drainage of necrotic material or abscesses.

PROGNOSIS
Children with uncomplicated acute pancreatitis do well and recover within 4-5 days. When pancreatitis is associated with trauma or systemic disease, the prognosis is typically related to the associated medical conditions.

Bibliography is available at Expert Consult.

Table 351-2 Differential Diagnosis of Hyperamylasemia

<table>
<thead>
<tr>
<th>PANCREATIC PATHOLOGY</th>
<th>SALIVARY GLAND PATHOLOGY</th>
<th>INTRAABDOMINAL PATHOLOGY</th>
<th>SYSTEMIC DISEASES</th>
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<tr>
<td>Acute or chronic pancreatitis</td>
<td>Parotitis (mumps, Staphylococcus aureus, cytomegalovirus, HIV, Epstein-Barr virus)</td>
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<tr>
<td>Complications of pancreatitis (pseudocyst, ascites, abscess)</td>
<td>Sialadenitis (calculus, radiation)</td>
<td>Biliary tract disease (cholelithiasis)</td>
<td>Metabolic acidosis (diabetes mellitus, shock)</td>
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<tr>
<td>Factitious pancreatitis</td>
<td>Eating disorders (anorexia nervosa, bulimia)</td>
<td>Peptic ulcer perforation</td>
<td>Renal insufficiency, transplantation</td>
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<td>Peritonitis</td>
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<td>Intestinal obstruction</td>
<td>Pregnancy</td>
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<td></td>
<td>Appendicitis</td>
<td>Drugs (morphine)</td>
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<td>Head injury</td>
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<td>Cardiopulmonary bypass</td>
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Chronic Pancreatitis

Steven L. Werlin and Michael Wilschanski

Chronic pancreatitis in children is often caused by genetic mutations or by congenital anomalies of the pancreatic or biliary ductal system. Mutations in the PRSS1 gene (cationic trypsinogen) located on the long arm of chromosome 7, in SPINK 1 gene (pancreatic trypsin inhibitor) located on chromosome 5, in the cystic fibrosis gene (CFTR), and in the chymotrypsin C gene (CTRC) may all lead to chronic pancreatitis (see Table 351-1).

Cationic trypsinogen has a trypsin-sensitive cleavage site. Loss of this cleavage site in the abnormal protein permits uncontrolled activation of trypsinogen to trypsin, which leads to autodigestion of the pancreas. Mutations in PRSS1 act in an autosomal dominant fashion with incomplete penetrance and variable expressivity. Symptoms often begin in the 1st decade but are usually mild at the onset. Although spontaneous recovery from each attack occurs in 4-7 days, episodes become progressively severe. Clinically, hereditary pancreatitis may be diagnosed by the presence of the disease in successive generations of

Table 351-2

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<thead>
<tr>
<th>PANCREATIC PATHOLOGY</th>
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<td>Cardiopulmonary bypass</td>
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Figure 351-1 CT and MRI appearance of pancreatitis. A, Mild acute pancreatitis. Arterial phase spiral CT. Diffuse enlargement of pancreas without fluid accumulation. B, Severe acute pancreatitis. Lack of enhancement of the pancreatic parenchyma due to the necrosis of the entire pancreatic gland. C, Pancreatic pseudocyst. A round fluid collection with thin capsule is seen within the lesser sac. D, Acute severe pancreatitis and peripancreatic abscess formation. Peripancreatic abscess formation is observed within the peripancreatic and the left anterior pararenal space. E, Pancreatic necrosis. A well-defined fluid attenuation collection in the pancreatic bed (white arrows) seen on contrast-enhanced CT imaging. F, The same collection is more complex appearing on the corresponding T2-weighted MR image. The internal debris and necrotic tissue are better appreciated because of the superior soft-tissue contrast of MRI (black arrows). (A-D from Elmas N: The role of diagnostic radiology in pancreatitis, Eur J Radiol 38[2]:120–132, 2001, Figs. 1, 3b, 4a, and 5. E-F from Soakar A, Rabinowitz CB, Sahani DV: Cross-sectional imaging in acute pancreatitis, Radiol Clin North Am 45[3]:447–460, 2007, Fig. 14.)
Bibliography


Cohen D: Reports of pancreatitis are 20–30 times more likely with GLP-1 drugs, *BMJ* 346:f2607, 2013.


a family. An evaluation during symptom-free intervals may be unrewarding until calcifications, pseudocysts, or pancreatic exocrine and endocrine insufficiency develops (Fig. 351-2). Chronic pancreatitis is a risk factor for future development of pancreatic cancer. Multiple mutations of the PRSS1 gene associated with hereditary pancreatitis have been described.

Trypsin inhibitor acts as a fail-safe mechanism to prevent uncontrolled autoactivation of trypsin. Mutations in the SPINK1 gene have been associated with recurrent or chronic pancreatitis. In SPINK1 mutations, this fail-safe mechanism is lost; this gene may be a modifier gene and not the direct etiologic factor.

Mutations of the cystic fibrosis gene (CFTR), associated with pancreatic sufficiency or which do not typically produce pulmonary disease, can cause chronic pancreatitis, possibly from ductal obstruction. Patients with genotypes associated with mild phenotypic effects have a greater risk of developing pancreatitis than patients with genotypes associated with moderate-severe phenotypes.

Mutations in the chymotrypsin C (CTRC) gene, which cause a gain of function, may also cause recurrent pancreatitis. Indications for genetic testing include recurrent episodes of acute pancreatitis, chronic pancreatitis, a family history of pancreatitis, or unexplained pancreatitis in children.

Other conditions associated with chronic, relapsing pancreatitis are hyperlipidemia (types I, IV, and V), hyperparathyroidism, and ascariasis. Previously, most cases of recurrent pancreatitis in childhood were considered idiopathic; with the discovery of gene families associated with recurrent pancreatitis, this has changed. Congenital anomalies of the ductal systems, such as pancreas divisum are more common than previously recognized.

Autoimmune pancreatitis typically manifests with jaundice, abdominal pain, and weight loss. The pancreas is typically enlarged and the pancreas is hypodense on CT. The pathogenesis is unknown. Type 1 is a systemic disease and is associated with high serum immunoglobulin (Ig) G4. In type 2 IgG4, levels are normal and the disease is limited to the pancreas. Both types respond to steroids. There have been only a few case reports of this condition in children.

Juvenile tropical pancreatitis is the most common form of chronic pancreatitis in developing equatorial countries. The highest prevalence is in the Indian state of Kerala. Tropical pancreatitis occurs during late childhood or early adulthood, manifesting with abdominal pain and irreversible pancreatic insufficiency followed by diabetes mellitus within 10 yr. The pancreatic ducts are obstructed with inspissated secretions, which later calcify. This condition is associated with mutations in the SPINK gene in 50% of cases.

A thorough diagnostic evaluation of every child with more than 1 episode of pancreatitis is indicated. Serum lipid, calcium, and phosphorus levels are determined. Stools are evaluated for ascaris, and a sweat test is performed. Plain abdominal films are evaluated for the presence of pancreatic calcifications. Abdominal ultrasound or CT scanning is performed to detect the presence of a pseudocyst (Figs. 351-3 and 351-4). The biliary tract is evaluated for the presence of stones. After genetic counseling, evaluation of PRSS1, SPINK1, CFTR, and CRTC genotypes can be measured.

Magnetic resonance cholangiopancreatography and endoscopic retrograde cholangiopancreatography are techniques that can be used to define the anatomy of the gland and are mandatory if surgery is considered. Magnetic resonance cholangiopancreatography is the test of choice when endotherapy is not being considered and should be performed as part of the evaluation of any child with idiopathic, nonresolving, or recurrent pancreatitis and in patients with a pseudocyst before drainage. In these cases a previously undiagnosed anatomic defect that may be amenable to endoscopic or surgical therapy may be detected. Endoscopic treatments include sphincterotomy, stone
extraction, drainage on pseudocysts, and insertion of pancreatic or biliary endoprosthesis stents. These treatments allow successful non-surgical management of conditions previously requiring surgical intervention. In patients with intractable pain total pancreatectomy and islet cell transfusion is performed in specialized centers.

Bibliography is available at Expert Consult.
Bibliography
Pancreatic pseudocyst formation is an uncommon sequela to acute or chronic pancreatitis. Pseudocysts are sacs delineated by a fibrous wall in the lesser peritoneal sac. They can enlarge or extend in almost any direction, thus producing a wide variety of symptoms (see Fig. 351-1C).
Bibliography
Pancreatic tumors can be of either endocrine or nonendocrine origin. Tumors of endocrine origin include insulinomas and gastrinomas. These and other functioning tumors occur in the autosomal dominantly inherited multiple endocrine neoplasia type 1 (MEN-1). Hypoglycemia accompanied by higher-than-expected insulin levels or refractory gastric ulcers (Zollinger-Ellison syndrome) indicate the possibility of a pancreatic tumor (see Chapter 345). Most gastrinomas arise outside of the pancreas. The treatment of choice is surgical removal. If the primary tumor cannot be found, or if it has metastasized, cure might not be possible. Treatment with a high dose of a proton pump inhibitor to inhibit gastric acid secretion is then indicated.

The watery diarrhea–hypokalemia–acidosis syndrome is usually produced by the secretion of vasoactive intestinal peptide by a non–α-cell tumor (VIPoma) (see Table 341-7). Vasoactive intestinal peptide levels are often, but not always, increased in the serum. Treatment is surgical removal of the tumor. When this is not possible, symptoms may be controlled by the use of octreotide acetate (cyclic somatostatin, Sandostatin), a synthetic analog of somatostatin. Pancreatic tumors secreting a variety of hormones, including glucagon, somatostatin, and pancreatic polypeptide have also been described. The treatment is surgical resection when possible.

Pancreatoblastomas, pancreatic adenocarcinomas, cystadenomas, and rhabdomyosarcomas are rarely encountered. Pancreatoblastoma, a malignant embryonal tumor that secretes α-fetoprotein and can contain both endocrine and exocrine elements, is the most common pancreatic neoplasm in young children. Presurgical chemotherapy
should be considered for lesions not primarily resectable. Resection can be curative; adjuvant chemotherapy has been used but its effectiveness is not established.

Carcinoma of the exocrine pancreas is a major problem in adults, accounting for 2% of diagnoses and 5% of deaths from cancer. It is very rare in childhood. No definite causes are known. Several genetic syndromes including mutations in the \textit{PRSS1} and \textit{MEN-1} genes lead to an increased incidence of pancreatic cancer in adult life. The Frantz tumor is a papillary cystic tumor usually found in girls and young women. Typical presenting symptoms are abdominal pain, mass, or jaundice. The treatment of choice is total surgical removal.

Insulinomas and persistent hyperinsulinemic hypoglycemia of infancy produce symptomatic hypoglycemia caused by mutations in a variety of genes, most commonly \textit{GUUD1} and \textit{KATP}. Massive subtotal or total pancreatectomy is the treatment of choice when medical treatment fails (see Chapter 86). These children might then develop pancreatic insufficiency and diabetes as a complication of surgery.

Pancreatic lesions in von Hippel-Lindau disease are usually benign and cystic. Cystadenomas, familial adenocarcinomas, and islet cell tumors are less common. Metastases have been reported, but adjuvant therapy after surgical excision cannot yet be recommended. The diagnosis is suggested by CT scanning.

Prognosis is good for completely resected endocrine tumors but very poor for carcinomas, even with extensive surgery. Children who survive partial or complete pancreatectomy may have decreased pancreatic exocrine and endocrine reserve.

\textit{Bibliography is available at Expert Consult.}
Bibliography


During the early embryonic process of gastrulation, the 3 embryonic germ layers (endoderm, mesoderm, ectoderm) are formed. The liver and biliary system arises from cells of the ventral foregut endoderm; their development can be divided into 3 distinct processes (Fig. 354-1). First, through unknown mechanisms, the ventral foregut endoderm acquires competence to receive signals arising from the cardiac mesoderm. These mesodermal signals, in the form of various fibroblast growth factors and bone morphogenetic proteins, lead to specification of cells that have the potential to form the liver and activate liver-specific genes. During this period of hepatic fate decision, “pioneer” transcription factors, including Foxa1, Foxa2, and Gata4, bind to specific binding sites in compacted chromatin, open the local chromatin structure, and mark genes as competent. But these will only be expressed if they are correctly induced by additional transcription factors. Newly specified cells then delaminate from the ventral foregut endoderm and migrate in a cranial ventral direction into the septum transversum in the 4th wk of human gestation to initiate liver morphogenesis.

The growth and development of the newly budded liver require interactions with endothelial cells. Certain proteins are important for liver development in animal models (Table 354-1). In addition to these proteins, microRNAs, which consist of small noncoding, single-stranded RNAs, have a functional role in the regulation of gene expression and hepatobiliary development in zebrafish and mouse models.

Within the ventral mesentery, proliferation of migrating cells form anastomosing hepatic cords, with the network of primitive liver cells, sinusoids, and septal mesenchyme establishing the basic architectural pattern of liver lobule (Fig. 354-2). The solid cranial portion of the hepatic diverticulum (pars hepatis) eventually forms the hepatic parenchyma and the intrahepatic bile ducts. The hepatic lobules are identifiable in the 6th wk of human gestation. The bile canaliculi structures, including microvilli and junctional complexes, are specialized loci of the liver cell membrane; these appear very early in gestation, and large canaliculi bounded by several hepatocytes are seen by 6-7 wk.

Hepatocytes and bile duct cells (cholangiocytes) originate from hepatoblasts as common precursors. Notch signaling, which is impaired in Alagille syndrome, promotes hepatoblast differentiation into biliary epithelium, whereas hepatocyte growth factor antagonizes differentiation. The development of the intrahepatic bile ducts is determined by the development and branching pattern of the portal vein. Around the 8th wk of gestation, starting at the hilum of the liver, primitive hepatoblasts adjacent to the mesenchyme around the portal vein branches form a cylindrical sleeve, termed the ductal plate. From 12 wk of gestation onward, a “remodeling” of the ductal plate occurs, with some segments of the ductal plate undergoing tubular dilation and excess ductal plate cells gradually disappearing. The ramification of the biliary tree continues throughout human fetal life and at the time of birth the most peripheral branches of the portal veins are still surrounded by ductal plates; these require 4 more weeks to develop into definitive portal ducts. Lack of remodeling of the ductal plate results in persistence of primitive ductal plate configurations, an abnormality called ductal plate malformation. This histopathologic lesion has been

<table>
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<th>Table 354-1</th>
<th>Selected Growth Factors, Receptors, Protein Kinases, and Transcription Factors Required for Normal Liver Development in Animal Models</th>
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<td><strong>INDUCTION OF HEPATOCYTE FATE THROUGH CARDIAC MESODERM</strong></td>
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<td><strong>INDUCTION OF HEPATOCYTE FATE THROUGH SEPTUM TRANSVERSUM</strong></td>
<td>Bone morphogenetic proteins 2, 4, 7</td>
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<td><strong>STIMULATION OF HEPATOBLAST GROWTH AND PROLIFERATION</strong></td>
<td>Hepatocyte growth factor (HGF) HGF receptor c-met “Pioneer” transcription factors Foxa1, Foxa2, and Gata4, Gata6 Transcription factors Xbp1, Foxm1b, Hlx, Hex, Prox1 Wnt signalling pathway, β-catenin</td>
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<td><strong>SPECIFICATION OF HEPATOCYTE LINEAGE</strong></td>
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</tr>
<tr>
<td><strong>SPECIFICATION OF CHOLANGIOCYTE LINEAGE</strong></td>
<td>Jagged 1 (Notch ligand) and Notch receptors 1, 2 HNF6, HNF1β Wnt signalling pathway, β-catenin Vacuolar sorting protein Vps33b</td>
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Figure 354-1 Processes involved in early liver development. A, The ventral foregut endoderm acquires competence to receive signals arising from the cardiac mesoderm. B, Specific cells of the ventral foregut endoderm undergo specification and activation of liver-specific genes under the influence of mesodermal signals. C, Liver morphogenesis is initiated as the newly specified cells migrate into the septum transversum under the influence of signaling molecules and extracellular matrix released by septum transversum mesenchymal cells and of primitive endothelial cells. (Reprinted from Zaret KS: Liver specification and early morphogenesis, Mech Dev 92:83–88, 2000; copyright 2000, with permission from Elsevier Science.)

Figure 354-2 Hepatic morphogenesis. A, Ventral outgrowth of hepatic diverticulum from foregut endoderm in the 3.5 wk embryo. B, Between the 2 vitelline veins, the enlarging hepatic diverticulum buds off epithelial (liver) cords that become the liver parenchyma, around which the endothelium of capillaries (sinusoids) align (4 wk embryo). C, Hemisection of embryo at 7.5 wk. D, Three-dimensional representation of the hepatic lobule as present in the newborn. (Reprinted from Andres JM, Mathis RK, Walker WA: Liver disease in infants. Part I: developmental hepatology and mechanisms of liver dysfunction, J Pediatr 90:686–697, 1977.)

observed in liver biopsies of a variety of liver conditions, including congenital hepatic fibrosis, Caroli disease, and biliary atresia.

The caudal part (pars cystica) of the hepatic diverticulum becomes the gallbladder, cystic duct, and common bile duct. The distal portions of the right and left hepatic ducts develop from the extrahepatic ducts, whereas the proximal portions develop from the first intrahepatic ductal plates. The extrahepatic bile ducts and the developing intrahepatic biliary tree maintain luminal continuity and patency from the beginning of organogenesis (see Fig. 354-2C).

Fetal hepatic blood flow is derived from the hepatic artery and from the portal and umbilical veins, which form the portal sinus. The portal venous inflow is directed mainly to the right lobe of the liver and umbilical flow primarily to the left. The ductus venosus shunts blood from the portal and umbilical veins to the hepatic vein, bypassing the sinusoidal network. After birth, the ductus venosus becomes obliterated when oral feedings are initiated. The fetal oxygen saturation is lower in portal than in umbilical venous blood; accordingly, the right hepatic lobe has lower oxygenation and greater hematopoietic activity than the left hepatic lobe.

The transport and metabolic activities of the liver are facilitated by the structural arrangement of liver cell cords, which are formed by rows of hepatocytes, separated by sinusoids that converge toward the tributaries of the hepatic vein (the central vein) located in the center of the lobule (see Fig. 354-2D). This establishes the pathways and patterns of flow for substances to and from the liver. In addition to arterial input from the systemic circulation, the liver also receives venous input from the gastrointestinal tract via the portal system. The products of the hepatobiliary system are released by 2 different paths: through the hepatic vein and through the biliary system back into the intestine. Plasma proteins and other plasma components are secreted by the liver. Absorbed and circulating nutrients arrive through the portal vein or the hepatic artery and pass through the sinusoids and past the hepatocytes to the systemic circulation at the central vein. Biliary components are transported via the series of enlarging channels from the bile canaliculi through the bile ductule to the common bile duct.

Bile secretion is first noted at the 12th wk of human gestation. The major components of bile vary with stage of development. Near term, cholesterol and phospholipid content is relatively low. Low concentrations of bile acids, the absence of bacterially derived (secondary) bile acids, and the presence of unusual bile acids reflect low rates of bile flow and immature bile acid synthetic pathways.

The liver reaches a peak relative size of approximately 10% of the fetal weight at the 9th wk. Early in development, the liver is a primary site of hematopoiesis. In the 7th wk, hematopoietic cells outnumber functioning hepatocytes in the hepatic anlage. These early hepatocytes are smaller than at maturity (~20 µm vs 30-35 µm) and contain less glycogen. Near term, the hepatocyte mass expands to dominate the organ, as cell size and glycogen content increase. Hematopoiesis is virtually absent by the 2nd postnatal month in full-term infants. As the density of hepatocytes increases with gestational age, the relative volume of the sinusoidal network decreases. The liver constitutes 5% of body weight at birth but only 2% in an adult.

Several metabolic processes are immature in a healthy newborn infant, owing in part to the fetal patterns of activity of various enzymatic processes. Many fetal hepatic functions are carried out by the maternal liver, which provides nutrients and serves as a route of elimination of metabolic end products and toxins. Fetal liver metabolism is devoted primarily to the production of proteins required for growth.
METABOLIC FUNCTIONS OF THE LIVER

Carbohydrate Metabolism

The liver regulates serum glucose levels closely via several processes, including storage of excess carbohydrate as glycogen, a polymer of glucose readily hydrolyzed to glucose during fasting. To maintain serum glucose levels, hepatocytes produce free glucose by either gluconeogenesis or gluconeogenesis. Immediately after birth, an infant is dependent on hepatic gluconeogenesis. Gluconeogenic activity is present at a low level in the fetal liver and increases rapidly after birth. Fetal glycogen synthesis begins at about the 9th wk of gestation, with glycogen stores most rapidly accumulated near term, when the liver contains 2-3 times the amount of glycogen of adult liver. Most of this stored glycogen is used in the immediate postnatal period. Reaccumulation is initiated at about the 2nd wk of postnatal life, and glycogen stores reach adult levels at approximately the 3rd wk in healthy full-term infants. In preterm infants, serum glucose levels fluctuate in part because efficient regulation of the synthesis, storage, and degradation of glycogen develops only near the end of full-term gestation. Dietary carbohydrates such as galactose are converted to glucose, but there is a substantial dependence on gluconeogenesis for glucose in early life, especially if glycogen stores are limited.

Protein Metabolism

During the rapid fetal growth phase, specific decarboxylases that are rate limiting in the biosynthesis of physiologically important polyamines have higher activities than in the mature liver. The rate of synthesis of albumin and secretory proteins in the developing liver parallels the quantitative changes in endoplasmic reticulum. Synthesis of albumin appears at approximately the 7th-8th wk in the human fetus and increases in inverse proportion to that of α-fetoprotein, which is the dominant fetal protein. By the 3rd-4th mo of gestation, the fetal liver is able to produce fibrinogen, transferrin, and low-density lipoproteins. From this period on, fetal plasma contains each of the major protein classes at concentrations considerably below those achieved at maturity.

The postnatal patterns of protein synthesis vary with the class of protein. Lipoproteins of each class rise abruptly in the 1st wk after birth to reach levels that vary little until puberty. Albumin concentrations are low in a neonate (∼2.5 g/dL), reaching adult levels (∼3.5 g/dL) after several months. Levels of ceruloplasmin and complement factors increase slowly to adult values in the 1st yr. In contrast, transferrin levels at birth are similar to those of an adult, decline for 3-5 mo, and rise thereafter to achieve their final concentrations. Low levels of activity of specific proteins have implications for the nutrition of an infant. A low level of cystathionine γ-lyase (cystathionase) activity impairs the trans-sulfuration pathway by which dietary methionine is converted to cysteine. Consequently, the latter must be supplied in the diet. Similar dietary requirements might exist for other sulfur-containing amino acids, such as taurine.

Lipid Metabolism

Fatty acid oxidation provides a major source of energy in early life, complementing gluconeogenesis and gluconeogenesis. Newborn infants are relatively intolerant of prolonged fasting, owing in part to a restricted capacity for hepatic ketogenesis. Rapid maturation of the ability of the liver to oxidize fatty acid occurs in the 1st few days of life. Milk provides the major source of calories in early life; this high-fat, low-carbohydrate diet mandates active gluconeogenesis to maintain blood glucose levels. When the glucose supply is limited, ketone body production from endogenous fatty acids can provide energy for hepatic gluconeogenesis and an alternative fuel for brain metabolism. When carbohydrates are in excess, the liver produces triglycerides. Metabolic processes involving lipids and lipoproteins are

Hepatocytes exhibit various ultrastructural features that reflect their biologic functions (Fig. 354-3). Hepatocytes, like other epithelial cells, are polarized, meaning that their structure and function are directionally oriented. One result of this polarity is that various regions of the hepatocyte plasma membrane exhibit specialized functions. Bidirectional transport occurs at the sinusoidal surface, where materials reaching the liver via the portal system enter and compounds secreted by the liver leave the hepatocyte. Canalicular membranes of adjacent hepatocytes form bile canaliculi, which are bounded by tight junctions, preventing transfer of secreted compounds back into the sinusoid. Within hepatocytes, metabolic and synthetic activities are contained within a number of different cell organelles. The oxidation and metabolism of heterogeneous classes of substrates, fatty acid oxidation, key processes in gluconeogenesis, and the storage and release of energy occur in the abundant mitochondria.

The endoplasmic reticulum, a continuous network of rough- and smooth-surfaced tubules and cisternae, is the site of various processes, including protein and triglyceride synthesis and drug metabolism. Low fetal activity of endoplasmic reticulum–bound enzymes accounts for a relative inefficiency of xenobiotic (drug) metabolism. The Golgi apparatus is active in protein packaging and possibly in bile secretion. Hepatocyte peroxisomes are single-membrane-limited cytoplasmic organelles that contain enzymes such as oxidases and catalase and those that have a role in lipid and bile acid metabolism. Lysosomes contain numerous hydrolases that have a role in intracellular digestion. The hepatocyte cytoskeleton, composed of actin and other filaments, is distributed throughout the cell and concentrated near the plasma membrane. Microfilaments and microtubules have a role in receptor-mediated endocytosis, in bile secretion, and in maintaining hepatocyte architecture and motility.
Biotransformation
Newborn infants have a decreased capacity to metabolize and detoxify certain drugs, owing to underdevelopment of the hepatic microsomal component that is the site of the specific oxidative, reductive, hydrolytic, and conjugation reactions required for these biotransformations. The major components of the monooxygenase system, such as cytochrome P450, cytochrome-c reductase, and the reduced form of nicotinamide-adenine dinucleotide phosphate, are present in low concentrations in fetal microsomal preparations. In full-term infants, hepatic uridine diphosphate glucuronosyltransferase and enzymes involved in the oxidation of polycyclic aromatic hydrocarbons are expressed at very low levels.

Age-related differences in pharmacokinetics vary from compound to compound. The half-life of acetaminophen in a newborn is similar to that of an adult, whereas theophylline has a half-life of approximately 100 hr in a premature infant, as compared to 5-6 hr in an adult. These differences in metabolism, as well as factors such as binding to plasma proteins and renal clearance, determine appropriate drug dosage to maximize effectiveness and to avoid toxicity. Dramatic examples of the susceptibility of newborn infants to drug toxicity are the responses to chloramphenicol (the “gray baby” syndrome) or to benzoyl alcohol and its metabolic products, which involve ineffectual glucuronide and glycine conjugation, respectively. The low concentrations of antioxidants (vitamin E, superoxide dismutase, glutathione peroxidase) in the fetal and early newborn liver lead to increased susceptibility to deleterious effects of oxygen toxicity and oxidant injury through lipid peroxidation.

Conjugation reactions, which convert drugs or metabolites into water-soluble forms that can be eliminated in bile, are also catalyzed by hepatic microsomal enzymes. Newborn infants have decreased activity of hepatic uridine diphosphate glucuronosyltransferase, which converts unconjugated bilirubin to the readily excreted glucuronide conjugate and is the rate-limiting enzyme in the excretion of bilirubin. There is rapid postnatal development of transferase activity irrespective of gestational age, which suggests that birth-related, rather than age-related, factors are of primary importance in the postnatal development of activity of this enzyme. Microsomal activity can be stimulated by administration of phenobarbital, rifampin, or other inducers of cytochrome P450. Alternatively, drugs such as cimetidine can inhibit microsomal P450 activity.

Hepatic Excretory Function
Hepatic excretory function and bile flow are closely related to hepatic bile acid excretion and enterohepatic recirculation. Bile acids, the major products of cholesterol degradation, are incorporated into mixed micelles with cholesterol and phospholipid. These micelles act as an efficient vehicle for solubilization and intestinal absorption of lipophilic compounds, such as dietary fats and fat-soluble vitamins. Secretion of bile acids by the liver cells is the major determinant of bile flow in the mature animal. Accordingly, maturity of bile acid metabolic processes affects overall hepatic excretory function, including biliary excretion of endogenous and exogenous compounds.

In humans, the 2 primary bile acids, cholic acid and chenodeoxycholic acid, are synthesized in the liver. Before excretion, they are conjugated with glycine and taurine. In response to a meal, contraction of the gallbladder delivers bile acids to the intestine to assist in fat digestion and absorption. After mediating fat digestion, the bile acids themselves are reabsorbed from the terminal ileum through specific active transport processes. They return to the liver via portal blood, are taken up by liver cells, and are reexcreted in bile. In an adult, this enterohepatic circulation involves 90-95% of the circulating bile acid pool. Bile acids that escape ileal reabsorption reach the colon, where the bacterial flora, through dehydroxylation and deconjugation, produce the secondary bile acids, deoxycholate and lithocholate. In an adult, the composition of bile reflects the excretion of the primary and also the secondary bile acids, which are reabsorbed from the distal intestinal tract.

Intraluminal concentrations of bile acids are low in newborn infants and increase rapidly after birth. The expansion of the bile acid pool is critical because bile acids are required to stimulate bile flow and absorb lipids, a major component of the diet of a newborn. Nuclear receptors, such as farnesoid X receptor, control intrahepatic bile acid homeostasis through several mechanisms, including regulation of expression of the genes encoding 2 key proteins, cholesterol 7α-hydroxylase (CYP7A1) and bile salt export pump (BSEP). These proteins are critical for bile acid synthesis and canaliculic secretion, respectively. Neonatal expression of these nuclear receptors varies depending on the studied animal model and is largely unknown for humans.

Because of inefficient ileal reabsorption of bile acids and the low rate of hepatic clearance of bile acids from portal blood, serum concentrations of bile acids are commonly elevated in healthy newborns, often to levels that would suggest liver disease in older persons. Transient phases of “physiologic cholestasis” and “physiologic steatorrhea” can often be observed in low birthweight infants and in full-term infants following perinatal stress, such as hypoxia or infection, but are otherwise uncommon in healthy full-term newborns.

Many of the processes related to immaturity of the newborn in liver morphogenesis and function as discussed earlier are implied in the increased susceptibility of infants to liver disease associated with parenteral nutrition. The reduced bile salt pool, hepatic glutathione depletion, and deficient sulfation contribute to production of toxic lithocholic bile acids and cholestasis, whereas deficiencies of essential amino acids, including taurine and cysteine, and excessive lipid infusion can lead to hepatic steatosis in these infants. Beyond the neonatal period, disturbances in bile acid metabolism may be responsible for diverse effects on hepatobiliary and intestinal function (Table 354-2).

Bibliography is available at Expert Consult.
Chapter 354  ◆  Morphogenesis of the Liver and Biliary System  1921.e1

Bibliography


**Chapter 355**

**Manifestations of Liver Disease**

James E. Squires and William F. Balistreri

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**PATHOLOGIC MANIFESTATIONS**

Alterations in hepatic structure and function can be acute or chronic, with varying patterns of reaction of the liver to cell injury. Hepatocyte injury can be caused by viral infection, drugs or toxins, hypoxia, immunologic disorders, or inborn errors of metabolism. The injury results in inflammatory cell infiltration or cell death (necrosis), which may be followed by a healing process of scar formation (fibrosis) and, potentially, nodule formation (regeneration). Cirrhosis is the end result of any progressive liver disease.

**Cholestasis** is an alternative or concomitant response to injury caused by extrahepatic or intrahepatic obstruction to bile flow. Substances that are normally excreted in bile, such as conjugated bilirubin, cholesterol, bile acids, and trace elements, accumulate in serum. Bile pigment accumulation in liver parenchyma can be seen in liver biopsy specimens. In extrahepatic obstruction, bile pigment may be visible in the intralobular bile ducts or throughout the parenchyma as bile lakes or infarcts. In intrahepatic cholestasis, an injury to hepatocytes or an alteration in hepatic physiology leads to a reduction in the rate of secretion of solute and water. Likely causes include alterations in enzymatic or canalicular transporter activity, permeability of the bile canalicular apparatus, organelles responsible for bile secretion, or ultrastructure of the cytoskeleton of the hepatocyte. The end result can be clinically indistinguishable from obstructive cholestasis.

**Cirrhosis**, defined histologically by the presence of bands of fibrous tissue that link central and portal areas and form parenchymal nodules, is a potential end stage of any acute or chronic liver disease. Cirrhosis can be macronodular, with nodules of various sizes (up to 5 cm) separated by fine septa; mixed forms occur. The progressive scarring of cirrhosis results in altered hepatic blood flow, with further impairment of liver cell function. Increased intrahepatic resistance to portal blood flow leads to portal hypertension.

The liver can be secondarily involved in neoplastic (metastatic) and nonneoplastic (storage diseases, fat infiltration) processes, as well as a number of systemic conditions and infectious processes. The liver can be affected by chronic passive congestion (congestive heart failure) or acute hypoxia, with hepatic cellular damage.

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**CLINICAL MANIFESTATIONS**

**Hepatomegaly**

Enlargement of the liver can be caused by several mechanisms (Table 355-1). Normal liver size estimations are based on age-related clinical indices, such as the degree of extension of the liver edge below the costal margin, the span of dullness to percussion, or the length of the vertical axis of the liver, as estimated from imaging techniques. In children, the normal liver edge can be felt up to 2 cm below the right costal margin. In a newborn infant, extension of the liver edge more than 3.5 cm below the costal margin in the right midclavicular line suggests hepatic enlargement. Measurement of liver span is carried out by percussing the upper margin of dullness and by palpating the lower edge in the right midclavicular line. This may be more reliable than an extension of the liver edge alone. The 2 measurements may correlate poorly.

The liver span increases linearly with body weight and age in both sexes, ranging from approximately 4.5-5.0 cm at 1 wk of age to approximately 7-8 cm in boys and 6.0-6.5 cm in girls by 12 yr of age. The lower edge of the right lobe of the liver extends downward (Riedel lobe) and can normally be palpated as a broad mass in some people. An

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**Table 355-1: Mechanisms of Hepatomegaly**

<table>
<thead>
<tr>
<th>INCREASE IN THE NUMBER OR SIZE OF THE CELLS INTRINSIC TO THE LIVER</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Storage</strong></td>
</tr>
<tr>
<td>Fat: malnutrition, obesity, diabetes mellitus, metabolic liver disease (diseases of fatty acid oxidation and Reye syndrome–like illnesses), lipid infusion (total parenteral nutrition), cystic fibrosis, medication related, pregnancy</td>
</tr>
<tr>
<td>Specific lipid storage diseases: Gaucher, Niemann-Pick, Wolman disease</td>
</tr>
<tr>
<td>Glycogen: glycogen storage diseases (multiple enzyme defects); total parenteral nutrition; infant of diabetic mother, Beckwith syndrome</td>
</tr>
<tr>
<td>Miscellaneous: α1-antitrypsin deficiency, Wilson disease, hypervitaminosis A, neonatal iron storage disease</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Inflammation</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatocyte enlargement (hepatitis)</td>
</tr>
<tr>
<td>• Viral: acute and chronic</td>
</tr>
<tr>
<td>• Bacterial: sepsis, abscess, cholangitis</td>
</tr>
<tr>
<td>• Toxic: drugs</td>
</tr>
<tr>
<td>• Autoimmune</td>
</tr>
<tr>
<td>Kupffer cell enlargement</td>
</tr>
<tr>
<td>• Sarcomiosis</td>
</tr>
<tr>
<td>• Systemic lupus erythematosus</td>
</tr>
<tr>
<td>• Macrophage activating syndrome</td>
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</tbody>
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<table>
<thead>
<tr>
<th><strong>Infiltration of Cells</strong></th>
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</thead>
<tbody>
<tr>
<td><strong>Primary Liver Tumors: Benign</strong></td>
</tr>
<tr>
<td>Hepatocellular</td>
</tr>
<tr>
<td>• Focal nodular hyperplasia</td>
</tr>
<tr>
<td>• Nodular regenerative hyperplasia</td>
</tr>
<tr>
<td>• Hepatoacinar adenoma</td>
</tr>
<tr>
<td>Mesodermal</td>
</tr>
<tr>
<td>• Infantile hemangioendothelioma</td>
</tr>
<tr>
<td>• Mesenchymal hamartoma</td>
</tr>
<tr>
<td>Cystic masses</td>
</tr>
<tr>
<td>• Choledochal cyst</td>
</tr>
<tr>
<td>• Hepatic cyst</td>
</tr>
<tr>
<td>• Hematoma</td>
</tr>
<tr>
<td>• Parasitic cyst</td>
</tr>
<tr>
<td>• Pyogenic or amebic abscess</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Primary Liver Tumors: Malignant</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatocellular</td>
</tr>
<tr>
<td>• Hepatoblastoma</td>
</tr>
<tr>
<td>• Hepatoacinar carcinoma</td>
</tr>
<tr>
<td>Mesodermal</td>
</tr>
<tr>
<td>• Angiosarcoma</td>
</tr>
<tr>
<td>• Undifferentiated embryonal sarcoma</td>
</tr>
<tr>
<td>Secondary or metastatic processes</td>
</tr>
<tr>
<td>• Lymphoma</td>
</tr>
<tr>
<td>• Leukemia</td>
</tr>
<tr>
<td>• Histiocytosis</td>
</tr>
<tr>
<td>• Neuroblastoma</td>
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</tbody>
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<table>
<thead>
<tr>
<th><strong>Increased Size of Vascular Space</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Intrahepatic obstruction to hepatic vein outflow</td>
</tr>
<tr>
<td>• Venoocclusive disease</td>
</tr>
<tr>
<td>• Hepatic vein thrombosis (Budd-Chiari syndrome)</td>
</tr>
<tr>
<td>• Hepatic vein web</td>
</tr>
<tr>
<td>Suprahepatic</td>
</tr>
<tr>
<td>• Congestive heart failure</td>
</tr>
<tr>
<td>• Pericardial disease</td>
</tr>
<tr>
<td>• Tamponade</td>
</tr>
<tr>
<td>Post-Fontan procedure</td>
</tr>
<tr>
<td>Constrictive pericarditis</td>
</tr>
<tr>
<td>Hematopoietic: sickle cell anemia, thalassemia</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Increased Size of Biliary Space</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Congenital hepatic fibrosis</td>
</tr>
<tr>
<td>Caroli disease</td>
</tr>
<tr>
<td>Extrahepatic obstruction</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Idiopathic</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Various</td>
</tr>
<tr>
<td>• Riedel lobe</td>
</tr>
<tr>
<td>• Normal variant</td>
</tr>
<tr>
<td>• Downward displacement of diaphragm</td>
</tr>
</tbody>
</table>
enlarged left lobe of the liver is palpable in the epigastrium of some patients with cirrhosis. Downward displacement of the liver by the diaphragm (hyperinflation) or thoracic organs can create an erroneous impression of hepatomegaly.

Examination of the liver should note the consistency, contour, tenderness, and presence of any masses or bruits, as well as assessment of spleen size. Documentation of the presence of ascites and any stigmata of chronic liver disease is important.

Ultrasound is useful in assessment of liver size and consistency, as well as gallbladder size. Gallbladder length normally varies from 1.5-5.5 cm (average: 3 cm) in infants to 4-8 cm in adolescents; width ranges from 0.5-2.5 cm for all ages. Gallbladder distention may be seen in infants with sepsis. The gallbladder is often absent in infants with biliary atresia.

**Jaundice (Icterus)**

Yellow discoloration of the sclera, skin, and mucous membranes is a sign of hyperbilirubinemia (see Chapter 102.3). Clinically apparent jaundice in children and adults occurs when the serum concentration of bilirubin reaches 2-3 mg/dL (34-51 µmol/L); the neonate might not appear icteric until the bilirubin level is >5 mg/dL (>85 µmol/L). Jaundice may be the earliest and only sign of hepatic dysfunction. Liver disease must be suspected in the infant who appears only mildly jaundiced but has dark urine or acholic (light-colored) stools. Immediate evaluation to establish the cause is required.

Measurement of the total serum bilirubin concentration allows quantitation of jaundice. Bilirubin occurs in plasma in 4 forms: *unconjugated* bilirubin tightly bound to albumin; *free* or *unbound* bilirubin (the form responsible for kernicterus, because it can cross cell membranes); *conjugated* bilirubin (the only fraction to appear in urine); and δ fraction (bilirubin covalently bound to albumin), which appears in serum when hepatic excretion of conjugated bilirubin is impaired in patients with hepatobiliary disease. The δ fraction permits conjugated bilirubin to persist in the circulation and delays resolution of jaundice. Although the terms *direct* and *indirect* bilirubin are used equivalently with conjugated and unconjugated bilirubin, this is not quantitatively correct, because the direct fraction includes both conjugated bilirubin and δ bilirubin.

Investigation of jaundice in an infant or older child must include determination of the accumulation of both unconjugated and conjugated bilirubin. Unconjugated hyperbilirubinemia might indicate increased production, hemolysis, reduced hepatic removal, or altered metabolism of bilirubin (Table 355-2). Conjugated hyperbilirubinemia reflects decreased excretion by damaged hepatic parenchymal cells or disease of the biliary tract, which may be a result of obstruction, sepsis, toxins, inflammation, and genetic or metabolic disease (Table 355-3).

**Pruritus**

Intense generalized itching can occur in patients with chronic liver disease often in association with cholestasis (conjugated hyperbilirubinemia). Symptoms can be generalized or localized (commonly to palms and soles), are usually worse at night, are exacerbated with stress and heat, and are relieved by cool temperatures. Pruritus is unrelated to the degree of hyperbilirubinemia; deeply jaundiced patients can be asymptomatic. Although retained components of bile are likely important, the cause is probably multifactorial, as evidenced by the symptomatic relief of pruritus after administration of various therapeutic agents including bile acid-binding agents (cholestyramine), choleretic agents (ursodeoxycholic acid), opiate antagonists, antihistamines, and antibiotics. Plasmapheresis, molecular adsorbent recirculating system therapy, and surgical diversion of bile (partial external biliary diversion) have been used in attempts to provide relief for medically refractory pruritus.

**Spider Angiomas**

Vascular spiders (telangiectasias), characterized by central pulsating arterioles from which small, wiry venules radiate, may be seen in patients with chronic liver disease; these are usually most prominent
### Differential Diagnosis of Neonatal and Infantile Cholestasis

<table>
<thead>
<tr>
<th>INFECTIOUS</th>
<th>Generalized bacterial sepsis</th>
<th>Viral hepatitis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hepatitis A, B, C, D, E</td>
<td>Cytomegalovirus</td>
</tr>
<tr>
<td></td>
<td>Rubella virus</td>
<td>Herpesviruses: herpes simplex, human herpesvirus 6 and 7</td>
</tr>
<tr>
<td></td>
<td>Varicella virus</td>
<td>Coxsackievirus</td>
</tr>
<tr>
<td></td>
<td>Echovirus</td>
<td>Reovirus type 3</td>
</tr>
<tr>
<td></td>
<td>Parvovirus B19</td>
<td>HIV</td>
</tr>
<tr>
<td></td>
<td>Adenovirus</td>
<td>Others</td>
</tr>
<tr>
<td></td>
<td>Toxoplasmosis</td>
<td>Syphilis</td>
</tr>
<tr>
<td></td>
<td>Tuberculosis</td>
<td>Listeriosis</td>
</tr>
<tr>
<td></td>
<td>Others</td>
<td>Urinary tract infection</td>
</tr>
</tbody>
</table>

| TOXIC | Sepsis | Parenteral nutrition related |
|       | Drug, dietary supplement, herbal related |

| METABOLIC | Disorders of amino acid metabolism |
|           | Tyrosinemia |
|           | Disorders of lipid metabolism |
|           | Wolman disease |
|           | Niemann-Pick disease (type C) |
|           | Gaucher disease |
|           | Cholesterol ester storage disease |
|           | Disorders of carbohydrate metabolism |
|           | Galactosemia |
|           | Fructosemia |
|           | Glycogenosis IV |
|           | Disorders of bile acid biosynthesis |
|           | Other metabolic defects |
|           | α-Antitrypsin deficiency |
|           | Cystic fibrosis |
|           | Hypopituitarism |
|           | Hypothyroidism |
|           | Zellweger (cerebrohepatorenal) syndrome |

| GENETIC OR CHROMOSOMAL | Trisomies 17, 18, 21 |
|                       | Wilson disease |
|                       | Neonatal iron storage disease |
|                       | Indian childhood cirrhosis/infantile copper overload |
|                       | Congenital disorders of glycosylation |
|                       | Mitochondrial hepatopathies |
|                       | Citrin deficiency |

<table>
<thead>
<tr>
<th>INTRAHEPATIC CHOLESTASIS SYNDROMES</th>
</tr>
</thead>
<tbody>
<tr>
<td>“Idiopathic” neonatal hepatitis</td>
</tr>
<tr>
<td>Alagille syndrome</td>
</tr>
<tr>
<td>Intrahepatic cholestasis (progressive familial intrahepatic cholestasis [PFIC])</td>
</tr>
<tr>
<td>FIC-1 deficiency</td>
</tr>
<tr>
<td>BSEP (bile salt export pump) deficiency</td>
</tr>
<tr>
<td>MDR3 deficiency</td>
</tr>
<tr>
<td>Familial benign recurrent cholestasis associated with lymphedema (Aagenaes syndrome)</td>
</tr>
<tr>
<td>ARC (arthrogryposis, renal dysfunction, and cholestasis) syndrome</td>
</tr>
<tr>
<td>Caroli disease (cystic dilation of intrahepatic ducts)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>EXTRAHEPATIC DISEASES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biliary atresia</td>
</tr>
<tr>
<td>Sclerosing cholangitis</td>
</tr>
<tr>
<td>Bile duct stricture/stenosis</td>
</tr>
<tr>
<td>Choledochal-pancreatic ductal junction anomaly</td>
</tr>
<tr>
<td>Spontaneous perforation of the bile duct</td>
</tr>
<tr>
<td>Choledochal cyst</td>
</tr>
<tr>
<td>Mass (neoplasia, stone)</td>
</tr>
<tr>
<td>Bile/mucous plug (“inspissated bile”)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>MISCELLANEOUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shock and hypoperfusion</td>
</tr>
<tr>
<td>Associated with enthesitis</td>
</tr>
<tr>
<td>Associated with intestinal obstruction</td>
</tr>
<tr>
<td>Neonatal lupus erythematosus</td>
</tr>
<tr>
<td>Myeloproliferative disease (trisomy 21)</td>
</tr>
<tr>
<td>Hemophagocytic lymphohistiocytosis (HLH)</td>
</tr>
<tr>
<td>COACH syndrome (coloboma, oligophrenia, ataxia, cerebellar vermis hypoplasia, hepatic fibrosis)</td>
</tr>
<tr>
<td>Choangiocyte cilia defects</td>
</tr>
</tbody>
</table>

In the superior vena cava distribution area (on the face and chest). Their size varies between 1 and 10 mm and they exhibit central clearing with pressure. They presumably reflect altered estrogen metabolism in the presence of hepatic dysfunction.

**Palmar Erythema**

Blotchy erythema, most noticeable over the thenar and hypothenar eminences and on the tips of the fingers, is also noted in patients with chronic liver disease. Abnormal serum estradiol levels and regional alterations in peripheral circulation have been identified as possible causes.

**Xanthomas**

The marked elevation of serum cholesterol levels (to >500 mg/dL) associated with some forms of chronic cholestasis can cause the deposition of lipid in the dermis and subcutaneous tissue. Brown nodules can develop, first over the extensor surfaces of the extremities; rarely, xanthelasma of the eyelids develops.

**Portal Hypertension**

Portal hypertension occurs when there is increased portal resistance and/or increased portal flow. The portal system drains the splanchnic area (abdominal portion of the gastrointestinal tract, pancreas, and spleen) into the hepatic sinusoids. Normal portal pressure is between 3 and 6 mm Hg. Portal hypertension is defined as a portal pressure greater than 10 mm Hg. Clinically significant portal hypertension exists when pressure exceeds a threshold of 12 mm Hg or greater. Portal hypertension is the main complication of cirrhosis, directly responsible for 2 of its most common and potentially lethal complications: ascites and variceal hemorrhage.

**Ascites**

Ascites is a consequence of increased hydrostatic and osmotic pressures within the hepatic and mesenteric capillaries resulting in transfer of fluid from the blood vessels to the lymphatics that overcomes the drainage capacity of the lymphatic system. Ascites can also be associated with nephrotic syndrome and other urinary tract abnormalities, metabolic diseases (such as lysosomal storage diseases), congenital or acquired heart disease, and hydrops fetalis. Factors favoring the intraabdominal accumulation of fluid include decreased plasma colloid osmotic pressure, increased capillary hydrostatic pressure, increased ascitic colloid osmotic fluid pressure, and decreased ascitic fluid hydrostatic pressure. Abnormal renal sodium retention must be considered.
Gastrointestinal Bleeding

Chronic liver disease may manifest as gastrointestinal hemorrhage. Bleeding may result from portal hypertensive gastropathy, gastric antral vascular ectasia, or varix rupture. Variceal hemorrhage is classically from an esophageal origin but may be caused by gastric, duodenal, peristomal, or rectal varices. Variceal hemorrhage results from increased pressure within the varix, which leads to changes in the diameter of the varix and increased wall tension. When the variceal wall strength is exceeded, physical rupture of the varix results. Given the high blood flow and pressure in the portosystemic collateral system, coupled with the lack of a natural mechanism to tamponade variceal bleeding, the rate of hemorrhage can be striking.

Encephalopathy

Hepatic encephalopathy can involve any neurologic function, and it can be prominent or present in subtle forms such as deterioration of school performance, sleep disturbances, depression, or emotional outbursts. It can be recurrent and precipitated by intercurrent illness, drugs, bleeding, or electrolyte and acid-base disturbances. The appearance of hepatic encephalopathy depends on the presence of portosystemic shunting, alterations in the blood–brain barrier, and the interactions of toxic metabolites with the central nervous system. Postulated causes include altered ammonia metabolism, synergistic neurotoxins, decreased cerebral oxygen metabolism and blood flow, or false neurotransmitters with plasma amino acid imbalance.

Endocrine Abnormalities

Endocrine abnormalities are more common in adults with hepatic disease than in children. They reflect alterations in hepatic synthetic, storage, and metabolic functions, including those concerned with hormonal metabolism in the liver. Proteins that bind hormones in plasma are synthesized in the liver, and steroid hormones are conjugated in the liver and excreted in the urine; failure of such functions can have clinical consequences. Endocrine abnormalities can also result from malnutrition or specific deficiencies.

Renal Dysfunction

Systemic disease or toxins can affect the liver and kidneys simultaneously, or parenchymal liver disease can produce secondary impairment of renal function. In hepatobiliary disorders, there may be renal alterations in sodium and water economy, impaired renal concentrating ability, and alterations in potassium metabolism. Ascites in patients with cirrhosis may be related to inappropriate retention of sodium by the kidneys and expansion of plasma volume, or it may be related to sodium retention mediated by diminished effective plasma volume. Hepatorenal syndrome is defined as functional renal failure in patients with end-stage liver disease. The pathophysiology of hepatorenal syndrome is related to splanchnic vasodilation, mesenteric angiogenesis, and decreased effective blood volume with resulting decreased renal perfusion. The hallmark is intense renal vasoconstriction (mediated by hemodynamic, humoral, or neurogenic mechanisms) with coexistent systemic vasodilation. The diagnosis is supported by the findings of oliguria (<1 mL/kg/day), a characteristic pattern of urine electrolyte abnormalities (urine sodium <10 mEq/L, fractional excretion of sodium of <1%, urine: plasma creatinine ratio <10, and normal urinary sediment), absence of hypovolemia, and exclusion of other kidney pathology. The best treatment of hepatorenal syndrome is timely liver transplantation, because complete renal recovery can be expected.

Pulmonary Involvement

Hepatopulmonary syndrome is characterized by the typical triad of hypoxemia, intrapulmonary vascular dilations, and liver disease. There is intrapulmonic right-to-left shunting of blood resulting from enlarged pulmonary vessels that prevents red blood cells traveling through the center of the vessel adequate exposure to oxygen-rich alveoli. Shunting of vasodilatory mediators from the mesentery away from the liver is thought to contribute. It should be suspected and investigated in the child with chronic liver disease with history of shortness of breath or exercise intolerance and clinical examination findings of cyanosis (particularly of the lips and fingers), digital clubbing, and oxygen saturations <96%, particularly in the upright position. Treatment is timely liver transplantation; resolution of pulmonary involvement usually follows. Portopulmonary hypertension is a condition characterized by an increase in the resistance to pulmonary arterial blood flow in the setting of portal hypertension. It is defined by a pulmonary arterial pressure >25 mm Hg at rest and above 30 mm Hg with exercise, elevated pulmonary vascular resistance with pulmonary arterial occlusion pressure, or a left-ventricular end-diastolic pressure of <15 mm Hg. Although the pathophysiology is unclear, symptoms suggesting a diagnosis include exertional dyspnea, fatigue, syncope, palpitations, and chest pain.

Recurrent Cholangitis

Ascending infection of the biliary system is often seen in pediatric cholestatic disorders, most commonly because of Gram-negative enteric organisms, such as Escherichia coli, Klebsiella, Pseudomonas, and Enterococcus. Liver transplantation is the definitive treatment for recurrent cholangitis, especially when medical therapy is not effective.

Miscellaneous Manifestations of Liver Dysfunction

Nonspecific signs of acute and chronic liver disease include anorexia, which often affects patients with anicteric hepatitis and with cirrhosis associated with chronic cholestasis; abdominal pain or distention resulting from ascites, spontaneous peritonitis, or visceromegaly; malnutrition and growth failure; and bleeding, which may be a result of altered synthesis of coagulation factors (biliary obstruction with vitamin K deficiency or excessive hepatic damage) or to portal hypertension with hypersplenism. In the presence of hypersplenism, there can be decreased synthesis of specific clotting factors, production of qualitatively abnormal proteins, or alterations in platelet number and function. Altered drug metabolism can prolong the biologic half-life of commonly administered medications.

Bibliography is available at Expert Consult.

355.1 Evaluation of Patients with Possible Liver Dysfunction

James E. Squires and William F. Balisteri

Adequate evaluation of an infant, child, or adolescent with suspected liver disease involves an appropriate and accurate history, a carefully performed physical examination, and skillful interpretation of signs and symptoms. Further evaluation is aided by judicious selection of diagnostic tests, followed by the use of imaging modalities or a liver biopsy. Most of the so-called liver function tests do not measure specific hepatic functions: a rise in serum aminotransferase levels reflects liver cell injury, an increase in immunoglobulin levels reflects an immunologic response to injury, or an elevation in serum bilirubin levels can reflect any of several disturbances of bilirubin metabolism (see Tables 355-2 and 355-3). Any single biochemical assay provides limited information, which must be placed in the context of the entire clinical picture. The most cost-efficient approach is to become familiar with the rationale, implications, and limitations of a selected group of tests so that specific questions can be answered. Young infants with cholestatic jaundice should be evaluated promptly to identify patients needing surgical intervention. For a patient with suspected liver disease, evaluation addresses the following issues in sequence: Is liver disease present? If so, what is its nature? What is its severity? Is specific treatment available? How can we monitor the response to treatment? What is the prognosis?
Bibliography


BIOCHEMICAL TESTS

Laboratory tests commonly used to screen for or to confirm a suspicion of liver disease include measurements of serum aminotransferase, bilirubin (total and fractionated), and alkaline phosphatase (AP) levels, as well as determinations of prothrombin time (PT) or international normalized ratio (INR) and albumin level. These tests are complementary, providing an estimation of synthetic and excretory functions, and might suggest the nature of the disturbance (inflammation or cholestasis).

The severity of the liver disease may be reflected in clinical signs or biochemical alterations. Clinical signs include encephalopathy, variceal hemorrhage, worsening jaundice, apparent shrinkage of liver mass owing to massive necrosis, or onset of ascites. Biochemical alterations include hypoglycemia, acidosis, hyperammonemia, electrolyte imbalance, continued hyperbilirubinemia, marked hypoalbuminemia, or a prolonged PT or INR that is unresponsive to parenteral administration of vitamin K.

Acute liver cell injury (parenchymal disease) caused by viral hepatitis, drug- or toxin-induced liver disease, shock, hypoxemia, or metabolic disease is best reflected by a marked increase in serum aminotransferase levels. Cholestasis (obstructive disease) involves regurgitation of bile components into serum; the serum levels of total and conjugated bilirubin and serum bile acids are elevated. Elevations in serum AP, 5′-nucleotidase, and γ-glutamyl transpeptidase levels are also sensitive indicators of obstruction or inflammation of the biliary tract. Fractionation of the total serum bilirubin level into conjugated and unconjugated bilirubin fractions helps to distinguish between elevations caused by processes such as hemolysis and those caused by hepatic dysfunction. A predominant elevation in the conjugated bilirubin level provides a relatively sensitive index of hepatic cellular disease or hepatic excretory dysfunction.

Alanine aminotransferase (ALT, serum glutamate pyruvate transaminase) is liver specific, whereas aspartate aminotransferase (AST, serum glutamic-oxaloacetic transaminase) is derived from other organs in addition to the liver. The most marked rises of AST and ALT levels can occur with acute hepatocellular injury; a several thousand-fold elevation can result from acute viral hepatitis, toxic injury, hypoxia, or hypoperfusion. After blunt abdominal trauma, parallel elevations in aminotransferase levels can provide an early clue to hepatic injury. A differential rise or fall in AST and ALT levels sometimes provides useful information. In acute hepatitis, the rise in ALT may be greater than the rise in AST. In alcohol-induced liver injury, fulminant echovirus infection, and various metabolic diseases, more predominant rises in the AST level are reported. In chronic liver disease or in intrahepatic and extrahepatic biliary obstruction, AST and ALT elevations may be less marked. Elevated serum aminotransferase levels are seen in patients with nonalcoholic fatty liver disease and nonalcoholic steatohepatitis (NASH), the notable characteristic is histology similar to alcoholic-induced liver injury in the absence of alcohol abuse.

Hepatic synthetic function is reflected in serum albumin and protein levels and in the PT or INR. Examination of serum globulin concentration and of the relative amounts of the globulin fractions may be helpful. Patients with autoimmune hepatitis often have high γ-globulin levels and increased titer of anti-smooth muscle, antinuclear, and anti-liver-kidney-microsome antibodies. Antimitochondrial antibodies may also be found in patients with autoimmune hepatitis. A resurgence in α-fetoprotein levels can suggest hepatoma, hepatoblastoma, or hereditary tyrosinemia. Hypoalbuminemia caused by depressed synthesis can complicate severe liver disease and serve as a prognostic factor. Deficiencies of factor V and of the vitamin K-dependent factors (II, VII, IX, and X) can occur in patients with severe liver disease or fulminant hepatic failure. If the PT or INR is prolonged as a result of intestinal malabsorption of vitamin K (resulting from cholestasis) or decreased nutritional intake of vitamin K, parenteral administration of vitamin K should correct the coagulopathy, leading to normalization within 12–24 hr. Unresponsiveness to vitamin K suggests severe hepatic disease. Persistently low levels of factor VII are evidence of a poor prognosis in fulminant liver disease.

Interpretation of results of biochemical tests of hepatic structure and function must be made in the context of age-related changes. The activity of AP varies considerably with age. Normal growing children have significant elevations of serum AP activity originating from influx into serum of the isoenzyme that originates in bone, particularly in rapidly growing adolescents. An isolated increase in AP does not indicate hepatic or biliary disease if other liver tests are normal. Other enzymes such as 5′-nucleotidase and γ-glutamyl transpeptidase are increased in cholestatic conditions and may be more specific for hepatobiliary disease. 5′-Nucleotidase is not found in bone. γ-Glutamyl transpeptidase exhibits high enzyme activity in early life that declines rapidly with age. Cholesterol concentrations increase throughout life. Cholesterol levels may be markedly elevated in patients with intra- or extrahepatic cholestasis and decreased in severe acute liver disease such as hepatitis.

Interpretation of serum ammonia values must be carried out with caution because of variability in their physiologic determinants and the inherent difficulty in laboratory measurement.

LIVER BIOPSY

Liver biopsy combined with clinical data can suggest a cause for hepatocellular injury or cholestatic disease in most cases. Specimens of liver tissue can be used to determine a precise histologic diagnosis in patients with neonatal cholestasis, chronic hepatitis, nonalcoholic fatty liver disease or nonalcoholic steatohepatitis, metabolic liver disease, intrahepatic cholestasis, congenital hepatic fibrosis, or undefined portal hypertension. The sample may be subjected to enzyme analysis to detect inborn errors of metabolism and to analysis of stored material such as iron, copper, or specific metabolites. Liver biopsies can monitor responses to therapy or detect complications of treatment with potentially hepatotoxic agents, such as aspirin, antiinfectives (minocycline, ketoconazole, isoniazid), antimetabolites, antineoplastics, or anticonvulsant agents.

In infants and children, needle biopsy of the liver is easily accomplished percutaneously. The amount of tissue obtained, even in small infants, is usually sufficient for histologic interpretation and for biochemical analyses, if the latter are deemed necessary. Percutaneous liver biopsy can be performed safely in infants as young as 1 wk of age. Contraindications to the percutaneous approach include prolonged PT or INR; thrombocytopenia; suspicion of a vascular, cystic, or infectious lesion in the path of the needle; and severe asces. If administration of fresh-frozen plasma or of platelet transfusions fails to correct a prolonged PT, INR, or thrombocytopenia, a tissue specimen can be obtained via alternative techniques. Considerations include either the open laparotomy (wedge) approach by a general surgeon or the transjugular approach under ultrasound and fluoroscopic guidance by an experienced pediatric interventional radiologist in an appropriately equipped fluoroscopy suite. The risk of development of a complication such as hemorrhage, hematoma, creation of an arteriovenous fistula, pneumothorax, or bile peritonitis is small.

HEPATIC IMAGING PROCEDURES

Various techniques help define the size, shape, and architecture of the liver and the anatomy of the intrahepatic and extrahepatic biliary trees. Although imaging might not provide a precise histologic and biochemical diagnosis, specific questions can be answered, such as whether hepatomegaly is related to accumulation of fat or glycogen or is caused by a tumor or cyst. These studies can direct further evaluation such as percutaneous biopsy and make possible prompt referral of patients with biliary obstruction to a surgeon. Choice of imaging procedure should be part of a carefully formulated diagnostic approach, with avoidance of redundant demonstrations by several techniques.

A plain x-ray study can suggest hepatomegaly, but a carefully performed physical examination gives a more reliable assessment of liver size. The liver might appear denser than normal in patients with fatty infiltration or denser with deposition of heavy metals such as iron. A hepatic or biliary tract mass can displace an air-filled loop of bowel. Calcifications may be evident in the liver (parasitic or neoplastic disease), in the vasculature (portal vein thrombosis), or in the
The 99mTc-sulfur colloid scan can detect focal lesions (tumors, cysts, abscesses) ≥2-3 cm in diameter. This modality can help to evaluate patients with possible cirrhosis and with patchy hepatic uptake and a shift of colloid uptake from liver to bone marrow.

Cholangiography, direct visualization of the intrahepatic and extrahepatic biliary tree after injection of opaque material, may be required in some patients to evaluate the cause, location, or extent of biliary obstruction. Percutaneous transhepatic cholangiography with a fine needle is the technique of choice in infants and young children. The likelihood of opacifying the biliary tract is excellent in patients in whom CT scanning, MRI, or ultrasound demonstrates dilated ducts.

Percutaneous transhepatic cholangiography has been used to outline the biliary ductal system.

Endoscopic retrograde cholangiopancreatography is an alternative method of examining the bile ducts in older children. The papilla of Vater is cannulated under direct vision through a fiberoptic endoscope, and contrast material is injected into the biliary and pancreatic ducts to outline the anatomy. The advantage of endoscopic retrograde cholangiopancreatography is that it allows therapeutic interventions of the extrahepatic biliary tree (stone extraction, stent placement, etc.).

Selective angiography of the celiac, superior mesenteric, or hepatic artery can be used to visualize the hepatic or portal circulation. Both arterial and venous circulatory systems of the liver can be examined. Angiography is often required to define the blood supply of tumors before surgery and is useful in the study of patients with known or presumed portal hypertension. The patency of the portal system, the extent of collateral circulation, and the caliber of vessels under consideration for a shunting procedure can be evaluated. MRI can provide similar information.

**DIAGNOSTIC APPROACH TO INFANTS WITH JAUNDICE**

Well-appearing infants can have cholestatic jaundice. Biliary atresia and neonatal hepatitis are the most common causes of cholestasis in early infancy. Biliary atresia portends a poor prognosis unless it is identified early. The best outcome for this disorder is with early surgical reconstruction (45-60 days of age). History, physical examination, and the detection of a conjugated hyperbilirubinemia via examination of total and direct bilirubin are the first steps in evaluating the jaundiced infant (Fig. 355-1). Consultation with a pediatric gastroenterologist should be sought early in the course of the evaluation.

**Bibliography is available at Expert Consult.**
Bibliography


Neonatal cholestasis is defined biochemically as prolonged elevation of the serum levels of conjugated bilirubin beyond the 1st 14 days of life. Jaundice that appears after 2 wk of age, continues to progress, or does not resolve at this time should be evaluated and a conjugated bilirubin level determined. Cholestasis in a newborn can be caused by infectious, genetic, metabolic, or undefined abnormalities giving rise to mechanical obstruction of bile flow or to functional impairment of hepatic excretory function and bile secretion (see Table 355-3). Mechanical lesions include stricture or obstruction of the common bile duct; biliary atresia is the prototypic obstructive abnormality. Functional impairment of bile secretion can result from congenital defects or damage to liver cells or to the biliary secretory apparatus.

Neonatal cholestasis can be divided into extrahepatic and intrahepatic disease (Fig. 356-1). The clinical features of any form of cholestasis are similar. In an affected neonate, the diagnosis of certain entities, such as galactosemia, sepsis, or hypothyroidism, is relatively simple and a part of most neonatal screening programs. In most cases, the cause of cholestasis is more obscure. Differentiation among biliary atresia and idiopathic neonatal hepatitis is particularly difficult.
Proposed Subtypes of Intrahepatic Cholestasis

MECHANISMS

Metabolic liver disease caused by inborn errors of bile acid metabolism or transport is associated with accumulation of atypical toxic primitive bile acids and failure to produce normal cholesteric and trophic bile acids. The clinical and histologic manifestations are nonspecific and are similar to those in other forms of neonatal hepatobiliary injury. Autoimmune mechanisms may also be responsible for some of the enigmatic forms of neonatal liver injury.

Some of the histologic manifestations of hepatic injury in early life are not seen in older patients. Giant cell transformation of hepatocytes occurs commonly in infants with cholestasis and can occur in any form of neonatal liver injury. It is more common and more severe in intrahepatic forms of cholestasis. The clinical and histologic findings that exist in patients with neonatal hepatitis and in those with biliary atresia are quite disparate; the basic process is an undefined initiating insult causing inflammation of the liver cells or of the cells within the biliary tract. If bile duct epithelium is the predominant site of disease, cholangitis can result and lead to progressive sclerosis and narrowing of the biliary tree, the ultimate state being complete obliteration (biliary atresia). Injury to liver cells can present the clinical and histologic picture of " neonatal hepatitis." This concept does not account for the precise mechanism, but it offers an explanation for well-documented cases of unexpected postnatal evolution of these disease processes; infants initially regarded as having neonatal hepatitis, with a patent biliary system shown on cholangiography, can later develop biliary atresia.

Functional abnormalities in the generation of bile flow can also have a role in neonatal cholestasis. Bile flow is directly dependent on effective hepatic bile acid excretion by the hepatocytes. During the phase of relatively inefficient liver cell transport and metabolism of bile acids in early life, minor degrees of hepatic injury can further decrease bile flow and lead to production of atypical and potentially toxic bile acids. Selective impairment of a single step in the series of events involved in hepatic excretion produces the full expression of a cholestatic syndrome. Specific defects in bile acid synthesis are found in infants with various forms of intrahepatic cholestasis (Table 356-1). Severe forms of familial cholestasis are associated with neonatal hemochromatosis and an aberration in the contractile proteins that compose the cytoskeleton of the hepatocyte. Neonatal hemochromatosis can also be an alloimmune-mediated gestational (maternal antibodies against fetal hepatocytes) disease responsive to maternal intravenous immunoglobulin. Sepsis is known to cause cholestasis, presumably mediated by an endotoxin produced by *Escherichia coli*.

EVALUATION

The evaluation of the infant with jaundice should follow a logical, cost-effective sequence in a multistep process (Table 356-2). Although cholestasis in the neonate may be the initial manifestation of numerous and potentially serious disorders, the clinical manifestations are usually similar and provide very few clues about etiology. Affected infants have icterus, dark urine, light or acholic stools, and hepatomegaly, all resulting from decreased bile flow as a result of either hepatocyte injury or bile duct obstruction. Hepatic synthetic dysfunction can lead to prothrombinemia and bleeding. Administration of vitamin K should be included in the initial treatment of cholestatic infants to prevent hemorrhage.

In contrast to unconjugated hyperbilirubinemia, which can be physiologic, cholestasis (conjugated bilirubin elevation of any degree) in the neonate is always pathologic and prompt differentiation is imperative. Thus the initial step is to identify the infant who has cholestasis. The next step is to recognize conditions that cause cholestasis and for which specific therapy is available to prevent further damage and avoid long-term complications such as sepsis, an endocrinopathy (hypothyroidism, panhypopituitarism), nutritional hepatotoxicity caused by a specific metabolic illness (galactosemia), or other metabolic diseases (tyrosinemia).

Hepatobiliary disease can be the initial manifestation of homozygous Q-antitrypsin deficiency or of cystic fibrosis. Neonatal liver disease can also be associated with congenital syphilis and specific viral infections, notably echovirus and herpesviruses including
cytomegalovirus. These account for a small percentage of cases of neonatal hepatitis syndrome. The hepatitis viruses (A, B, C) rarely cause neonatal cholestasis.

The final and critical step in evaluating neonates with cholestasis is to differentiate extrahepatic biliary atresia from neonatal hepatitis.

### INTRAHEPATIC CHOLESTASIS

**Neonatal Hepatitis**

The term neonatal hepatitis implies intrahepatic cholestasis (see Fig. 356-1), which has various forms (see Tables 356-1 and 356-3).

**Idiopathic neonatal hepatitis**, which can occur in either a sporadic or a familial form, is a disease of unknown cause. Patients with the sporadic form presumably have a specific yet undefined metabolic or viral disease. Familial forms, on the other hand, presumably reflect a genetic or metabolic aberration; in the past, patients with α1-antitrypsin deficiency were included in this category.

**Aagenaes syndrome** is a form of idiopathic familial intrahepatic cholestasis associated with lymphedema of the lower extremities. The relationship between liver disease and lymphedema is not understood and may be attributable to decreased hepatic lymph flow or hepatic lymphatic hypoplasia. Affected patients usually present with episodic cholestasis with elevation of serum aminotransferases, alkaline phosphatase, and bile acids. Between episodes, the patients are usually asymptomatic and biochemical indices improve. Compared to other types of hereditary neonatal cholestasis, patients with Aagenaes syndrome have a relatively good prognosis because more than 50% can expect a normal life span. The locus for Aagenaes syndrome is mapped to a 6.6 cM interval on chromosome 15q.

**Zellweger (cerebrohepatorenal) syndrome** is a rare autosomal recessive genetic disorder marked by progressive degeneration of the liver and kidneys (see Chapter 80.2). The incidence is estimated to be 1 in 100,000 births; the disease is usually fatal in 6-12 mo. Affected infants have severe, generalized hypotonia and markedly impaired neurologic function with psychomotor retardation. Patients have an abnormal head shape and unusual facies, hepatomegaly, renal cortical cysts, stippled calcifications of the patellas and greater trochanter, and ocular abnormalities. Hepatic cells on ultrastructural examination show an absence of peroxisomes. MRI performed in the 3rd trimester can allow analysis of cerebral gyration and myelination, facilitating the prenatal diagnosis of Zellweger syndrome.

**Neonatal iron storage disease (neonatal hemochromatosis)** is a rapidly progressive disease characterized by increased iron deposition in the liver, heart, and endocrine organs without increased iron stores in the reticuloendothelial system. Patients have multiorgan failure and shortened survival. Familial cases are reported, and repeated affected neonates in the same family are common. This is an alloimmune disorder with maternal antibodies directed against the fetal liver. Laboratory findings include hypoglycemia, hyperbilirubinemia, hypoalbuminemia, elevated ferritin and profound hypoprothrombinemia. Serum aminotransferase levels may be high initially but normalize with the progression of the disease. The diagnosis is usually confirmed by buccal mucosal biopsy or MRI demonstrating extrahepatic siderosis. The prognosis is poor; however, liver transplantation can be curative. Despite initially encouraging reports, the use of a combination of antioxidants and prostaglandin infusion with chelation might not uniformly improve outcome in patients with neonatal iron storage disease. Although recovery from neonatal iron storage disease either spontaneously or with medical therapy is unusual, the potential for histologic recovery with regression of fibrosis has been reported. The differential diagnosis includes familial hemophagocytic lymphohistiocytosis, mitochondrial respiratory chain disorders, galactosemia, tyrosinemia, viral hepatitis (HSV, CMV), congenital syphilis, and idiopathic neonatal hepatitis.

**Neonatal hemochromatosis** seems to be a gestational alloimmune disease, and reoccurrence of severe neonatal hemochromatosis at-risk pregnancies may be reduced by maternal treatment with weekly (beginning gestational age 18 wk) high-dose intravenous immunoglobulin (1 g/kg) during gestation. After birth, affected neonates are treated with exchange transfusions and intravenous immunoglobulin (1 g/kg), which improves survival and reduces the need for liver transplantation.

### Disorders of Transport, Secretion, Conjugation, and Biosynthesis of Bile Acids

**Progressive familial intrahepatic cholestasis type 1 (PFIC 1) or FIC1 disease** (formerly known as Byler disease) is a severe form of intrahepatic cholestasis. The disease was initially described in the Amish kindred of Jacob Byler. Affected patients present with steatorrhea, pruritus, vitamin D–deficient rickets, gradually developing cirrhosis, and low γ-glutamyl transpeptidase (GGT) levels. The absence of bile duct paucity and extrahepatic features differentiate this disorder from Alagille syndrome.

PFIC 1 (FIC1 deficiency) has been mapped to chromosome 18q12 and results from defect in the gene for FIC1 (ATP8B1; see Tables 356-3 and 356-4). FIC1 is a P-type adenosine triphosphatase that functions as aminophospholipid flipase, facilitating the transfer of phosphatidyl

<table>
<thead>
<tr>
<th>Table 356-2</th>
<th>Value of Specific Tests in the Evaluation of Patients with Suspected Neonatal Cholestasis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TEST</strong></td>
<td><strong>RATIONALE</strong></td>
</tr>
<tr>
<td>Serum bilirubin fractionation (i.e., assessment of the serum level of conjugated bilirubin)</td>
<td>Indicates cholestasis</td>
</tr>
<tr>
<td>Assessment of stool color (does the baby have pigmented or acholic stools?)</td>
<td>Indicates bile flow into intestine</td>
</tr>
<tr>
<td>Urine and serum bile acids measurement</td>
<td>Confirms cholestasis; might indicate inborn error of bile acid biosynthesis</td>
</tr>
<tr>
<td>Hepatic synthetic function (albumin, coagulation profile)</td>
<td>Indicates severity of hepatic dysfunction</td>
</tr>
<tr>
<td>a1-Antitrypsin phenotype</td>
<td>Suggests (or excludes) PiZZ</td>
</tr>
<tr>
<td>Thyroxine and TSH</td>
<td>Suggests (or excludes) endocrinopathy</td>
</tr>
<tr>
<td>Sweat chloride and mutation analysis</td>
<td>Suggests (or excludes) cystic fibrosis</td>
</tr>
<tr>
<td>Urine and serum amino acids and urine reducing substances</td>
<td>Suggests (or excludes) metabolic liver disease</td>
</tr>
<tr>
<td>Ultrasonography</td>
<td>Suggests (or excludes) choledochal cyst; might detect the triangular cord sign, suggesting biliary atresia</td>
</tr>
<tr>
<td>Hepatobiliary scintigraphy</td>
<td>Documents bile duct patency or obstruction</td>
</tr>
<tr>
<td>Liver biopsy</td>
<td>Distinguishes biliary atresia; suggests alternative diagnosis</td>
</tr>
</tbody>
</table>

PiZZ, protease inhibitor ZZ phenotype; TSH, thyroid-stimulating hormone.
serine and phosphatidyl ethanolamine from the outer to inner hemi-leaft of the cellular membrane. FIC1 might also play a role in intestinal bile acid absorption, as suggested by the high level of expression in the intestine. Defective FIC1 might also result in another form of intrahepatic cholestasis: **benign recurrent intrahepatic cholestasis (BRIC) type 1.** The disease is characterized by recurrent bouts of cholestasis, jaundice, and severe pruritus lasting from 2 wk to 6 mo; it can last up to 5 yr. The episodes vary from few episodes per year to 1 episode per decade and can profoundly affect the quality of life. Non-sense, frame shift, and deletional mutations cause PFIC type 1; missense and split-type mutations result in BRIC type 1. Typically, patients with BRIC type 1 have normal cholesterol and GGT levels. 

**PFIC type 2 (BSEP deficiency)** is mapped to chromosome 2q24 and is similar to PFIC 1 but is present in non-Amish families (Middle Eastern and European). The disease results from defects in the canalicular adenosine triphosphate–dependent bile acid transporter BSEP (ABCB11). The progressive liver disease results from accumulation of bile acids secondary to reduction in canalicular bile acid secretion. Mutation in **ABCB11** is also described in another disorder, BRIC type 2, characterized by recurrent bouts of cholestasis.

In contrast to PFIC 1 and PFIC 2, patients with **PFIC type 3 (MDR3 disease)** have high levels of GGT. The disease results from defects in a canalicular phospholipids flipase, MDR3 (ABCB4), which results in deficient translocation of phosphatidycholine across the canalicular membrane. Mothers who are heterozygous for this gene can develop intrahepatic cholestasis during pregnancy.

**Familial hypercholanemia** is characterized by elevated serum bile acid concentration, pruritus, failure to thrive, and coagulopathy. Familial hypercholanemia is a complex genetic trait associated with mutation of bile acid coenzyme A (C3A), amino acid N-acyltransferase (encoded by **BAAT**), as well as mutations in tight junction protein 2 (encoded by **TJP 2**, also known as **ZO-2**). Mutation of **BAAT**, which

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**Table 356-3  Molecular Defects Causing Liver Disease**

<table>
<thead>
<tr>
<th>GENE</th>
<th>PROTEIN</th>
<th>FUNCTION, SUBSTRATE</th>
<th>DISORDER</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATP8b1</td>
<td>FIC1</td>
<td>P-type ATPase; aminophospholipid translocase that flips phosphatidylserine and phosphatidylethanolamine from the outer to the inner layer of the canalicular membrane</td>
<td>PFIC 1 (Byler disease), BRIC 1, GFC</td>
</tr>
<tr>
<td>ABCB11</td>
<td>BSEP</td>
<td>Canalicular protein with ATP-binding cassette (ABC family of proteins); works as a pump transporting bile acids through the canalicular domain</td>
<td>PFIC 2, BRIC 2</td>
</tr>
<tr>
<td>ABCB4</td>
<td>MDR3</td>
<td>Canalicular protein with ATP-binding cassette (ABC family of proteins); works as a phospholipid flipase in canalicular membrane</td>
<td>PFIC 3, ICP, cholelithiasis</td>
</tr>
<tr>
<td>AKR1D1</td>
<td>Sβ-reductase</td>
<td>3-oxoa-4-steroid Sβ-reductase gene; regulates bile acid synthesis</td>
<td>BAS: neonatal cholestasis with giant cell hepatitis</td>
</tr>
<tr>
<td>HSD3B7</td>
<td>C27-3β-HSD</td>
<td>3β-hydroxy-5-C27-steroid oxidoreductase (C27-3β-HSD) gene; regulates bile acid synthesis</td>
<td>BAS: chronic intrahepatic cholestasis</td>
</tr>
<tr>
<td>CYP7B1</td>
<td>CYP7B1</td>
<td>Oxysterol 7α-hydroxylase; regulates the acidic pathway of bile acid synthesis</td>
<td>BAS: neonatal cholestasis with giant cell hepatitis</td>
</tr>
<tr>
<td>JAG1</td>
<td>JAG1</td>
<td>Transmembrane, cell-surface proteins that interact with Notch receptors to regulate cell fate during embryogenesis</td>
<td>Alagille syndrome</td>
</tr>
<tr>
<td>TJP2</td>
<td>Tight Junction protein</td>
<td>Belonged to the family of membrane-associated guanylate kinase homologs that are involved in the organization of epithelial and endothelial intercellular junction; regulates paracellular permeability</td>
<td>FHC</td>
</tr>
<tr>
<td>BAAT</td>
<td>BAAT</td>
<td>Enzyme that transfers the bile acid moiety from the acyl coenzyme A to either glycerine or taunine</td>
<td>FHC</td>
</tr>
<tr>
<td>EPHX1</td>
<td>Epoxide hydrolase</td>
<td>Microsomal epoxide hydrolase regulates the activation and detoxification of exogenous chemical</td>
<td>FHC</td>
</tr>
<tr>
<td>ABCC2</td>
<td>MRP2</td>
<td>Canalicular protein with ATP-binding cassette (ABC family of proteins); regulates canalicular transport of GSH conjugates and arsenic</td>
<td>Dubin-Johnson syndrome</td>
</tr>
<tr>
<td>ATP7B</td>
<td>ATP7B</td>
<td>P-type ATPase; function as copper export pump</td>
<td>Wilson disease</td>
</tr>
<tr>
<td>CLDN1</td>
<td>Claudin 1</td>
<td>Tight junction protein</td>
<td>NSC</td>
</tr>
<tr>
<td>CIRH1A</td>
<td>Cirhin</td>
<td>Cell signaling?</td>
<td>NAICC</td>
</tr>
<tr>
<td>CFTR</td>
<td>CFTR</td>
<td>Chloride channel with ATP-binding cassette (ABC family of proteins); regulates chloride transport</td>
<td>Cystic fibrosis</td>
</tr>
<tr>
<td>PKHD1</td>
<td>Fibrocytin</td>
<td>Protein involved in ciliary function and tubulogenesis</td>
<td>ARPKD</td>
</tr>
<tr>
<td>PRKCSH</td>
<td>Hepatocystin</td>
<td>Assembles with glucosidase II α subunit in endoplasmic reticulum</td>
<td>ADPLD</td>
</tr>
<tr>
<td>VPS33B</td>
<td>Vascular Protein sorting 33</td>
<td>Regulates fusion of proteins to cellular membrane</td>
<td>ARC</td>
</tr>
</tbody>
</table>

ADPLD, autosomal dominant polycystic liver disease; ARC, arthrogryposis–renal dysfunction–cholestasis syndrome*; ARPKD, autosomal recessive polycystic kidney disease; ATP, adenosine triphosphate; ATPase, adenosine triphosphatase; BAAT, bile acid transporter; BAS, bile acid synthetic defect; BRIC, benign recurrent intrahepatic cholestasis; BSEP, bile salt export pump; CFTR, cystic fibrosis transmembrane conductance regulator; FHC, familial hypercholanemia; GFC, Greenland familial cholestasis; GSH, glutathione; ICP, intrahepatic cholestasis of pregnancy; NAICC, North American Indian childhood cirrhosis; NSC, neonatal sclerosing cholangitis with cholestasis, leukocyte vacuoles, and alopecia; PFIC, progressive familial intrahepatic cholestasis*. (*Low γ-glutamyl transpeptidase [PFIC types 1 and 2, BRIC types 1 and 2, ARC]*)

is a bile acid–conjugating enzyme, abrogates the enzyme activity. Patients who are homozygous for this mutation have only unconjugated bile acids in their bile. Mutation of both BAAT and TJP 2 can disrupt bile acid transport and circulation. Patients with familial hypercholesterolemia usually respond to the administration of ursodeoxycholic acid.

**Defective bile acid biosynthesis** is postulated to be an initiating or perpetuating factor in neonatal cholestatic disorders; the hypothesis is that inborn errors in bile acid biosynthesis lead to absence of normal trophic or cholesteric primary bile acids and accumulation of atypical (hepatotoxic) metabolites. Inborn errors of bile acid biosynthesis cause acute and chronic liver disease; early recognition allows institution of targeted bile acid replacement, which reverses the hepatic injury. Several specific defects have been described:

- **Deficiency of Δ5-3-oxo-steroid-5β-reductase**, the 4th step in the pathway of cholesterol degradation to the primary bile acids, manifests with significant cholestasis and liver failure developing shortly after birth, with coagulopathy and metabolic liver injury resembling tyrosinemia. Hepatic histology is characterized by lobular disarray with giant cells, pseudocanular transformation, and canalicular bile stasis. Mass spectrometry is required to document increased urinary bile acid excretion and the predominance of oxo-hydroxy and o xo-dihydroxy chenolenoic acids. **Treatment** with cholic acid and ursodeoxycholic acid is associated with normalization of biochemical, histologic, and clinical features.

- **Deficiency of 3β-hydroxy-Δ7-cholesterol oxidoreductase (3β-HSD)**, the 2nd step in bile acid biosynthesis, causes progressive familial intrahepatic cholestasis. Affected patients usually have jaundice with increased aminotransferase levels and hepatomegaly; GGT levels and serum cholyglycine levels are normal. The histology is variable, ranging from giant cell hepatitis to chronic hepatitis. The diagnosis, suggested by mass spectrometry detection of C27 bile acids in urine, which retain the 3β-hydroxy-Δ7 structure, can be confirmed by determination of 3β-HSD activity in cultured fibroblasts using 7α-hydroxy-Δ7 cholesterol as a substrate. Primary bile acid therapy, administered orally to down regulate cholesterol 7α-hydroxylase activity, to limit the production of 3β-hydroxy-Δ7 bile acids, and to facilitate hepatic clearance, has been effective in reversing hepatic injury.

**BILE ACID–COENZYME A LIGASE DEFICIENCY**

Conjugation with the amino acids glycine and taurine is the final step in bile acid synthesis. Two enzymes catalyze the amidation of bile acids. In the first reaction, a CoA thioester is formed by the rate-limiting bile acid–CoA ligase. The other reaction involves the coupling of glycine or taurine to the activated bile acid, called bile acid–CoA ligase. Several patients with bile acid–CoA ligase deficiency have been reported. The patients present with conjugated hyperbilirubinemia, growth failure, or fat-soluble vitamin deficiency, and are identified with mutation of the bile acid–CoA ligase gene. Administration of conjugates of the primary bile acid, glycocholic acid may be beneficial and can correct the fat-soluble vitamin malabsorption and improve growth.

**DISORDERS OF EMBRYOGENESIS**

**Alagille syndrome** (arteriohepatic dysplasia) is the most common syndrome with intrahepatic bile duct paucity. Bile duct “paucity” (often erroneously called intrahepatic biliary atresia) designates an absence or marked reduction in the number of interlobular bile ducts in the portal triads, with normal-size branches of portal vein and hepatic arteriole. Biopsy in early life often reveals an inflammatory process involving the bile ducts; subsequent biopsy specimens then show subсидence of the inflammation, with residual reduction in the number and diameter of bile ducts, analogous to the “disappearing bile duct syndrome” noted in adults with immune-mediated disorders. Serial assessment of hepatic histology often suggests progressive destruction of bile ducts.

**Clinical manifestations** of Alagille syndrome are expressed in various degrees and can be nonspecific; they include unusual facial characteristics (broad forehead; deep-set, widely spaced eyes; long, straight nose; and an underdeveloped mandible). There may also be

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**Table 356-4** Progressive Familial Intrahepatic Cholestasis

<table>
<thead>
<tr>
<th>Transmission</th>
<th>PFIC 1</th>
<th>PFIC 2</th>
<th>PFIC 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chromosome</td>
<td>Autosomal recessive</td>
<td>Autosomal recessive</td>
<td>Autosomal recessive</td>
</tr>
<tr>
<td>Gene</td>
<td>ABCB11/BSEP</td>
<td>ABCB4/MDR3</td>
<td></td>
</tr>
<tr>
<td>Protein</td>
<td>FIC1</td>
<td>MDR3</td>
<td></td>
</tr>
<tr>
<td>Location</td>
<td>Hepatocyte canalicular membrane</td>
<td>Hepatocyte canalicular membrane</td>
<td>Hepatocyte canalicular membrane</td>
</tr>
<tr>
<td>Function</td>
<td>ATP-dependent bile acid transport</td>
<td>ATP-dependent bile acid transport</td>
<td>ATP-dependent phosphatidylcholine translocation</td>
</tr>
<tr>
<td>Phenotype</td>
<td>Progressive cholestasis, diarrhea, steatorrhea, growth failure, severe pruritus</td>
<td>Rapidly progressive cholestatic giant cell hepatitis, growth failure, pruritus</td>
<td>Later-onset cholestasis, portal hypertension, minimal pruritus, intraductal and gallbladder lithiasis</td>
</tr>
<tr>
<td>Histology</td>
<td>Initial bland cholestatic; coarse, granular canalicular bile on EM</td>
<td>Neonatal giant cell hepatitis, amorphous canalicular bile on EM</td>
<td>Proliferation of bile ductules, periportal fibrosis, eventually biliary cirrhosis</td>
</tr>
<tr>
<td>Biochemical features</td>
<td>Normal serum GGT; high serum, low biliary bile acid concentrations</td>
<td>Normal serum GGT; high serum, low biliary bile acid concentrations</td>
<td>Elevated serum GGT; low to absent biliary PC; absent serum LPX; normal biliary bile acid concentrations</td>
</tr>
<tr>
<td>Treatment</td>
<td>Biliary diversion, ileal exclusion, liver transplantation, but post-OLT diarrhea, steatorrhea, fatty liver</td>
<td>Biliary diversion, liver transplantation</td>
<td>UDCA if residual PC secretion; liver transplantation</td>
</tr>
</tbody>
</table>

ATP, adenosine triphosphate; BSEP, bile salt export pump; EM, electron microscopy; GGT, γ-glutamyl transpeptidase; LPX, lipoprotein X; OLT, orthotopic liver transplantation; PC, phosphatidylcholine; PFIC, progressive familial intrahepatic cholestasis; UDCA, ursodeoxycholic acid.

BILIARY ATRESIA

The term biliary atresia is imprecise because the anatomy of abnormal bile ducts in affected patients varies markedly. A more appropriate terminology would reflect the pathophysiology, namely noncystic obliterative cholangiopathy. The term oblitative cholangiopathy may be divided into 2 major types: cystic and noncystic. The cystic disorder will incorporate the different types of choledochal cysts, while the noncystic form will encompass the 2 types of biliary atresia (fetal and perinatal) in addition to neonatal sclerosing cholangitis.

Patients can have distal segmental bile duct obliteration with patent extrahepatic ducts up to the porta hepatis. This is a surgically correctable lesion, but it is uncommon. The most common form of biliary atresia, accounting for approximately 95% of the cases, is obligatory of the entire extrahepatic biliary tree at or above the porta hepatis. This presents a much more difficult problem in surgical management. Most patients with biliary atresia (85-90%) are normal at birth and have a postnatal progressive obliteration of bile ducts; the embryonic or fetal-onset form manifests at birth and is associated with other congenital anomalies (situs inversus, polysplenia, intestinal malrotation, complex congenital heart disease) within the polysplenia spectrum (biliary atresia splenic malformation) (Fig. 356-2; see Chapter 431.11). The postnatal onset may be an immune- or infection-mediated process.

Biliary atresia has been detected in 1 in 10,000-15,000 live births. Biliary atresia is more common in East Asian countries; patients may be born term or preterm. Screening for biliary atresia in infants after birth is not universal, but in high-risk locations, stool color cards that help detect acholic stools have been used with some success. In addition, any infant with new onset or persistent jaundice beyond 8 wk of life should be screened with a total and direct reacting bilirubin level to detect cholestasis.

Differentiation of Idiopathic Neonatal Hepatitis from Biliary Atresia

It may be difficult to clearly differentiate infants with biliary atresia, who require surgical correction, from those with intrahepatic disease.
(neonatal hepatitis) and patent bile ducts. No single biochemical test or imaging procedure is entirely satisfactory. Diagnostic schemas incorporate clinical, historical, biochemical, and radiologic features.

Idiopathic neonatal hepatitis has a familial incidence of approximately 20%, whereas biliary atresia is unlikely to recur within the same family. A few infants with fetal onset of biliary atresia have an increased incidence of other abnormalities, such as the polysplenia syndrome with abdominal heterotaxia, malrotation, levocardia, and intraabdominal vascular anomalies. Neonatal hepatitis appears to be more common in infants who are premature or small for gestational age. Persistently acholic stools suggest biliary obstruction (biliary atresia), but patients with severe idiopathic neonatal hepatitis can have a transient severe impairment of bile excretion. Consistently pigmented stools rule against biliary atresia. The finding of bile-stained fluid on duodenal intubation also excludes biliary atresia. Palpation of the liver might find an abnormal size or consistency in patients with biliary atresia; this is less common with idiopathic neonatal hepatitis.

Abdominal ultrasound is a helpful diagnostic tool in evaluating neonatal cholestasis because it identifies choledocholitiasis, perforation of the bile duct, or other structural abnormalities of the biliary tree such as a choledochal cyst. In patients with biliary atresia, ultrasound can detect associated anomalies such as abdominal polysplenia and vascular malformations. The gallbladder either is not visualized or is a microgallbladder in patients with biliary atresia. Children with intrahepatic cholestasis caused by idiopathic neonatal hepatitis, cystic fibrosis, or total parenteral nutrition can have similar ultrasonographic findings. Ultrasonographic triangular cord sign, which represents a cone-shaped fibrotic mass cranial to the bifurcation of the portal vein, may be seen in patients with biliary atresia (Figs. 356-3 and 356-4). The echogenic density, which represents the fibrous remnants at the porta hepatis of biliary atresia cases at surgery, may be a helpful diagnostic tool in evaluating patients with neonatal cholestasis.

Hepatobiliary scintigraphy with technetium-labeled iminodiacetic acid derivatives is a sensitive but not specific test for biliary atresia. It fails to identify other structural abnormalities of the biliary tree or vascular anomalies. The lack of the specificity of the test and the need to wait for 5 days makes this procedure less practical and of limited usefulness in the evaluation of children with suspected biliary atresia.

Percutaneous liver biopsy is the most valuable procedure in the evaluation of neonatal hepatobiliary diseases and provides the most reliable discriminatory evidence. Biliary atresia is characterized by bile ductular proliferation, the presence of bile plugs, and portal or perilobular edema and fibrosis, with the basic hepatic lobular architecture intact. In neonatal hepatitis, there is severe, diffuse hepatocellular disease, with distortion of lobular architecture, marked infiltration with inflammatory cells, and focal hepatocellular necrosis; the bile ductules show little alteration. Giant cell transformation is found in infants with either condition and has no diagnostic specificity.

The histologic changes seen in patients with idiopathic neonatal hepatitis can occur in other diseases, including α1-antitrypsin deficiency, galactosemia, and various forms of intrahepatic cholestasis. Although paucity of intrahepatic bile ductules may be detected on liver biopsy even in the 1st few wk of life, later biopsies in such patients reveal a more characteristic pattern.

Management of Patients with Suspected Biliary Atresia

All patients with suspected biliary atresia should undergo exploratory laparotomy and direct cholangiography to determine the presence and site of obstruction. Direct drainage can be accomplished in the few patients with a correctable lesion. When no correctable lesion is found, an examination of frozen sections obtained from the transected porta hepatis can detect the presence of biliary epithelium and determine the size and patency of the residual bile ducts. In some cases, the cholangiogram indicates that the biliary tree is patent but of diminished caliber, suggesting that the cholestasis is not due to biliary tract obstruction but to bile duct paucity or markedly diminished flow in the

Figure 356-4 Biliary atresia in an 8 wk old male with elevated direct bilirubin. Transverse sonogram shows the triangular cord sign seen as a linear cord of echogenicity (arrowhead) along the right portal vein (RPV). (From Lowe LH: Imaging hepatobiliary disease in children, Semin Roentgenol 43:39–49, 2008, Fig. 1B.)

Figure 356-3 Surgical findings of biliary atresia. A, Photograph of surgical specimen of obliterated extrahepatic bile ducts shows the fibrous ductal remnant (black arrowheads) in the porta hepatitis, atretic gallbladder (arrow), and fibrous common bile duct (white arrowhead). The fibrous ductal remnant is a triangular cone-shaped mass. B, Schematic represents the anatomic relationship between the fibrous ductal remnant and blood vessels around the porta hepatitis. The triangular, cone-shaped, fibrous ductal remnant (black arrowheads, green) is positioned anterior and slightly superior to the portal vein (long arrow, blue) and the hepatic artery (short arrow, red). (A from Park WH, Choi SO, Lee HJ, et al: A new diagnostic approach to biliary atresia with emphasis on the ultrasonographic triangular cord sign: comparison of ultrasonography, hepatobiliary scintigraphy, and liver needle biopsy in the evaluation of infantile cholestasis, J Pediatr Surg 32:1555–1559, 1997.)
presence of intrahepatic disease. In these cases, transection of or further dissection into the porta hepatitis should be avoided.

For patients in whom no correctable lesion is found, the hepatopancreatenterostomy (Kasai) procedure should be performed. The rationale for this operation is that minute bile duct remnants, representing residual channels, may be present in the fibrous tissue of the porta hepatitis; such channels may be in direct continuity with the intrahepatic ductule system. In such cases, transection of the porta hepatitis with anastomosis of bowel to the proximal surface of the transection might allow bile drainage. If flow is not rapidly established in the 1st mo of life, progressive obliteration and cirrhosis ensue. If microscopic channels of patency > 150 µm in diameter are found, postoperative establishment of bile flow is likely. The success rate for establishing good bile flow after the Kasai operation is much higher (90%) if performed before 8 wk of life. Therefore, early referral and prompt evaluation of infants with suspected biliary atresia is important.

Some patients with biliary atresia, even of the “noncorrectable” type, derive long-term benefits from interventions such as the Kasai procedure. In most, a degree of hepatic dysfunction persists. Patients with biliary atresia usually have persistent inflammation of the intrahepatic biliary tree, which suggests that biliary atresia reflects a dynamic process involving the entire hepatobiliary system. This might account for the ultimate development of complications such as portal hypertension. The short-term benefit of hepatopancreatenterostomy is decompression and drainage sufficient to forestall the onset of cirrhosis and sustain growth until a successful liver transplantation can be done.

**MANAGEMENT OF CHRONIC CHOLESTASIS**

With any form of neonatal cholestasis, whether the primary disease is idiopathic neonatal hepatitis, intrahepatic cholestasis, or biliary atresia, affected patients are at increased risk for progression and complications of chronic cholestasis. These reflect various degrees of residual hepatic functional capacity and are due directly or indirectly to diminished bile flow. Any substance normally excreted into bile is retained in the liver, with subsequent accumulation in tissue and in serum. Involved substances include bile acids, bilirubin, cholesterol, and trace elements. Decreased delivery of bile acids to the proximal intestine leads to inadequate digestion and absorption of dietary long-chain triglycerides and fat-soluble vitamins. Impairment of hepatic metabolic function can alter hormonal balance and utilization of nutrients. Progressive liver damage can lead to biliary cirrhosis, portal hypertension, and liver failure.

Treatment of such patients is empirical, and is guided by careful monitoring (Table 356-5). No therapy is known to be effective in halting the progression of cholestasis or in preventing further hepatocellular damage and cirrhosis.

Growth failure is a major concern and is related in part to malabsorption and malnutrition resulting from ineffective digestion and absorption of dietary fat. Use of a medium-chain triglyceride-containing formula can improve caloric balance.

With chronic cholestasis and prolonged survival, children with hepatobiliary disease can experience deficiencies of the fat-soluble vitamins (A, D, E, K). Inadequate absorption of fat and fat-soluble vitamins may be exacerbated by administration of the bile acid binder cholestyramine. Metabolic bone disease is common.

Serum vitamin A concentration can usually be maintained at normal levels in patients who have chronic cholestasis and who receive oral supplementation of vitamin A esters. It is essential to monitor the vitamin A status in such patients.

A degenerative neuromuscular syndrome was found in patients with chronic cholestasis, caused by fat soluble vitamin malabsorption and vitamin E deficiency; affected children experience progressive areflexia, cerebellar ataxia, ophthalmoplegia, and decreased vibratory sensation. Specific morphologic lesions were found in the central nervous system, peripheral nerves, and muscles. These lesions are preventable and are not commonly seen today; they were potentially reversible in children younger than 3–4 yr of age. Affected children have low serum vitamin E concentrations, increased hydrogen peroxide hemolysis, and low ratios of serum vitamin E to total serum lipids (<0.6 mg/g for children younger than 12 yr and <0.8 mg/g for older patients). Vitamin E deficiency may be prevented by oral administration of large doses (up to 1,000 IU/day); patients unable to absorb sufficient quantities may require administration of d-α-tocopheryl polyethylene glycol 1,000 succinate orally. Serum levels may be monitored as a guide to efficacy.

Pruritus is a particularly troublesome complication of chronic cholestasis, often with the appearance of xanthomas. Both features seem to be related to the accumulation of cholesterol and bile acids in serum and in tissues. Elimination of these retained compounds is difficult when bile ducts are obstructed, but if there is any degree of bile duct patency, administration of ursodeoxycholic acid can increase bile flow or interrupt the enterohepatic circulation of bile acids and thus decrease the xanthomas and ameliorate the pruritus (see Table 356-5). Ursodeoxycholic acid therapy can also lower serum cholesterol levels. The recommended initial dose is 15 mg/kg/24 hr.

**Table 356-5** Suggested Medical Management of Persistent Cholestasis

<table>
<thead>
<tr>
<th>CLINICAL IMPAIRMENT</th>
<th>MANAGEMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malnutrition resulting from malabsorption of dietary long-chain triglycerides</td>
<td>Replace with dietary formula or supplements containing medium-chain triglycerides</td>
</tr>
<tr>
<td>Fat-soluble vitamin malabsorption:</td>
<td></td>
</tr>
<tr>
<td>Vitamin A deficiency (night blindness, thick skin)</td>
<td>Replace with 10,000-15,000 IU/day as Aquasol A</td>
</tr>
<tr>
<td>Vitamin E deficiency (neuromuscular degeneration)</td>
<td>Replace with 50-400 IU/day as oral α-tocopherol or TPGS</td>
</tr>
<tr>
<td>Vitamin D deficiency (metabolic bone disease)</td>
<td>Replace with 5,000-8,000 IU/day of D₃ or 3-5 µg/kg/day of 25-hydroxycholecalciferol</td>
</tr>
<tr>
<td>Vitamin K deficiency (hypoprothrombinemia)</td>
<td>Replace with 2.5-5.0 mg every other day as water-soluble derivative of menadione</td>
</tr>
<tr>
<td>Micronutrient deficiency</td>
<td>Calcium, phosphate, or zinc supplementation</td>
</tr>
<tr>
<td>Deficiency of water-soluble vitamins</td>
<td>Supplement with twice the recommended daily allowance</td>
</tr>
<tr>
<td>Retention of biliary constituents such as cholesterol (itch or xanthomas)</td>
<td>Administer choleretic bile acids (ursodeoxycholic acid, 15-30 mg/kg/day)</td>
</tr>
<tr>
<td>Progressive liver disease; portal hypertension (variceal bleeding, ascites, hypersplenism)</td>
<td>Interim management (control bleeding; salt restriction; spironolactone)</td>
</tr>
<tr>
<td>End-stage liver disease (liver failure)</td>
<td>Transplantation</td>
</tr>
</tbody>
</table>

TPGS, α-tocopherol polyethylene glycol 1,000 succinate.
Partial external biliary diversion is efficacious in managing pruritus refractory to medical therapy and provides a favorable outcome in a select group of patients with chronic cholestasis who have not yet developed cirrhosis. The surgical technique involves resecting a segment of intestine to be used as a biliary conduit. One end of the conduit is attached to the gallbladder and the other end is brought out to the skin, forming a stoma. The main drawback of the procedure is the need to use an ostomy bag.

Progressive fibrosis and cirrhosis lead to the development of portal hypertension and consequently to ascites and variceal hemorrhage. The presence of ascites is a risk factor for the development of spontaneous bacterial peritonitis. The 1st step in the management of patients with ascites is to rule out spontaneous bacterial peritonitis and restrict sodium intake to 0.5 g (~1-2 mEq/kg/24 hr). There is no need for fluid restriction in patients with adequate renal output. Should this be ineffective, diuretics may be helpful. The diuretic of choice is spironolactone (3-5 mg/kg/24 hr in 4 doses). If spironolactone alone does not control ascites, the addition of another diuretic such as thiazide or furosemide may be beneficial. Patients with ascites but without peripheral edema are at risk for reduced plasma volume and decreased urine output during diuretic therapy. Tense ascites alters renal blood flow and systemic hemodynamics. Paracentesis and intravenous albumin infusion can improve hemodynamics, renal perfusion, and symptoms. Follow-up includes dietary counseling and monitoring of serum and urinary electrolyte concentrations.

In patients with portal hypertension, variceal hemorrhage and the development of hypersplenism are common. It is important to ascertain the cause of bleeding because episodes of gastrointestinal hemorrhage in patients who have chronic liver disease may be from gastritis or peptic ulcer disease. Because the management of these various complications differs, differentiation, perhaps via endoscopy, is necessary before treatment is initiated. If the patient is volume depleted, blood transfusion should be carefully administered, avoiding overttransfusion, which can precipitate further bleeding. Balloon tamponade is not recommended in children because it can be associated with significant complications. Sclerotherapy or endoscopic variceal ligation may be useful palliative measures in the management of bleeding varices and may be superior to surgical alternatives.

For patients with advanced liver disease, hepatic transplantation has a success rate >85%. If the operation is technically feasible, it will prolong life and might correct the metabolic error in diseases such as α1-antitrypsin deficiency, tyrosinemia, and Wilson disease. Success depends on adequate intraoperative, preoperative, and postoperative care, and on cautious use of immunosuppressive agents. Scarcity of donors of small livers severely limits the application of liver transplantation for infants and children. The use of reduced-size transplants and living donors increases the ability to treat small children successfully.

**Prognosis**

For patients with idiopathic neonatal hepatitis, the variable prognosis might reflect the heterogeneity of the disease. In sporadic cases, 60-70% recover with no evidence of hepatic structural or functional impairment. Approximately 5-10% have persistent fibrosis or inflammation, and a smaller percentage have more severe liver disease, such as cirrhosis. Infants usually die early in the course of the illness, owing to hemorrhage or sepsis. Of infants with idiopathic neonatal hepatitis of the familial variety, only 20-30% recover; 10-15% acquire chronic liver disease with cirrhosis. Liver transplantation may be required.

**Bibliography is available at Expert Consult.**

### 356.2 Cholestasis in the Older Child

_H. Hesham Abdel-Kader Hassan and William F. Balistreri_

Cholestasis with onset after the neonatal period is most often caused by acute viral hepatitis or exposure to hepatotoxic drugs. However, many of the conditions causing neonatal cholestasis can also cause chronic cholestasis in older patients. Consequently, older children and adolescents with conjugated hyperbilirubinemia should be evaluated for acute and chronic viral hepatitis, α1-antitrypsin deficiency, Wilson disease, liver disease associated with inflammatory bowel disease, autoimmune hepatitis, drug-induced liver injury, and the syndromes of intrahepatic cholestasis. Other causes include obstruction caused by cholelithiasis, abdominal tumors, enlarged lymph nodes, or hepatic inflammation resulting from drug ingestion. Management of cholestasis in the older child is similar to that proposed for neonatal cholestasis (see Table 356-5).
Bibliography


Metabolic liver diseases in children, although individually rare, altogether represent a significant cause of morbidity and mortality. The liver has a central role in synthetic, degradative, and regulatory pathways involving carbohydrate, protein, lipid, trace element, and vitamin metabolism. Inborn errors of metabolism result in metabolic abnormalities, specific enzyme deficiencies or defects, and disorders of protein transport that can have primary or secondary effects on the liver (Table 357-1). Liver disease can arise when absence of an enzyme produces a block in a metabolic pathway, when unmetabolized substrate accumulates proximal to a block, when deficiency of an essential substance produced distal to an aberrant chemical reaction develops, or when synthesis of an abnormal metabolite occurs. The spectrum of pathologic changes includes hepatocyte injury, with subsequent failure of other metabolic functions, often eventuating in cirrhosis, liver tumors, or both; storage of lipid, glycogen, or other products manifested as hepatomegaly, often with complications specific to deranged metabolism (hypoglycemia with glycogen storage disease); and absence of structural change despite profound metabolic effects, as with urea cycle defects. Clinical manifestations of metabolic diseases of the liver mimic infections, intoxications, and hematologic and immunologic diseases (Table 357-2). Many metabolic diseases are detected in expanded newborn metabolic screening programs (see Chapter 84). Clues are provided by family history of a similar illness or by the observation that the onset of symptoms is closely associated with a change in dietary habits; in patients with hereditary fructose intolerance, symptoms follow ingestion of fructose (sucrose). Clinical and laboratory evidence often guides the evaluation. Liver biopsy offers morphologic study and permits enzyme assays, as well as quantitative and qualitative assays of various other constituents (e.g., hepatic copper content in Wilson disease). Genetic/molecular diagnostic approaches are also available. Such studies require cooperation of experienced laboratories and careful attention to collection and handling of specimens. Treatment depends on the specific type of defect and although relatively uncommon, altogether metabolic diseases of the liver account for up to 10% of the indications for liver transplantation in children, a number that may be underestimated given the acute nature of some of these conditions, precluding complete diagnostic investigation prior to transplantation.
### Table 357-1 Inborn Errors of Metabolism That Affect the Liver

| DISORDERS OF CARBOHYDRATE METABOLISM | Disorders of galactose metabolism  
Galactosemia (galactose-1-phosphate uridylytransferase deficiency)  
Disorders of fructose metabolism  
Hereditary fructose intolerance (aldolase deficiency)  
Fructose-1,6 diphosphatase deficiency  
Glycogen storage diseases  
Type I  
Von Gierke (glucose-6-phosphatase deficiency)  
Type Ib (glucose-6-phosphatase transport defect)  
Type III (Corn/Forbes (glucagon debrancher deficiency)  
Type IV (Andersen (glycogen branching enzyme deficiency)  
Type VI (Hers (liver phosphorylase deficiency)  
Congenital disorders of glycosylation (multiple subtypes) |

| DISORDERS OF AMINO ACID AND PROTEIN METABOLISM | Disorders of tyrosine metabolism  
Hereditary tyrosinemia type I (fumarylacetoacetate deficiency)  
Tyrosinemia, type II (tyrosine aminotransferase deficiency)  
Inherited urea cycle enzyme defects  
CPS deficiency (carbamoyl phosphate synthetase I deficiency)  
OTC deficiency (ornithine transcarbamoylase deficiency)  
Citrullinemia type I (argininosuccinate synthetase deficiency)  
Argininosuccinic aciduria (argininosuccinate synthetase deficiency)Argininosuccinase (arginase deficiency)  
N-AGS deficiency (N-acetylglutamate synthetase deficiency)  
Maple syrup urine disease (multiple possible defects*) |

| DISORDERS OF LIPID METABOLISM | Wolman disease (lysosomal acid lipase deficiency)  
Cholesteryl ester storage disease (lysosomal acid lipase deficiency)  
Homozgous familial hypercholesterolemia (low-density lipoprotein receptor deficiency)  
Gaucher disease type I (β-glucocerebrosidase deficiency)  
Nieman-Pick type C (NPC 1 and 2 mutations) |

| DISORDERS OF BILE ACID METABOLISM | Defects in bile acid synthesis  
Zellweger syndrome—cerebrohepatorenal (multiple mutations in peroxisome biogenesis genes) |

| DISORDERS OF METAL METABOLISM | Wilson disease (ATP7B mutations)  
Hepatic copper overload  
Indian childhood cirrhosis (ICC)  
Neonatal iron storage disease |

| DISORDERS OF BILIRUBIN METABOLISM | Crigler-Najjar (bilirubin-uridine diphosphoglucuronate glucuronosyltransferase (UDPGT)  
UDPGT activity is deficient or altered in 3 genetically and functionally distinct disorders (Crigler-Najjar [CN] syndromes type I and II and Gilbert syndrome), producing congenital nonobstructive, nonhemolytic, unconjugated hyperbilirubinemia. UGT1A1 is the primary UDPGT isoform needed for bilirubin glucuronidation, and complete absence of UGT1A1 activity causes CN type I. CN type II is caused by decreased UGT1A1 activity. |

| 357.1 Inherited Deficient Conjugation of Bilirubin (Familial Nonhemolytic Unconjugated Hyperbilirubinemia)  
Alexandra N. Menchise and William F. Balistreri  
Bilirubin is the metabolic end product of heme. Before excretion into bile, it is first glucuronidated by the enzyme bilirubin-uridine diphosphoglucuronate glucuronosyltransferase (UDPGT). UDPGT activity is deficient or altered in 3 genetically and functionally distinct disorders (Crigler-Najjar [CN] syndromes type I and II and Gilbert syndrome), producing congenital nonobstructive, nonhemolytic, unconjugated hyperbilirubinemia. UGT1A1 is the primary UDPGT isoform needed for bilirubin glucuronidation, and complete absence of UGT1A1 activity causes CN type I. CN type II is caused by decreased UGT1A1 activity. |

| Gibel syndrome is caused by a common polymorphism, a TA insertion in the promoter region of UGT1A1 that leads to decreased binding of the TATA binding protein and decreases normal gene activity but only to approximately 30%. Snapback primer genotyping can distinguish all UGT1A1 promoter genotypes. Unlike the CN syndromes, Gilbert syndrome usually occurs after puberty; it is not associated with chronic liver disease and no treatment is required. However, it is more common, affecting up to 5-10% of the white population with total serum bilirubin concentrations that fluctuate from 1-6 mg/dL. Because UGT1A1 is involved in glucuronidation of multiple substrates other than bilirubin (e.g., pharmaceutical drugs, endogenous hormones, environmental toxins, and aromatic hydrocarbons) and glucuronidation leads to inactivation of these substrates, mutations in the UGT1A1 gene are implicated in cancer risk and the predisposition to drug toxicity specifically in cancer chemotherapy and episodes of jaundice when exposed to the agents. |

| CRIGLER-NAJJAR SYNDROME TYPE I (GLUCURONYL TRANSFERASE DEFICIENCY)  
CN type I is rare and inherited as an autosomal recessive trait and is usually secondary to mutations that cause a premature stop codon or frameshift mutation and thereby abolish UGT1A1 activity. As many as 59 mutations have been identified to date. Parents of affected children have partial defects in conjugation as determined by hepatic specific enzyme assay or by measurement of glucuronide formation; their serum unconjugated bilirubin concentrations are normal.  
Clinical Manifestations  
Severe unconjugated hyperbilirubinemia develops in homozygous affected infants in the 1st 3 days of life, and without treatment, serum unconjugated bilirubin concentrations of 25-35 mg/dL are reached in the 1st mo. Kernicterus, an almost universal complication of this disorder, is usually first noted in the early neonatal period; some treated infants have survived childhood without clinical sequelae. Stools are |
pale yellow. Persistence of unconjugated hyperbilirubinemia at levels >20 mg/dL after the 1st wk of life in the absence of hemolysis should suggest the syndrome.

**Diagnosis**
The diagnosis of CN type I is based on the early age of onset and the extreme level of bilirubin elevation in the absence of hemolysis. In the bili, bilirubin concentration is <10 mg/dL compared with normal concentrations of 50-100 mg/dL; there is no bilirubin glucuronide. Definitive diagnosis is established by measuring hepatic glucuronyl transferase activity in a liver specimen obtained by a closed biopsy; open biopsy should be avoided because surgery and anesthesia can precipitate kernicterus. DNA diagnosis is also available and may be preferable. Identification of the heterozygous state in parents also strongly suggests the diagnosis. The differential diagnosis of unconjugated hyperbilirubinemia is discussed in Chapter 102.3.

**Treatment**
The serum unconjugated bilirubin concentration should be kept to <20 mg/dL for at least the 1st 2-4 wk of life; in low birthweight infants, the levels should be kept lower. This usually requires repeated exchange transfusions and phototherapy in the immediate neonatal period. Oral calcium phosphate supplementation renders phototherapy more effective as it forms complexes with bilirubin in the gut. Phenobarbital therapy, through CYP450 enzyme induction, should be considered to determine responsiveness and differentiation between types I and II. In patients with CN type I there is no response to phenobarbital treatment.

The risk of kernicterus persists into adult life, although the serum bilirubin levels required to produce brain injury beyond the neonatal period are considerably higher (usually >35 mg/dL). Therefore, phototherapy is generally continued through the early years of life. In older infants and children, phototherapy is used mainly during sleep so as not to interfere with normal activities. Despite the administration of increasing intensities of light for longer periods, the serum bilirubin response to phototherapy decreases with age. Additional adjuvant therapy using agents that bind photobilirubin products such as cholestyramine or agar can also be used to interfere with the enterohepatic recirculation of bilirubin.

Prompt treatment of intercurrent infections, febrile episodes, and other types of illness might help prevent the later development of kernicterus, which can occur at bilirubin levels of 45-55 mg/dL. All patients with CN type I have eventually experienced severe kernicterus by young adulthood.

Orthotopic liver transplantation cures the disease and has been successful in a small number of patients; isolated hepatocyte transplantation has been reported as bridge therapy to liver transplantation, with most, but not all patients eventually requiring orthotopic transplantation. Other therapeutic modalities have included plasmapheresis and limitation of bilirubin production. The latter option, inhibiting bilirubin generation, is possible via inhibition of heme oxygenase using metalloporphyrin therapy.

**CRIGLER-NAJJAR SYNDROME TYPE II (PARTIAL GLUCURONYL TRANSFERASE DEFICIENCY)**
Like CN type I, CN type II is an autosomal recessive disease; it is caused by homozygous missense mutations in UGT1A1, resulting in reduced (partial) enzymatic activity. More than 45 mutations have been identified to date. Type II disease can be distinguished from type I by the marked decline in serum bilirubin level that occurs in type II disease after treatment with phenobarbital secondary to an inducible phenobarbital response element on the UGT1A1 promoter.

**Clinical Manifestations**
When this disorder appears in the neonatal period, unconjugated hyperbilirubinemia usually occurs in the 1st 3 days of life; serum bilirubin concentrations can be in a range compatible with physiologic jaundice or can be at pathologic levels. The concentrations characteristically remain elevated into and after the 3rd wk of life, persisting in a range of 1.5-22 mg/dL; concentrations in the lower part of this range can create uncertainty about whether chronic hyperbilirubinemia is present. Development of kernicterus is unusual, and the infants are without clinical signs or symptoms of disease. There is no evidence of hemolysis. Liver enzymes and synthetic function tests are typically normal.

**Diagnosis**
Concentration of bilirubin in bile is nearly normal in patients with CN type II. Jaundiced infants and young children with type II syndrome respond readily to 5 mg/kg/24 hr of oral phenobarbital, with a decrease in serum bilirubin concentration to 2-3 mg/dL in 7-10 days.

**Treatment**
Long-term reduction in serum bilirubin levels can be achieved with continued administration of phenobarbital at 5 mg/kg/24 hr. The cosmetic and psychosocial benefit should be weighed against the risks of an effective dose of the drug because there is a small long-term risk of kernicterus even in the absence of hemolytic disease. Orlistat, an irreversible inhibitor of intestinal lipase, increases fecal fat excretion and decreases plasma unconjugated bilirubin concentrations (~10%) in patients with CN types I and II.

**INHERITED CONJUGATED HYPERBILIRUBINEMIA**
Conjugated hyperbilirubinemia can be caused by a small number of rare autosomal recessive conditions characterized by mild jaundice. The transfer of bilirubin and other organic anions from the liver cell to bile is defective. Chronic mild conjugated hyperbilirubinemia is usually detected during adolescence or early adulthood but can occur as early as the second year of life. The results of routine liver function tests are normal. Jaundice can be exacerbated by infection, pregnancy, oral contraceptives, alcohol consumption, and surgery. There is usually no morbidity and life expectancy is normal, but these disorders can initially present difficult problems in the differential diagnosis of more serious diseases.

**DUBIN-JOHNSON SYNDROME**
Dubin-Johnson syndrome is an autosomal recessive inherited defect with variable penetrance in hepatocyte secretion of bilirubin glucuronide. The defect in hepatic excretory function is not limited to conjugated bilirubin excretion but also involves several organic anions normally excreted from the liver cell into bile. Absent function of multiple drug-resistant protein 2 (MRP2), an adenosine triphosphate–dependent canalicular transporter, is the responsible defect. More than 10 different mutations, including compound heterozygous mutation in the CMOAT gene, have been identified and either affect localization of MRP2 with resultant increased degradation or impair MRP2 transport activity in the canalicular membrane. Bile acid excretion and serum bile acid levels are normal. Total urinary coproporphyrin excretion is normal in quantity but coproporphyrin I excretion increases to approximately 80% with a concomitant decrease in coproporphyrin III excretion. Normally, coproporphyrin III is >75% of the total. Cholangiography fails to visualize the biliary tract and x-ray of the gallbladder is also abnormal. Liver histology demonstrates normal architecture, but hepatocytes contain black pigment similar to melanin. Liver function is normal and prognosis is excellent. The most commonly reported symptoms are abdominal pain and fatigue, jaundice, dark urine, and slight enlargement of the liver. Jaundice fluctuates in intensity and is aggravated by intercurrent disease.

**Rotor Syndrome**
Patients with Rotor syndrome have an additional deficiency in organic anion uptake. Biallelic inactivating mutations in the linked genes SLC01B1 and SLC01B3 result in functional deficiencies of both
protein products (OATP1B1 and OATP1B, respectively) and are reported to cause Rotor syndrome. Importantly, these mutations may confer significant drug toxicity risk. Unlike Dubin-Johnson syndrome, total urinary coproporphyrin excretion is elevated, with a relative increase in the amount of the coproporphyrin I isomer. The gallbladder is normal by roentgenography, and liver cells contain no black pigment. In Dubin-Johnson and Rotor syndromes, sulfobromophthalein excretion is often abnormal.

Bibliography is available at Expert Consult.

357.2 Wilson Disease

Alexandra N. Menchise and William F. Balistreri

Wilson disease (hepatolenticular degeneration) is an autosomal recessive disorder that can be associated with degenerative changes in the brain, liver disease, and Kayser-Fleischer rings in the cornea (Fig. 357-1). The incidence is 1 in 55,000 births in the United States and 1 in 30,000 to 1 in 50,000 births worldwide. It is progressive and potentially fatal if untreated; specific effective treatment is available. Rapid diagnostic investigation of the possibility of Wilson disease in a patient presenting with any form of liver disease, particularly if older than 5 yr of age, not only facilitates early institution of management of Wilson disease and related genetic counseling but also allows appropriate treatment of non-Wilsonian liver disease once copper toxicity is ruled out.

PATHOGENESIS

The abnormal gene for Wilson disease is localized to the long arm of chromosome 13 (13q14.3). The Wilson disease gene encodes a copper transporting P-type adenosine triphosphatase (ATPase), ATP7B, which is mainly but not exclusively expressed in hepatocytes and is critical for biliary copper excretion and for copper incorporation into ceruloplasmin. Absence or malfunction of ATP7B results in decreased biliary copper excretion and diffuse accumulation of copper in the cytosol of hepatocytes. With time, liver cells become overloaded and copper is redistributed to other tissues, including the brain and kidneys, causing toxicity, primarily as a potent inhibitor of enzymatic processes. Ionic copper inhibits pyruvate oxidase in brain and ATPase in membranes, leading to decreased adenine triphosphate-phosphocreatine and potassium content of tissue.

More than 500 mutations in the gene have been identified from which 380 have a confirmed role in the pathogenesis of the disease, making diagnosis by DNA mutational analysis a difficult task unless a proband mutation is known. Most patients are compound heterozygotes. Mutations that completely knock out gene function are associated with an onset of disease symptoms as early as 2-3 yr of age, when Wilson disease might not typically be considered in the differential diagnosis. Milder mutations can be associated with neurologic symptoms or liver disease as late as 80 yr of age.

CLINICAL MANIFESTATIONS

Forms of Wilsonian hepatic disease include asymptomatic hepatomegaly (with or without splenomegaly), subacute or chronic hepatitis, and acute hepatic failure (with or without hemolytic anemia). Cryptogenic cirrhosis, portal hypertension, ascites, edema, variceal bleeding, or other effects of hepatic dysfunction (delayed puberty, amenorrhea, coagulation defects) can be manifestations of Wilson disease.

Disease presentations are variable, with a tendency to familial patterns. The younger the patient, the more likely hepatic involvement will be the predominant manifestation. Girls are 3 times more likely than boys to present with acute hepatic failure. Clinically evident liver disease may precede neurologic manifestations by as much as 10 yr. After 20 yr of age, neurologic symptoms predominate.

Neurologic disorders can develop insidiously or precipitously, with intention tremor, dysarthria, rigid dystonia, Parkinsonism, choreiform movements, lack of motor coordination, deterioration in school performance, or behavioral changes. Kayser-Fleischer rings are absent in young patients with hepatic Wilson disease up to 50% of the time but are present in 95% of patients with neurologic symptoms and somewhat over half of those without neurologic symptoms. Psychiatric manifestations include depression, personality changes, anxiety, or psychosis.

Coombs-negative hemolytic anemia may be an initial manifestation, possibly related to the release of large amounts of copper from damaged hepatocytes; this form of Wilson disease is usually fatal without transplantation. During hemolytic episodes, urinary copper excretion and serum copper levels (not ceruloplasmin bound) are markedly elevated. Manifestations of renal Fanconi syndrome and progressive renal failure with alterations in tubular transport of amino acids, glucose, and uric acid may be present. Unusual manifestations include arthritis, pancreatitis, nephrolithiasis, infertility or recurrent miscarriages, cardiomyopathy, and endocrinopathies (hypoparathyroidism).

PATHOLOGY

All grades of hepatic injury occur in patients with Wilson disease with steatosis, hepatocellular ballooning and degeneration, glycogen granules, minimal inflammation, and enlarged Kupffer cells being most common. The earliest histologic feature is often mild steatosis and this may be misdiagnosed as nonalcoholic fatty liver disease or nonalcoholic steatohepatitis. Additionally, the lesion may be indistinguishable from that of autoimmune hepatitis. With progressive parenchymal damage, fibrosis and cirrhosis develop. Ultrastructural changes primarily involve the mitochondria and include increased density of the matrix material, inclusions of lipid and granular material, and increased intracisternal space with dilution of the tips of the cristae.

DIAGNOSIS

Wilson disease should be considered in children and teenagers with unexplained acute or chronic liver disease, neurologic symptoms of unknown cause, acute hemolysis, psychiatric illnesses, behavioral changes, Fanconi syndrome, or unexplained bone (osteoporosis, fractures) or muscle disease (myopathy, arthralgia). The clinical suspicion is confirmed by study of indices of copper metabolism.

Most patients with Wilson disease have decreased ceruloplasmin levels (<20 mg/dL). The failure of copper to be incorporated into ceruloplasmin leads to a plasma protein with a shorter half-life and, therefore, a reduced steady-state concentration of ceruloplasmin in the circulation. Caution should be used in interpreting serum ceruloplasmin levels, because they may be elevated in acute inflammation and in states of elevated estrogen such as pregnancy, estrogen supplementation, or oral contraceptive use and may be low in autoimmune hepatitis, celiac disease, familial aceruloplasminemia or in heterozygous carriers of ATP7B mutations who do not show copper overload disease.

Figure 357-1 Kayser-Fleischer (K-F) ring. There is a brown discoloration at the outer margin of the cornea because of the deposition of copper in Descemet’s membrane. Here it is clearly seen against the light green iris. Slit-lamp examination is required for secure detection. (From Ala A, Walker AP, Ashkan K, et al: Wilson’s disease, Lancet 369:397–408, 2007.)
Bibliography


The serum “free” copper level may be elevated in early Wilson disease (>1.6 µmol/L), and urinary copper excretion (usually <40 µg/day) is increased to >100 µg/day and often up to 1,000 µg or more per day (typical findings in Wilson disease: urine copper excretion >1.6 µmol/24 hr, >0.64 µmol/24 hr in children). In equivocal cases, the response of urinary copper output to chelation may be of diagnostic help. During the 24 hr urine collection patients are given two 500 mg oral doses of d-penicillamine 12 hr apart; affected patients excrete >1,600 µg/24 hr.

Demonstration of Kayser-Fleischer rings, which might not be present in younger children, requires a slit-lamp examination by an ophthalmologist. After adequate treatment, Kayser-Fleischer rings resolve.

Liver biopsy is of value for determining the extent and severity of liver disease and for measuring the hepatic copper content (normally <10 µg/g dry weight) but is only required if clinical signs and noninvasive tests do not allow a final diagnosis or if another liver disorder is suspected. Hepatic copper accumulation is the hallmark of Wilson disease and measurement of hepatic parenchymal copper concentration is the method of choice for diagnosis. In Wilson disease, hepatic copper content usually exceeds 250 µg/g dry weight (>4 µmol/g dry weight is the best biochemical evidence for Wilson disease but lowering the threshold to 1.2µmol/g dry weight improves sensitivity without significantly affecting specificity). In healthy heterozygotes, levels may be intermediate. In later stages of Wilson disease hepatic copper content can be unreliable because cirrhosis leads to variable hepatic copper distribution and sampling error.

Family members of patients with proven cases require screening for presymptomatic Wilson disease. Such screening should include determination of the serum ceruloplasmin level and urinary copper excretion. If these results are abnormal or equivocal, liver biopsy should be carried out to determine morphology and hepatic copper content. Genetic screening by either linkage analysis or direct DNA mutation analysis is possible, especially if the mutation for the proband case is known or the patient is from an area where a specific mutation is known (in central and eastern Europe, the H1069Q mutation is present in 50-80% of patients).

**TREATMENT**

A major effort should be made to restrict dietary copper intake to <1 mg/day. Foods such as liver, shellfish, nuts, and chocolate should be avoided. If the copper content of the drinking water exceeds 0.1 mg/L, it may be necessary to demineralize the water. Once the diagnosis has been made, treatment needs to be lifelong.

The initial treatment in symptomatic patients is the administration of copper-chelating agents, which leads to rapid excretion of excess deposited copper. Chelation therapy is managed with oral administration of d-penicillamine (β-3-dimethylcysteine) in a dose of 1 g/day in 2 doses before meals for adults and 20 mg/kg/day for pediatric patients or triethylenetetramine dihydrochloride (Trien, TETA, trientine) at 2 doses before meals in children. Trientine has few side effects (i.e., Goodpasture syndrome, systemic lupus erythematosus, polymyositis), interaction with collagen and elastin, deficiency of other elements such as zinc, and aplastic anemia and nephrosis. Because penicillamine is an antimetabolite of vitamin B6, additional amounts of this vitamin are necessary. For these reasons, triethylenetetramine dihydrochloride is a preferred alternative, and is considered first-line therapy for some patients. Trientine has few known side effects. Ammonium tetrathiomolybdate is another alternative chelating agent under investigation for patients with neurologic disease; initial results suggest that significantly fewer patients experience neurologic deterioration with this drug compared to penicillamine. The initial dose is 120 mg/day (20 mg between meals tid and 20 mg with meals tid). Side effects include anemia, leukopenia, thrombocytopenia, and mild elevations of transaminases. Because of its extensive decoppering effect, ammonium tetrathiomolybdate also has antiangiogenic effects.

Zinc has also been used as adjuvant therapy, maintenance therapy, or primary therapy in presymptomatic patients, owing to its unique ability to impair the gastrointestinal absorption of copper. Zinc acetate is given in adults at a dose of 25-50 mg of elemental zinc 3 times a day, and 25 mg 3 times a day in children older than 5 yr of age. Side effects are mostly limited to gastric irritation but also include reduced leukocyte chemotaxis and elevations in serum lipase and/or amylase. Current guidelines recommend that all symptomatic patients with Wilson disease receive a chelating agent (penicillamine or trientine). Zinc may have a role as a first-line therapy in patients with neurologic disease but exclusive monotherapy with zinc in symptomatic liver disease is controversial and not recommended.

Antioxidants (vitamin E and curcumin) and pharmacologic chaperones (4-phenylbutyrate and curcumin) may have a role as adjunctive treatment but more research is needed.

**PROGNOSIS**

Untreated patients with Wilson disease can die of hepatic, neurologic, renal, or hematologic complications. Medical therapy is rarely effective in those presenting with acute liver failure. The prognosis for patients receiving prompt and continuous penicillamine is variable and depends on the time of initiation of and the individual response to chelation. Liver transplantation should be considered for patients with fulminant liver disease, decompensated cirrhosis, or progressive neurologic disease; the last indication remains controversial. Liver transplantation is curative, with a survival rate of approximately 85-90%. In asymptomatic siblings of affected patients, early institution of chelation or zinc therapy can prevent expression of the disease.

**Bibliography** is available at Expert Consult.

### 357.3 Indian Childhood Cirrhosis

**Alexandra N. Menchise and William F. Balistreri**

Indian childhood cirrhosis (ICC) is a chronic liver disease of young children unique to the Indian subcontinent. ICC manifests with jaundice, pruritus, lethargy, and hepatosplenomegaly. Untreated ICC has a mortality of 40-50% within 4 wks. Histologically, it is characterized by hepatocyte necrosis, Mallory bodies, intralobular fibrosis, and inflammation.

The etiology has remained elusive; it was once believed that excess copper ingestion in the setting of a genetic susceptibility to copper toxicity was the most likely cause. Epidemiologic data demonstrates that the copper toxicity theory is unlikely. The increased hepatic copper content, usually >700 µg/g dry weight, seen in ICC is only seen in the late stages of disease and is accompanied by even higher levels of zinc, a non-hepatotoxic metal. The copper-contaminated utensils used to feed babies and implicated in excess copper ingestion are found in only 10-15% of all cases. The current hypothesis implicates the postnatal use of local hepatotoxic therapeutic remedies, although the exact causative agent is unknown.

Over the last few decades, as the awareness of the disease has increased, the incidence of ICC has decreased and has even been virtually eliminated in some areas of India although established and non-typical cases are probably being missed because of lack of histologic confirmation and unawareness of the protean manifestations and natural history of this disease. Variants of this syndrome have been named according to the population where it has been described, such as Tyrolean childhood cirrhosis or North American ICC. It has also been reported in the Middle East, West Africa, and North and Central America.

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Neonatal iron storage disease (NISD), also known as neonatal hemosiderosis, is a rare form of fulminant liver disease that manifests in the 1st few days of life. It is unrelated to the familial forms of hereditary hemosiderosis that occur later in life. NISD has a high rate of recurrence in families, with approximately 80% probability that subsequent infants will be affected. NISD is postulated to be a gestational alloimmune disease and has also been classified as congenital alloimmune hepatitis. Alloimmunity develops in the pregnant mother of the affected infant when she is exposed to an unknown fetal hepatocyte cell surface antigen that she does not recognize as self. Maternal immunoglobulin G to this fetal antigen then crosses the placenta and induces hepatic injury via immune system activation. The defining feature of gestational alloimmune liver disease is complement-mediated hepatocyte injury, the evidence for which comes from detection of the C5b-9 complex by immunohistochemistry. Additional evidence of a gestational insult is given by the fact that affected infants may be born prematurely or with intrauterine growth restriction. Several infants with NISD also have renal dysgenesis.

Excess non–transferrin-bound iron in gestational alloimmune liver disease may result from fetal liver injury that causes reduced synthesis of key iron regulatory and transport proteins. The pattern of extrapathic siderosis appears to be determined by the normal capacity of various tissues to import non–transferrin-bound iron and not export cellular iron. It is now thought that fetal liver injury is the primary event leading to the development of the neonatal hemosiderosis phenotype providing further evidence that this is not a primary iron overload disease.

NISD is a rapidly fatal, progressive illness characterized by hepatomegaly, hypoglycemia, hypoprothrombinemia, hypoalbuminemia, hyperferritinemia, and hyperbilirubinemia. The coagulopathy is refractory to therapy with vitamin K. Liver pathology demonstrates severe liver injury with acute and chronic inflammation, fibrosis, and cirrhosis. The diagnosis can be confirmed in the neonate with severe liver injury and extrapathic siderosis (biopsy material of buccal mucosal glands is laden with iron) or MRI determination of iron overload in organs such as the pancreas.

The prognosis for affected infants is generally poor, but some patients with NISD have been successfully treated with iron-chelating agents (deferoxamine) combined with aggressive antioxidant therapy. Combining this therapy with double volume exchange transfusion followed by administration of intravenous immunoglobulin (IVIG) has also been shown to remove the injury-causing maternal immunoglobulin G. Liver transplantation should also be an early consideration. Recurrences of NISD may be modified with IVIG administered to the mother once a wk from the 18th wk of gestation until delivery. The largest experience reports 48 women with previous infants with NISD who successfully delivered 52 babies after IVIG treatment. The majority of infants had biochemical evidence of liver disease with elevated serum α-fetoprotein and ferritin. All infants survived with medical therapy or no therapy.

Bibliography is available at Expert Consult.

357.5 Miscellaneous Metabolic Diseases of the Liver

Alexandra N. Menchise and William F. Balistreri

α₁-Antitrypsin Deficiency

A small percentage of patients homozygous for deficiency of the major serum protease inhibitor α₁-antitrypsin manifest neonatal cholestasis or later-onset childhood cirrhosis. α₁-Antitrypsin deficiency is caused by mutation in the SERPINA1 gene and it is an autosomal recessive disorder. α₁-Antitrypsin, a protease inhibitor synthesized by the liver, protects lung alveolar tissues from destruction by neutrophil elastase (see Chapter 393). α₁-Antitrypsin is present in more than 20 different codominant alleles, only a few of which are associated with defective protease inhibitors. The most common allele of the protease inhibitor (Pi) system is M, and the normal phenotype is PiMM. The Z allele predisposes to clinical deficiency; patients with liver disease are usually PiZZ homozygotes and have serum α₁-antitrypsin levels <2 mg/mL (~10–20% of normal). The incidence of the PiZZ genotype in the white population is estimated at 1 in 2,000–4,000 live births. Compound heterozygotes PiMZ, PiSZ, PiZI are not a cause of liver disease alone but can act as modifier genes, increasing the risk of progression in other liver disease such as nonalcoholic fatty liver disease and hepatitis C. The null phenotype because of stop codons in the coding exon of the α₁-antitrypsin gene or complete deletion of α₁-antitrypsin coding exons leads to the complete absence of any protein and causes only lung disease.

Newly formed α₁-antitrypsin peptide normally enters the endoplasmic reticulum, where it undergoes enzymatic modification and folding before transport to the plasma membrane, where it is excreted as a 55 kDa glycoprotein. In affected patients with PiZZ, the rate at which the α₁-antitrypsin peptide folds is decreased, and this delay allows the formation of polymers that are retained in the endoplasmic reticulum. How the polymers cause liver damage is not completely elucidated, but research indicates that accumulation of abnormally folded protein leads to activation of stress and proinflammatory pathways in the endoplasmic reticulum and hepatocyte programmed cell death. In liver biopsies from patients, polymerized α₁-antitrypsin peptides can be seen by electron microscopy and histochemically as periodic acid–Schiff–positive diastase-resistant globules primarily in perportal hepatocytes, but also in Kupffer cells and biliary epithelial cells. The pattern of neonatal liver injury can be highly variable, and liver biopsies might demonstrate hepatocellular necrosis, inflammatory cell infiltration, bile duct proliferation, periportal fibrosis, or cirrhosis.

In affected patients, the course of liver disease is also highly variable. Prospective studies in Sweden have shown that only 10% of patients develop clinically significant liver disease by their 4th decade. Genetic traits or environmental factors must influence the development of disease in α₁-antitrypsin–deficient patients. Infants with liver disease are indistinguishable from other infants with “idiopathic” neonatal hepatitis, of whom they constitute approximately 5–10%. Jaundice, acholic stools, and hepatomegaly are present in the 1st wk of life, but the jaundice usually clears in the 2nd–4th mo. Complete resolution, persistent liver disease, or the development of cirrhosis can follow. Older children can present with asymptomatic hepatomegaly or manifestations of chronic liver disease or cirrhosis, with evidence of portal hypertension. Emphysema is not typically observed in children but an increased risk for developing asthma is reported. Cigarette smoking promotes development of lung disease so children should be counseled on avoidance or smoking cessation as part of their anticipatory guidance. Long-term patients are at risk for hepatocellular carcinoma.

Therapy is supportive; liver transplantation has been curative.

Citrin Deficiency

Neonatal intrahepatic cholestasis caused by citrin deficiency presents in the 1st few mo of life with manifestations that initially may be indistinguishable from other causes of neonatal cholestasis, especially biliary atresia. Patients may have jaundice, hepatomegaly, liver dysfunction with coagulopathy, fatty liver infiltration, hyperammonemia with or without hypoglycemia. Presymptomatic patients may be identified from the newborn metabolic screen with hypergalactosemia, hypermethionemia, and hyperphenylalanemia, not all patients are identified by newborn screening.

Neonatal intrahepatic cholestasis caused by citrin deficiency is caused by a mutation in the SLC25A13 gene, which encodes citrin, a mitochondrial carrier protein (calcium binding aspartate-glutamate carrier) and is involved in the urea cycle, gluconeogenesis and glycolysis. The mutation is most common among East Asian populations.
Bibliography
Affected infants have hypergalactosemia, elevated bile acids, vitamin K–dependent coagulopathy, and elevated levels of citrulline and methionine. Treatment includes that for neonatal cholestasis and in many patients but more severely affected patients may develop progressive hepatic failure requiring liver transplantation in the 1st yr of life.

Bibliography is available at Expert Consult.
Bibliography
Viral hepatitis continues to be a major health problem in both developing and developed countries. This disorder is caused by at least 5 pathogenic hepatotropic viruses recognized to date: hepatitides A (HAV), B (HBV), C (HCV), D (HDV), and E (HEV) viruses (Table 358-1). Many other viruses (and diseases) can cause hepatitis, usually as 1 component of a multisystem disease. These include herpes simplex virus, cytomegalovirus, Epstein-Barr virus, varicella-zoster virus, HIV, rubella, adenoviruses, enteroviruses, parvovirus B19, and arboviruses (Table 358-2).

The hepatotropic viruses are a heterogeneous group of infectious agents that cause similar acute clinical illness. In most pediatric patients, the acute phase causes no or mild clinical disease. Morbidity is related to rare cases of acute liver failure (ALF) in susceptible patients, and to the chronic disease state and attendant complications that 3 of these viruses (hepatitides B, C, and D) can cause.

**ISSUES COMMON TO ALL FORMS OF VIRAL HEPATITIS**

**Differential Diagnosis**

Often what brings the patient with hepatitis to medical attention is clinical icterus, with yellow skin and/or mucous membranes. The liver is usually enlarged and tender to palpation and percussion. Splenomegaly and lymphadenopathy may be present. Extrahepatic symptoms (rashes, arthritis) are more readily seen in HBV and HCV infections. Clinical signs of altered sensorium or hyperreflexia should be carefully sought, because they mark the onset of encephalopathy and ALF.

The differential diagnosis varies with age of presentation.

In the newborn period, infection is a common cause of conjugated hyperbilirubinemia; the infectious cause is either a bacterial agent (e.g., *Escherichia coli*, *Listeria*, *syphilis*) or a nonhepatotropic virus (e.g., herpes simplex virus, enteroviruses, cytomegalovirus). Metabolic (α-antitrypsin deficiency, cystic fibrosis, tyrosinemia), and anatomic causes (biliary atresia, choledochal cysts) and inherited forms of intrahepatic cholestasis should always be excluded.

In later childhood, extrahepatic obstruction (gallstones, primary sclerosing cholangitis, pancreatic pathology), inflammatory conditions (autoimmune hepatitis, juvenile rheumatoid arthritis, Kawasaki disease), immune dysregulation (hemophagocytic lymphohistiocytosis), infiltrative disorders (malignancies), toxins and medications, metabolic disorders (Wilson disease, cystic fibrosis), and infection (Epstein-Barr virus, varicella, malaria, leptospirosis, *syphilis*) should be ruled out.

**Pathogenesis**

The acute response of the liver to hepatotropic viruses involves a direct cytopathic and an immune-mediated injury. The entire liver is involved. Necrosis is usually most marked in the centrilobular areas. An acute mixed inflammatory infiltrate predominates in the portal areas but also affects the lobules. The lobular architecture remains intact, although balloon degeneration and necrosis of single or groups of parenchymal cells commonly occurs. Fatty change is rare except with HCV infection. Bile duct proliferation but not bile duct damage is common. Diffuse Kupffer cell hyperplasia is noticeable in the sinusoids. Neonates often respond to hepatic injury by forming giant cells.

In fulminant hepatitis, parenchymal collapse occurs on the just-described background.

With recovery, the liver morphology returns to normal within 3 mo of the acute infection. If chronic hepatitis develops, the inflammatory infiltrate settles in the periportal areas and often leads to progressive scarring. Both of these hallmarks of chronic hepatitis are seen in cases of HBV and HCV.

**Common Biochemical Profiles in the Acute Infectious Phase**

Acute liver injury caused by the hepatotropic viruses manifests in 3 main functional liver biochemical profiles. These serve as an important guide to supportive care and monitoring in the acute phase of the infection for all viruses.

As a reflection of cytopathic injury to the hepatocytes, there is a rise in serum levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST). The magnitude of enzyme elevation does not correlate with the extent of hepatocellular necrosis and has little prognostic value. There is usually slow improvement over several weeks, but AST and ALT levels lag behind the serum bilirubin level, which tends to normalize first. Rapidly falling aminotransferase levels can predict a poor outcome, particularly if their decline occurs in conjunction with a rising bilirubin level and a prolonged prothrombin time; this combination of findings usually indicates that massive hepatic injury has occurred.

**Cholestasis**, defined by elevated serum conjugated bilirubin levels, results from abnormal bile flow at the canaliculal and cellular level as a result of hepatocyte damage and inflammatory mediators. Elevation of serum alkaline phosphatase, 5’-nucleotidase, γ-glutamyl transpeptidase, and urobinigen mark cholestasis. Improvement tends to parallel the acute hepatitis phase. Absence of cholestatic markers

**Table 358-1 Features of the Hepatotropic Viruses**

<table>
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<th>HCV RNA</th>
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Altered synthetic function is the most important marker of liver injury. Monitoring of synthetic function should be the main focus in clinical follow-up to define the severity of the disease. In the acute phase, the degree of liver synthetic dysfunction guides treatment and helps to establish intervention criteria. Abnormal liver synthetic function is a marker of liver failure and is an indication for prompt referral to a transplant center. Serial assessment is necessary because liver dysfunction does not progress linearly. Synthetic dysfunction is reflected by a combination of abnormal protein synthesis (prolonged prothrombin time, high international normalized ratio, low serum albumin levels), metabolic disturbances (hypoglycemia, lactic acidosis, hyperammonemia), poor clearance of medications dependent on liver function, and altered sensorium with increased deep tendon reflexes (hepatic encephalopathy).

**HEPATITIS A**

HAV infection is the most prevalent hepatotropic virus. This virus is also responsible for most forms of acute and benign hepatitis; although fulminant hepatic failure can occur, it is rare (<1% of cases in the United States) and occurs more often in adults than in children.

**Etiology**

HAV is an RNA virus, a member of the picornavirus family. It is heat stable and has limited host range—namely, the human and other primates.

**Epidemiology**

HAV infection occurs throughout the world but is most prevalent in developing countries. In the United States, 30–40% of the adult population has evidence of previous HAV infection. Hepatitis A is thought to account for approximately 50% of all clinically apparent acute viral hepatitis in the United States. As a result of aggressive implementation of a childhood vaccination strategy, the prevalence of symptomatic HAV cases in the United States has declined significantly. However, outbreaks in daycare centers (where the spread from young, nonicteric, infected children can occur easily) as well as multiple foodborne and waterborne outbreaks have justified the implementation of a universal vaccination program.

HAV is highly contagious. Transmission is almost always by person-to-person contact through the fecal–oral route. Perinatal transmission occurs rarely. No other form of transmission is recognized. HAV infection during pregnancy or at the time of delivery does not appear to result in increased complications of pregnancy or clinical disease in the newborn. In the United States, increased risk of infection is found in contacts with infected persons, childcare centers, and household contacts. Infection is also associated with contact with contaminated food or water and after travel to endemic areas. Common source foodborne and waterborne outbreaks have occurred, including several caused by contaminated shellfish, frozen berries, and raw vegetables; no known source is found in about half of the cases. The mean incubation period for HAV is approximately 3 wk. Fecal excretion of the virus starts late in the incubation period, reaches its peak just before the onset of symptoms, and resolves by 2 wk after the onset of jaundice in older subjects. The duration of viral excretion is prolonged in infants. The patient is, therefore, contagious before clinical symptoms are apparent and remains so until viral shedding ceases.

**Clinical Manifestations**

HAV is responsible for acute hepatitis only. Often, this is an anicteric illness, with clinical symptoms indistinguishable from other forms of viral gastroenteritis, particularly in young children.

The illness is much more likely to be asymptomatic in older adolescents or adults, in patients with underlying liver disorders, and in those who are immunocompromised. It is characteristically an acute febrile illness with an abrupt onset of anorexia, nausea, malaise, vomiting, and jaundice. The typical duration of illness is 7-14 days (Fig. 358-1).

Other organ systems can be affected during acute HAV infection. Regional lymph nodes and the spleen may be enlarged. The bone marrow may be moderately hypoplastic, and aplastic anemia has been reported. Tissue in the small intestine might show changes in villous architecture, with villous atrophy and a decrease in the number of epithelial cells.

**Table 358-2** Causes and Differential Diagnosis of Hepatitis in Children

<table>
<thead>
<tr>
<th>INFECTIOUS</th>
<th>Causes and Differential Diagnosis of Hepatitis in Children</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatotropic viruses</td>
<td>• HAV • HBV • HCV • HDV • HEV • Hepatitis non-A-E viruses</td>
</tr>
<tr>
<td>Systemic infection that can include hepatitis</td>
<td>• Adenovirus • Arbovirus • Coxsackievirus • Cytomegalovirus • Enterovirus • Epstein-Barr virus</td>
</tr>
<tr>
<td>• “Exotic” viruses (e.g., yellow fever) • Herpes simplex virus • Human immunodeficiency virus • Paramyxovirus • Rubella • Varicella zoster</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>NONVIRAL LIVER INFECTIONS</td>
</tr>
<tr>
<td>Abscess</td>
<td>Amebiasis</td>
</tr>
<tr>
<td>Bacterial sepsis</td>
<td>Brucellosis</td>
</tr>
<tr>
<td>Fitz-Hugh-Curtis syndrome</td>
<td>Histoplasmosis</td>
</tr>
<tr>
<td>Leptospirosis</td>
<td>Tuberculosis</td>
</tr>
<tr>
<td>Other</td>
<td>AUTOIMMUNE</td>
</tr>
<tr>
<td>Autoimmune hepatitis</td>
<td>Sclerosing cholangitis</td>
</tr>
<tr>
<td>Other (e.g., systemic lupus erythematosus, juvenile rheumatoid arthritis)</td>
<td>METABOLIC</td>
</tr>
<tr>
<td>α1-Antitrypsin deficiency</td>
<td>Tyrosinemia</td>
</tr>
<tr>
<td>Wilson disease</td>
<td>Other</td>
</tr>
<tr>
<td>TOXIC</td>
<td>iatrogenic or drug induced (e.g., acetaminophen)</td>
</tr>
<tr>
<td>Environmental (e.g., pesticides)</td>
<td>ANATOMIC</td>
</tr>
<tr>
<td>Choledochal cyst</td>
<td>Biliary atresia</td>
</tr>
<tr>
<td>Other</td>
<td>HEMODYNAMIC</td>
</tr>
<tr>
<td>Shock</td>
<td>Congestive heart failure</td>
</tr>
<tr>
<td>Budd-Chiari syndrome</td>
<td>Other</td>
</tr>
<tr>
<td>NONALCOHOLIC FATTY LIVER DISEASE</td>
<td>Idiopathic</td>
</tr>
<tr>
<td>Reye syndrome</td>
<td>Other</td>
</tr>
</tbody>
</table>

reported, though rarely, and nephritis, arthritis, vasculitis, and cryoglobulinemia can result from circulating immune complexes.

**Diagnosis**

Acute HAV infection is diagnosed by detecting antibodies to HAV, specifically, anti-HAV (immunoglobulin [Ig] M) by radioimmunoassay or, rarely, by identifying viral particles in stool. A viral polymerase chain reaction (PCR) assay is available for research use (Table 358-3). Anti-HAV is detectable when the symptoms are clinically apparent, or, rarely, by identifying viral particles in stool. A viral polymerase specifically, anti-HAV (immunoglobulin [Ig] M) by radioimmunoassay

**Complications**

Although most patients achieve full recovery, 2 distinct complications can occur. ALF from HAV infection is a rare but not infrequent complication of HAV. Those at risk for this complication are adolescents and adults, but also immunocompromised patients or those with underlying liver disorders. The height of HAV viremia may be linked to the severity of hepatitis. Whereas in the United States, HAV represents < 0.5% of pediatric-age ALF, it is responsible for up to 3% mortality in the adult population with ALF. In endemic areas of the world, HAV constitutes up to 40% of all cases of pediatric ALF. HAV can also progress to a prolonged cholestatic syndrome that waxes and wanes over several months. Pruritus and fat malabsorption are problematic and require symptomatic support with antipruritic medications and fatsoluble vitamins. This syndrome occurs in the absence of any liver synthetic dysfunction and resolves without sequelae.

**Treatment**

There is no specific treatment for hepatitis A. Supportive treatment consists of intravenous hydration as needed and antipruritic agents and fat-soluble vitamins for the prolonged cholestatic form of disease. Serial monitoring for signs of ALF and, if ALF is diagnosed, a prompt referral to a transplantation center can be lifesaving.

**Prevention**

Patients infected with HAV are contagious for 2 wk before and approximately 7 days after the onset of jaundice and should be excluded from school, childcare, or work during this period. Careful hand-washing is necessary, particularly after changing diapers and before preparing or serving food. In hospital settings, contact and standard precautions are recommended for 1 wk after onset of symptoms.

**Immunoglobulin**

Indications for intramuscular administration of Ig (0.02 mL/kg) include preexposure and postexposure prophylaxis (Table 358-4).

- Ig is recommended for preexposure prophylaxis for susceptible travelers to countries where HAV is endemic, and it provides effective protection for up to 3 mo. HAV vaccine given any time before travel is preferred for preexposure prophylaxis in healthy persons, but Ig ensures an appropriate prophylaxis in children younger than 12 mo old, patients allergic to a vaccine component, or those who elect not to receive the vaccine. If travel is planned in <2 wk, older patients, immunocompromised hosts, and those with chronic liver disease or other medical conditions should receive both Ig and the HAV vaccine.

- Ig prophylaxis in postexposure situations should be used as soon as possible (not effective more than 2 wk after exposure). It is exclusively used for children younger than 12 mo old, immunocompromised hosts, those with chronic liver disease or in whom vaccine is contraindicated. Ig is preferred in patients older than 40 yr of age, with HAV

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**Table 358-3** Diagostic Blood Tests: Serology and Viral PCR

<table>
<thead>
<tr>
<th>HAV</th>
<th>HBV</th>
<th>HCV</th>
<th>HDV</th>
<th>HEV</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ACUTE/ACTIVE INFECTION</strong></td>
<td>Anti-HAV IgM(+)</td>
<td>Anti-HBc IgM(+)</td>
<td>Anti-HCV(+)</td>
<td>Anti-HDV IgM(+)</td>
</tr>
<tr>
<td>Blood PCR positive*</td>
<td>HBsAg(+)</td>
<td>HCV RNA(+) (PCR)</td>
<td>Blood PCR positive</td>
<td>HBsAg(+)</td>
</tr>
<tr>
<td><strong>PAST INFECTION (RECOVERED)</strong></td>
<td>Anti-HAV IgG(+)</td>
<td>Anti-HBs(+)</td>
<td>Anti-HCV(+)</td>
<td>Anti-HDV IgG(+)</td>
</tr>
<tr>
<td>Anti-HBc IgG(+)</td>
<td>Anti-HBc IgG(+)</td>
<td>Blood PCR(–)</td>
<td>Blood PCR (–)</td>
<td>Blood PCR (–)</td>
</tr>
<tr>
<td><strong>CHRONIC INFECTION</strong></td>
<td>Anti-HBc IgG(+)</td>
<td>Anti-HBsAg(+)</td>
<td>Anti-HCV(+)</td>
<td>Anti-HDV IgG(+)</td>
</tr>
<tr>
<td>N/A</td>
<td>Anti-HBsAg(+)</td>
<td>Blood PCR (–)</td>
<td>Blood PCR (–)</td>
<td>Blood PCR (–)</td>
</tr>
<tr>
<td><strong>VACCINE RESPONSE</strong></td>
<td>Anti-HAV IgG(+)</td>
<td>Anti-HBs(+)</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

*Research tool.

HAV, hepatitis A virus; HBs, hepatitis B surface; HBsAg, hepatitis B surface antigen; Ig, immunoglobulin; PCR, polymerase chain reaction.
Vaccine preferred in healthy persons 12 mo-40 yr old. An alternative approach is to immunize previously unvaccinated patients who are 12 mo old or older with the age-appropriate vaccine dosage as soon as possible. Ig is not routinely recommended for sporadic nonhousehold exposure (e.g., protection of hospital personnel or schoolmates). The vaccine has several advantages over Ig, including long-term protection, availability and ease of administration, with cost similar to, or less than, that of Ig.

Vaccine
The availability of 2 inactivated, highly immunogenic, and safe HAV vaccines has had a major impact on the prevention of HAV infection. Both vaccines are approved for children older than 12 mo. They are administered intramuscularly in a 2-dose schedule, with the 2nd dose given 6-12 mo after the 1st dose. Seroconversion rates in children exceed 90% after an initial dose and approach 100% after the 2nd dose; protective antibody titer persists for longer than 10 yr in the vast majority of patients. The immune response in immunocompromised persons, older patients, and those with chronic illnesses may be suboptimal; in those patients, combining the vaccine with Ig for pre- and postexposure prophylaxis is indicated. HAV vaccine may be administered simultaneously with other vaccines. A combination HAV and HBV vaccine is approved in adults older than age 18 yr. For healthy persons at least 12 mo old, vaccine is preferable to Ig for preexposure and postexposure prophylaxis (see Table 358-3).

In the United States and some other countries, universal vaccination is now recommended for all children older than 12 mo. Nevertheless, studies show <50% of U.S. adolescents have received 1 dose of the vaccine, and <30% have received the complete vaccine series. The vaccine is effective in curbing outbreaks of HAV because of rapid seroconversion and the long incubation period of the disease.

Prognosis
The prognosis for the patient with HAV is excellent, with no long-term sequelae. The only feared complication is ALF. HAV infection remains a major cause of morbidity; it has a high socioeconomic impact during epidemics and in endemic areas.

HEPATITIS B
Etiology
HBV is a member of the Hepadnaviridae family. HBV has a circular, partially double-stranded DNA genome composed of approximately 3,200 nucleotides. Four genes have been identified: the S (surface), C (core), X, and P (polymer) genes. The surface of the virus includes particles designated hepatitis B surface antigen (HBsAg), which is a 22 nm diameter spherical particle and a 22 nm wide tubular particle with a variable length of up to 200 nm. The inner portion of the virion contains hepatitis B core antigen (HBcAg), the nucleocapsid that encodes the viral DNA, and a nonstructural antigen called hepatitis B e antigen (HBeAg), a nonparticulate soluble antigen derived from HBcAg by proteolytic self-cleavage. HBeAg serves as a marker of active viral replication and usually correlates with HBV DNA levels. Replication of HBV occurs predominantly in the liver but also occurs in the lymphocytes, spleen, kidney, and pancreas.

Epidemiology
HBV has been detected worldwide, with an estimated 400 million persons chronically infected. The areas of highest prevalence of HBV infection are sub-Saharan Africa, China, parts of the Middle East, the Amazon basin, and the Pacific Islands. In the United States, the native population in Alaska had the highest prevalence rate before the implementation of universal vaccination programs. An estimated 1.25 million persons in the United States are chronic HBV carriers, with approximately 300,000 new cases of HBV occurring each year, the highest incidence being among adults 20-39 yr of age. One in 4 chronic HBV carriers will develop serious sequelae in their lifetime. The number of new cases in children reported each year is thought to be low but is difficult to estimate because many infections in children are asymptomatic. In the United States, since 1982 when the first vaccine for HBV was introduced, the overall incidence of HBV infection has been reduced by more than half. Since the implementation of universal vaccination programs in Taiwan and the United States, substantial progress has been made toward eliminating HBV infection in children in these countries. In fact, in Alaska, where HBV nears epidemic proportions, universal newborn vaccination with mass screening and immunization of susceptible Alaska Natives virtually eliminated symptomatic HBV and secondary hepatocellular carcinoma.

HBV is present in high concentrations in blood, serum, and serous exudates and in moderate concentrations in saliva, vaginal fluid, and semen. Efficient transmission occurs through blood exposure and sexual contact. Risk factors for HBV infection in children and adolescents include acquisition by intravenous drugs or blood products, contaminated needles used for acupuncture or tattoos, sexual contact, institutional care, and intimate contact with carriers. No risk factors are identified in approximately 40% of cases. HBV is not thought to be transmitted via indirect exposure, such as sharing toys.

### Table 358-4: Hepatitis A Virus Prophylaxis

<table>
<thead>
<tr>
<th>AGE</th>
<th>EXPECTED EXPOSURE DURATION</th>
<th>DOSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1 year of age</td>
<td>3 months</td>
<td>Ig 0.02 mL/kg</td>
</tr>
<tr>
<td>3-5 months</td>
<td></td>
<td>Ig 0.06 mL/kg</td>
</tr>
<tr>
<td>Long term (5 months)</td>
<td></td>
<td>Ig 0.06 mL/kg at departure and every 5 mo thereafter</td>
</tr>
<tr>
<td>≥1 year of age</td>
<td>Healthy host</td>
<td>HAV vaccine</td>
</tr>
<tr>
<td>Immunocompromised host, or one with chronic liver disease or chronic health problems</td>
<td></td>
<td>HAV vaccine and Ig 0.02 mL/kg</td>
</tr>
</tbody>
</table>

**POSTEXPOSURE PROPHYLAXIS**

<table>
<thead>
<tr>
<th>EXPOSURE</th>
<th>RECOMMENDATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤2 wk since exposure</td>
<td>&lt;1 year-old: Ig 0.02 mL/kg</td>
</tr>
<tr>
<td></td>
<td>Immunocompromised host, or host with chronic liver disease or chronic health problems: Ig 0.02 mL/kg and HAV vaccine</td>
</tr>
<tr>
<td></td>
<td>&gt;1 year and healthy host: HAV vaccine, Ig remains optional</td>
</tr>
<tr>
<td></td>
<td>Sporadic non–household or close contact exposure: prophylaxis not indicated*</td>
</tr>
<tr>
<td>&gt;2 wk since exposure</td>
<td>None</td>
</tr>
</tbody>
</table>

*Decision for prophylaxis in nonhousehold contacts should be tailored to individual exposure and risk. Ig, Immunoglobulin.
In children, the most important risk factor for acquisition of HBV remains perinatal exposure to an HBsAg-positive mother. The risk of transmission is greatest if the mother is also HBeAg-positive; up to 90% of these infants become chronically infected if untreated. Intrauterine infection occurs in 2.5% of these infants. In most cases, serologic markers of infection and antigenemia appear 1-3 mo after birth, suggesting that transmission occurred at the time of delivery. Virus contained in amniotic fluid or in maternal feces or blood may be the source. Immunoprophylaxis with hepatitis B immunoglobulin (HBIG) and the HBV vaccine, given within 12 hr of delivery is very effective in preventing infection and protects >95% of neonates born to HBsAg-positive mothers. Of the 22,000 infants born each year to HBsAg-positive mothers in the United States, >98% receive immunoprophylaxis and are thus protected. Infants who fail to receive the complete vaccination series (e.g., homeless children, international adoptees, and children born outside the United States), however, have the highest incidence of developing chronic HBV. These and all infants born to HBsAg-positive mothers should have follow-up HBsAg and anti-HBs tested to determine appropriate follow-up.

HBsAg is inconsistently recovered in human milk of infected mothers. Breastfeeding of nonimmunized infants by infected mothers does not confer a greater risk of hepatitis than does formula feeding.

The risk of developing chronic HBV infection, defined as being positive for HBsAg for longer than 6 mo, is inversely related to age of acquisition. In the United States, although <10% of infections occurs in children, these infections account for 20-30% of all chronic cases. This risk of chronic infection is 90% in children younger than 1 yr; the risk is 30% for those 1-5 yr and 2% for adults. Chronic infection is associated with the development of chronic liver disease and hepatocellular carcinoma. The carcinoma risk is independent of the presence of cirrhosis and was the most prevalent cancer-related death in young adults in Asia where HBV was endemic.

HBV has 8 genotypes (A-H). A is pandemic, B and C are prevalent in Asia, D is seen in Southern Europe, E in Africa, F in the United States, G in the United States and France, and H in Central America. Genetic variants have become resistant to antiviral agents. After infection, the incubation period ranges from 45-160 days, with a mean of approximately 120 days.

Pathogenesis
The acute response of the liver to HBV is the same as for all hepatotropic viruses. Persistence of histologic changes in patients with hepatitis B indicates development of chronic liver disease. HBV, unlike the other hepatotropic viruses, is a predominantly nontypopathogenic virus that causes injury mostly by immune-mediated processes. The severity of hepatic injury reflects the degree of the immune response, with the most complete immune response being associated with the greatest likelihood of viral clearance but also the most severe injury to hepatocytes. The 1st step in the process of acute hepatitis is infection of hepatocytes by HBV, resulting in expression of viral antigens on the cell surface. The most important of these viral antigens may be the nucleocapsid antigens HBCAg and HBeAg. These antigens, in combination with class I major histocompatibility proteins, make the cell a target for cytotoxic T-cell lysis.

The mechanism for development of chronic hepatitis is less well understood. To permit hepatocytes to continue to be infected, the core protein or major histocompatibility class I protein might not be recognized, the cytotoxic lymphocytes might not be activated, or some other, yet unknown mechanism might interfere with destruction of hepatocytes. This tolerance phenomenon predominates in the perinatally acquired cases, resulting in a high incidence of persistent infection in children with no or little inflammation in the liver, normal liver enzymes, and markedly elevated HBV viral load. Although end-stage liver disease rarely develops in those patients, the inherent hepatocellular carcinoma risk is very high, possibly related, in part, to uncontrolled viral replication cycles.

ALF has been seen in infants of chronic carrier mothers who have anti-HBe or are infected with a precore-mutant strain. This fact led to the postulate that HBeAg exposure in utero in infants of chronic carriers likely induces tolerance to the virus once infection occurs postnatally. In the absence of this tolerance, the liver is massively attacked by T cells and the patient presents with ALF.

Immune-mediated mechanisms are also involved in the extrahepatic conditions that can be associated with HBV infections. Circulating immune complexes containing HBsAg can result in polyarteritis nodosa, membranous or membranoproliferative glomerulonephritis, polymyalgia rheumatica, leukocytoclastic vasculitis, and Guillain-Barré syndrome.

Clinical Manifestations
Many acute cases of HBV infection in children are asymptomatic, as evidenced by the high carriage rate of serum markers in persons who have no history of acute hepatitis. The usual acute symptomatic episode is similar to that of HAV and HCV infections but may be more severe and is more likely to include involvement of skin and joints (Fig. 358-2). The first biochemical evidence of HBV infection is elevation of serum ALT levels, which begin to rise just before development of fatigue, anorexia, and malaise, which occurs approximately 6-7 wk after exposure. The illness is preceded in a few children by a viral sickness–like prodrome marked by arthralgia or skin lesions, including urticarial, purpuric, macular, or maculopapular rashes. Poplar acrodermatitis, the Gianotti-Crosti syndrome, can also occur. Other extrahepatic conditions associated with HBV infections in children include polyarteritis nodosa, glomerulonephritis, and aplastic anemia. Jaundice is present in approximately 25% of acutely infected patients and usually begins approximately 8 wk after exposure and lasts approximately 4 wk.

In the usual course of resolving HBV infection, symptoms are present for 6-8 wk. The percentage of children in whom clinical evidence of hepatitis develops is higher for HBV than for HAV, and the rate of ALF is also greater. Most patients do recover, but the “chronic carrier state” complicates up to 10% of cases acquired in adulthood. The rate of development of chronic infection depends largely on the mode and age of acquisition and occurs in up to 90% of perinatal cases. Chronic hepatitis, cirrhosis, and hepatocellular carcinoma are only seen with chronic infection. Chronic HBV infection has 3 identified phases: immune tolerant, immune active, and inactive. Most children fall in the immune-tolerant phase, against which no effective therapy has been developed. Most treatments target the immune active phase of the disease, characterized by active inflammation, elevated ALT/AST levels, and progressive fibrosis. Spontaneous HBeAg seroconversion, defined as the development of anti-HBe and becoming HBeAg-negative, occurs in the immune-tolerant phase, albeit at low rates of 4-5% per year. It is more common in childhood-acquired HBV rather than in vertically transmitted infections. Seroconversion can occur over many years, during which time significant damage to
the liver may take place. There are no large studies that help accurately assess the lifetime risks and morbidities of children with chronic HBV infection, making the timing of still less-than-ideal treatments ever so hard to decide. Reactivation of chronic infection has been reported in immunosuppressed children (treated with chemotherapy, biologic immunomodulators such as infliximab, T-cell depleting agents), leading to an increased risk of ALF or to rapidly progressing fibrotic liver disease.

Diagnosis
The serologic profile of HBV infection is more complex than for HAV infection and differs depending on whether the disease is acute or chronic (Fig. 358-3). Several antigens and antibodies are used to confirm the diagnosis of acute HBV infection (see Table 358-3). Routine screening for HBV infection requires assay of multiple serologic markers (HBsAg, anti-HBe, anti-HBs). HBsAg is the first serologic marker of infection to appear and is found in almost all infected persons; its rise closely coincides with the onset of symptoms. Persistence of HBsAg beyond 6 mo defines the chronic infection state. During recovery from acute infection, because HBsAg levels fall before symptoms wane, IgM antibody to HBCAg (anti-HBc IgM) might be the only marker of acute infection. Anti-HBe IgM rises early after the infection and remains positive for many months before being replaced by anti-HBc IgG, which then persists for years. Anti-HBc is therefore a valuable serologic marker of acute HBV infection. Anti-HBs marks serologic recovery and protection. Only anti-HBs is present in persons immunized with hepatitis B vaccine, whereas both anti-HBs and anti-HBc are detected in persons with resolved infection. HBeAg is present in active acute or chronic infection and is a marker of infectivity. The development of anti-HBe, termed seroconversion, marks improvement, and the emergence of a mutant viral strain (YMDD) poses a barrier to its long-term use. Combination therapy in children using IFN and lamivudine did not seem to improve the rates of response in most series.

Lamivudine is an oral synthetic nucleoside analog that inhibits the viral enzyme reverse transcriptase. In children older than age 2 yr, its use for 52 wk resulted in HBeAg clearance in 34% of patients with an ALT > 2 times normal; 88% remained in remission at 1 yr. It has a good safety profile. Lamivudine has to be used for ≥26 mo after viral clearance, and the emergence of a mutant viral strain (YMDD) poses a barrier to its long-term use. Combination therapy in children using IFN and lamivudine did not seem to improve the rates of response in most series.

Adefovir is a purine analog that inhibits viral replication is approved for use in children older than 12 yr of age, in whom a prospective 1-year study showed 23% seroconversion. No viral resistance was noted in that study but has been reported in adults.

Entecavir is an oral synthetic nucleoside analog that inhibits replication) is approved for use in children older than age 16 yr. Prospective data has shown a 21% seroconversion rate in adults with minimal resistance developing. Patients in whom resistance to lamivudine developed, have an increased risk of resistance developing to entecavir.

Tenaflovir is a nucleotide analog that inhibits viral replication is also approved for use in children older than age 16 yr. Data have shown efficacy in children older than age 12 yr. Prospective data have shown a 21% seroconversion rate with a very low rate of resistance developing. Patients with lamivudine-resistant mutations do not appear to have an increased rate of resistance. Concern exists over long-term use and bone mineral density.

PEGinterferon-α, has the same mechanism of action as IFN, but is given once weekly. This formulation has not been approved in the United States but is recommended for the treatment of chronic HBV in other countries. Patients most likely to respond to currently available drugs have low serum HBV DNA titers, are HBeAg-positive, have active hepatic inflammation (ALT greater than twice the upper limit of normal for at least 6 mo), and recently acquired disease.

Immune tolerant patients—those with normal ALT and AST, who are HBsAg-positive with elevated viral load—are currently not considered for treatment, although the emergence of new treatment
deposition of complement and HBeAg in glomerular capillaries is a rare complication of HBV infection.

Treatment
Treatment of acute HBV infection is largely supportive. Close monitoring for liver failure and extrahepatic morbidities is key.

Treatment of chronic HBV infection is in evolution; no one drug currently achieves consistent, complete eradication of the virus. The natural history of chronic HBV in children is complex, and there is a lack of reliable long-term outcome data on which to base treatment recommendations. Treatment of chronic HBV infection in children should be individualized and done under the care of a pediatric gastroenterologist experienced in treating liver disease.

The goal of treatment is to reduce viral replication defined by having undetectable HBV DNA in the serum and development of anti-HBe, termed seroconversion. The development of anti-HBe transforms the disease into an inactive form, thereby decreasing infectivity, active liver injury and inflammation, fibrosis progression, and the risk of hepatocellular carcinoma.

Currently, treatment is only indicated for patients in the immune-active form of the disease, as evidenced by elevated ALT and/or AST, who have fibrosis on liver biopsy, putting the child at higher risk for cirrhosis during childhood.

Treatment Strategies
Interferon-α2b (IFN-α2b) has immunomodulatory and antiviral effects. It has been used in children, with long-term viral response rates similar to the 25% rate reported in adults. Interferon (IFN) use is limited by its subcutaneous administration, treatment duration of 24 wk, and possible side effects (flu-like symptoms, marrow suppression, depression, retinal changes, autoimmune disorders). IFN is further contraindicated in decompensated cirrhosis. One advantage of IFN, compared to other treatments, is that viral resistance does not develop with its use.

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Immune tolerant patients—those with normal ALT and AST, who are HBsAg-positive with elevated viral load—are currently not considered for treatment, although the emergence of new treatment
paradigms are promising for this large, yet hard-to-treat, subgroup of patients.

Prevention
The most effective prevention strategies have resulted from the screening of pregnant mothers and the use of HBIG and hepatitis B vaccine in infants as noted earlier. In HBsAg-positive and HBeAg-positive mothers, a 10% risk of chronic HBV infection exists compared to 1% in HBeAg-negative mothers. This knowledge offers screening strategies that may affect both mother and infant through the use of antiviral medications during the 3rd trimester. Recent guidelines suggest that mothers with a HBV DNA viral load >200,000 IU/mL receive an antiviral such as telbivudine, lamivudine, or tenofovir during the 3rd trimester, especially if they had a previous child who developed chronic HBV after receiving HBIG and the hepatitis B vaccine.

Household, sexual, and needle-sharing contacts should be identified and vaccinated if they are susceptible to HBV infection. Patients should be advised about the perinatal and intimate contact risk of transmission of HBV. HBV is not spread by breastfeeding, kissing, hugging, or sharing water or utensils. Children with HBV should not be excluded from school, play, childcare, or work, unless they are prone to biting. A support group might help children to cope better with their disease. Families should not feel obligated to disclose the diagnosis as this information may lead to prejudice or mistreatment of the patient or the patient's family. All patients positive for HBsAg should be reported to the state or local health department, and chronicity is diagnosed if they remain positive past 6 mo.

Hepatitis B Immunoglobulin
HBIG is indicated only for specific postexposure circumstances and provides only temporary protection (3-6 mo; Table 358-5). It plays a pivotal role in preventing perinatal transmission when administered within 12 hr of birth.

Universal Vaccination
In 2005, the Centers for Disease Control and Prevention Advisory Committee on Immunization Practices revised its recommendations regarding HBV vaccination. These recommendations have been incorporated into the American Academy of Pediatrics Vaccine schedule. A main focus is universal infant vaccination, beginning at birth, to provide a safety net for preventing perinatal infection, prevent early childhood infection, facilitate implementation of universal vaccine recommendations, and prevent infection in adolescents and adults. The ultimate goal is to eliminate HBV transmission in the United States and integrate HBV vaccination in a harmonized childhood vaccination.

Two single-antigen vaccines (Recombivax HB and Engerix-B) are approved for children and are the only preparations approved for infants younger than age 6 mo. Three combination vaccines can be used for subsequent immunization dosing and enable integration of the HBV vaccine into the regular immunization schedule. The safety profile of HBV vaccine is excellent. The most reported side effects are pain at the injection site (up to 29% of cases) and fever (up to 6% of cases). Seropositivity is >95% with all vaccines, achieved after the 2nd dose in most patients. The 3rd dose serves as a booster and may have an effect on maintaining long-term immunity. In immunosuppressed patients and infants whose birthweight is <2,000 g, a 4th dose is recommended, as is checking for seroconversion. Despite declines in the anti-HBs titer in time, most healthy vaccinated persons remain protected against HBV infection.

Current HBV vaccination recommendations are as follows (see Table 358-5):

- Infants born to HBsAg-negative mothers:
  - For all medically stable infants weighing >2,000 g at birth and born to HBsAg-negative mothers, the 1st dose of HBV vaccine should be administered before hospital discharge. Single-dose antigen HBV vaccine should be used for the birth dose. Subsequent doses to complete the series are given at 1-4 mo and at 6-18 mo of age. Routine postvaccination testing of immunized infants born to HBsAg-negative women or with anti-HBs is not recommended.
  - In rare circumstances (on a case-by-case basis), the 1st dose may be delayed (up to 2 mo) until after hospital discharge. When a decision to delay is made, however, a physician’s order to withhold the birth dose, along with a copy of the original laboratory report indicating that the mother was HBsAg-negative, should be placed on the medical record.

<table>
<thead>
<tr>
<th>Table 358-5</th>
<th>Indications and Dosing Schedule for Hepatitis B Vaccine and Hepatitis B Immunoglobulin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>VACCINE DOSE</strong></td>
<td><strong>SCHEDULE</strong></td>
</tr>
<tr>
<td><strong>RECOMBIVAX HB (µg)</strong></td>
<td><strong>ENGEX-B (µg)</strong></td>
</tr>
<tr>
<td><strong>UNIVERSAL PROPHYLAXIS</strong></td>
<td></td>
</tr>
<tr>
<td>Infants of HBsAg(-) women</td>
<td>5</td>
</tr>
<tr>
<td>Children and adolescents (11-19 yr old)</td>
<td>5</td>
</tr>
<tr>
<td><strong>POSTEXPOSURE PROPHYLAXIS IN SUSCEPTIBLE INDIVIDUALS</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Contact with HBsAg(+) Source</strong></td>
<td></td>
</tr>
<tr>
<td>Infants of HBsAg(+) women</td>
<td>5</td>
</tr>
<tr>
<td><strong>Intimate or Identifiable Blood Exposure</strong></td>
<td></td>
</tr>
<tr>
<td>0-19 yr old</td>
<td>5</td>
</tr>
<tr>
<td>&gt;19 yr old</td>
<td>10</td>
</tr>
<tr>
<td><strong>Household</strong></td>
<td></td>
</tr>
<tr>
<td>0-19 yr old</td>
<td>5</td>
</tr>
<tr>
<td>&gt;19 yr old</td>
<td>10</td>
</tr>
<tr>
<td>Casual†</td>
<td>None</td>
</tr>
<tr>
<td>Immunocompromised‡</td>
<td>40</td>
</tr>
<tr>
<td><strong>Contact with Unknown HBsAg Status; Intimate or Identifiable Blood Exposure</strong></td>
<td></td>
</tr>
<tr>
<td>&gt;19 yr old</td>
<td>10</td>
</tr>
<tr>
<td>Immunocompromised‡</td>
<td>40</td>
</tr>
</tbody>
</table>

*Both HBIG and vaccine should be administered within 12 hr of the infant’s birth and within 24 hr of identifiable blood exposure. HBIG can be given up to 14 days after sexual exposure.
‡HBIG dose: 0.5 µL for newborns of HBsAg-positive mothers, and 0.06 µL/kg for all others when recommended.
§Seroconversion status of immunocompromised patients should be checked 1-2 mo after the last dose of vaccine, and yearly thereafter. Booster doses of vaccine should be administered if the anti-HBs titer is <10 mIU/mL. Nonresponsive patients should be considered at high risk for HBV acquisition and counseled about preventive measures.
HBs, hepatitis B surface; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus.

Immunocompromised‡ | 40 | 40 |
• Preterm infants weighing <2,000 g at birth and born to HBsAg-negative mothers should have their initial dose delayed until 1 mo of age or before hospital discharge.

• To increase coverage of children and adolescents not previously vaccinated, many states have made immunization a requirement for entry into junior high school (middle school).

• Infants born to HBsAg-positive or HBsAg-unknown mothers:
  • To prevent perinatal transmission through improved maternal screening and immunoprophylaxis, infants born to HBsAg-positive women should receive vaccine at birth, 1–2 mo, and 6 mo of age (see Table 358-4). The 1st dose should be accompanied by administration of 0.5 mL of HBIG as soon after delivery as possible (within 12 hr) because the effectiveness decreases rapidly with increased time after birth.
  • If mother’s HBsAg status is unknown, the vaccine should be administered within 12 hr of birth regardless of birthweight. For infants weighing <2,000 g, HBIG and the HBV vaccine should be administered within 12 hr of birth. The mother’s HBsAg status should be administered as soon as possible and, if she is HBsAg-positive, HBIG should be given for infants weighing ≥2,000 g (no later than age 1 wk).

Postvaccination testing for HBsAg and anti-HBs should be done at 9–18 mo. If the result is positive for anti-HBs, the child is immune to HBV. If the result is positive for HBsAg only, the parent should be counseled and the child evaluated by a pediatric gastroenterologist. If the result is negative for both HBsAg and anti-HBs, a second complete hepatitis B vaccine series should be administered, followed by testing for anti-HBs to determine if subsequent doses are needed.

Administration of 4 doses of vaccine is permissible when combination vaccines are used after the birth dose; this does not increase vaccine response.

Postexposure Prophylaxis

Recommendations for postexposure prophylaxis for prevention of hepatitis B infection depend on the conditions under which the person is exposed to HBV (see Table 358-5). Vaccination should never be postponed if written records of the exposed person’s immunization history are not available, but every effort should still be made to obtain those records.

Special Populations

Patients with cirrhosis may not respond as well to the HBV vaccine and repeating anti-HBs titers should be performed. Adult studies suggest higher dosage or shorter interval between dosages may increase the immunization effectiveness. Recent evidence has shown patients with inflammatory bowel disease frequently have not been immunized, or did not develop complete immunity to HBV, as demonstrated by inadequate anti-HBs levels. These patients may be at risk for fulminant HBV when immunosuppression is started as part of their treatment regimen, specifically with biologic agents such as infliximab.

Prognosis

In general, the outcome after acute HBV infection is favorable, despite a risk of ALF. The risk of developing chronic infection brings the risks of liver cirrhosis and hepatocellular carcinoma to the forefront. Perinatal transmission leading to chronicity is responsible for the high incidence of hepatocellular carcinoma in young adults in endemic areas. Importantly, HBV infection and its complications are effectively controlled and prevented with vaccination and multiple clinical trials are ongoing in an effort to improve and guide treatment regimens.

HEPATITIS C

Etiology

HCV is a single-stranded RNA virus, classified as a separate genus within the Flaviviridae family, with marked genetic heterogeneity. It has 6 major genotypes and numerous subtypes and quasi-species, which permit the virus to escape host immune surveillance. Genotype variation might partially explain the differences in clinical course and response to treatment. Genotype 1b is the most common genotype in the United States and is the least responsive to the currently available medications.

Epidemiology

In the United States, HCV infection is the most common cause of chronic liver disease in adults and causes 8,000–10,000 deaths per year. Approximately 4 million people in the United States and 170 million people worldwide are estimated to be infected with HCV. Approximately 85% of infected adults remain chronically infected. In children, seroprevalence of HCV is 0.2% in those younger than age 11 yr and 0.4% in children age 11 yr or older. However, even more children may be infected as only a small percentage of HCV-infected children are identified, and an even smaller number subsequently receive treatment. Appropriate identification, and screening, for infected individuals should be implemented.

Risk factors for HCV transmission in the United States included blood transfusion before 1992 as the most common route of infection, but, with current screening practices, the risk of HCV transmission is approximately 0.001% per unit transfused. Illegal drug use with exposure to blood or blood products from HCV-infected persons accounts for more than half of adult cases in the United States. Sexual transmission, especially through multiple sexual partners, is the second most common cause of infection. Other risk factors include occupational exposure, but approximately 10% of new infections have no known transmission source. In children, perinatal transmission is the most prevalent mode of transmission (see Table 358-1). Perinatal transmission occurs in up to 5% of infants born to viremic mothers. HIV coinfection and high viremia titers (HCV RNA-positive) in the mother can increase the transmission rate to 20%. The incubation period is 7–9 wk (range: 2–24 wk).

Pathogenesis

The pattern of acute hepatic injury is indistinguishable from that of other hepatotropic viruses. In chronic cases, lymphoid aggregates or follicles in portal tracts are found, either alone or as part of a general inflammatory infiltrate of the portal areas. Steatosis is also often seen in these liver specimens. HCV appears to cause injury primarily by cytopathic mechanisms, but immune-mediated injury can also occur. The cytopathic component appears to be mild, because the acute illness is typically the least severe of all hepatotropic virus infections.

Clinical Manifestations

Acute HCV infection tends to be mild and insidious in onset (Fig. 358-4; see also Table 358-1). ALF rarely occurs. HCV is the most likely
hepatotropic virus to cause chronic infection (Fig. 358-5). Of affected adults, <15% clear the virus; the rest develop chronic hepatitis. In pediatric studies, 6-19% of children achieved spontaneous sustained clearance of the virus during a 6 yr follow-up.

**Chronic HCV infection** is also clinically silent until a complication develops. Serum aminotransferase levels fluctuate and are sometimes normal, but histologic inflammation is universal. Progression of liver fibrosis is slow over several years, unless comorbid factors are present, which can accelerate fibrosis progression. Approximately 25% of infected patients ultimately progress to cirrhosis, liver failure, and, occasionally, primary hepatocellular carcinoma (HCC) within 20-30 yr of the acute infection. Although progression is rare within the pediatric age range, cirrhosis and HCC from HCV have been reported in children. The long-term morbidities constitute the rationale for diagnosis and treatment in children with HCV.

Chronic HCV infection can be associated with small vessel vasculitis and is a common cause of essential mixed cryoglobulinemia. Other extrahepatic manifestations, predominantly seen in adults, include cutaneous vasculitis, peripheral neuropathy, cerebritis, membranoproliferative glomerulonephritis, and nephrotic syndrome. Antibodies to smooth muscle, antinuclear antibodies, and low thyroid hormone levels may also be present.

**Diagnosis**

Clinically available assays for detection of HCV infection are based on detection of antibodies to HCV antigens or detection of viral RNA (see Table 358-3); neither can predict the severity of liver disease.

The most widely used serologic test is the third-generation enzyme immunoassay to detect anti-HCV. The predictive value of this assay is greatest in high-risk populations, but the false-positive rate can be as high as 50-60% in low-risk populations. False-negative results also occur because antibodies remain negative for as long as 1-3 mo after clinical onset of illness. Anti-HCV is not a protective antibody and does not confer immunity; it is usually present simultaneously with the virus.

The most commonly used virologic assay for HCV is a PCR assay, which permits detection of small amounts of HCV RNA in serum and tissue samples within days of infection. The qualitative PCR detection is especially useful in patients with recent or perinatal infection, hypogammaglobulinemia, or immunosuppression and is very sensitive. The quantitative PCR aids in identifying patients who are likely to respond to therapy and in monitoring response to therapy.

**Screening** for HCV should include all patients with the following risk factors: history of illegal drug use (even if only once), receiving clotting factors made before 1987 (when inactivation procedures were introduced) or blood products before 1992, hemodialysis, idiopathic liver disease, and children born to HCV-infected women (qualitative PCR in infancy and anti-HCV after 12-18 mo of age). In children, it is also important to consider whether the mother has any of the risk factors noted above that would increase her possibility of developing HCV. Routine screening of all pregnant women is not recommended. The Centers for Disease Control, did however, recommend in 2012 that all individuals born between 1945 and 1965 be screened.

Determining HCV genotype is also important, particularly when therapy is considered, because the response to the current therapeutic agents varies greatly. Genotype 1 is poorly responsive; genotypes 2 and 3 are more reliably responsive to therapy (as discussed later).

Aminotransferase levels typically fluctuate during HCV infection and do not correlate with the degree of liver fibrosis.

A liver biopsy is the only means to assess the presence and extent of hepatic fibrosis, outside of overt signs of chronic liver disease. A liver biopsy is indicated only before starting any treatment and to rule out other causes of overt liver disease.

**Complications**

The risk of ALF caused by HCV is low, but the risk of chronic hepatitis is the highest of all the hepatotropic viruses. In adults, risk factors for progression to hepatic fibrosis include older age, obesity, male sex, and even moderate alcohol ingestion (two 1 oz drinks per day). Progression to cirrhosis or HCC is a major cause of morbidity and the most common indication for liver transplantation in adults in the United States.

**Treatment**

In adults, peginterferon (subcutaneous, weekly) combined with ribavirin (oral, daily) was standard therapy until 2012 for genotype 1. Currently recommended first-line adult therapy for genotype 1 includes these 2 medications with the use of sofosbuvir, an oral, direct-acting antiviral agent, for only 12 wk or an oral regimen of sofosbuvir, simeprevir, and possibly ribavirin. Ongoing studies suggest that future treatments will be even more effective, with fewer side effects.

Traditionally, patients most likely to respond had mild hepatitis, shorter duration of infection, low viral titers and either genotype 2 or 3 virus. Patients with genotype 1 virus responded poorly. Response to peginterferon alfa/ribavirin may be predicted by single-nucleotide polymorphisms near the interleukin 28B gene, but with these newer treatment regimens excellent response rates are being reported with shorter duration, IFN-free regimens. The goal of treatment is to achieve a sustained viral response (SVR), as defined by the absence of viremia 6 mo after stopping the medications; SVR is associated with improved histology and decreased risk of morbidities.

The natural history of HCV infection in children is still being defined. It is believed that children have a higher rate of spontaneous clearance than adults (up to 45% by age 19 yr). A multicenter study followed 359 children infected with HCV over 10 yr. Only 7.5% had cleared the virus, and 1.8% progressed to decompensated cirrhosis. Treatment in adults with acute HCV in a pilot study showed an 88% SVR in genotype 1 subjects (treated with IFN and ribavirin for 24 wk). Such data, if confirmed, could actually raise the question whether children, with shorter duration of infection and fewer comorbid conditions than their adult counterparts, could be “ideal” candidates for treatment. Given the adverse effects of currently available therapy, this strategy is not recommended outside of clinical trials.

Peginterferon (Scherin), IFN-α2b, and ribavirin are approved by the FDA for use in children older than 3 yr of age with HCV hepatitis. Studies of IFN monotherapy in children demonstrated a higher SVR than in adults, with better compliance and fewer side effects. An SVR up to 49% for genotype 1 was achieved in multiple studies. Factors associated with a higher likelihood of response are age younger than 12 yr, genotypes 2 and 3, and, in patients with genotype 1b, an RNA titer of <2 million copies/mL of blood, and viral response (PCR at weeks 4 and 12 of treatment). Side effects of medications lead to discontinuation of treatment in a high proportion of patients; these include influenza-like symptoms, anemia, and neutropenia. Long-term
effects of these medicines also need to be evaluated as significant differences were noted in children’s weight, height, body mass index, and body composition. Most of these delays improved following cessation of treatment, but height z-scores continued to lag behind.

Treatment should be considered for all children infected with genotypes 2 and 3, because they have an 80-90% response rate to therapy with peginterferon and ribavirin. If the child has genotype 1b virus, the treatment choice remains more controversial. Pediatric guidelines recommend treatment to eradicate HCV infection, prevent progression of liver disease and development of HCC, and to remove the stigma associated with HCV. Treatment should be considered for patients with evidence of advanced fibrosis or injury on liver biopsy. The currently approved treatment consists of 48 wk of peginterferon and ribavirin (therapy should be stopped if still detectable on viral PCR at 24 wk of therapy). Treatment of children with normal biochemical profile and mild histologic inflammation should be reserved to a clinical study context.

Newer Treatments
Peginterferon and direct-acting antivirals, including telaprevir and boceprevir (viral protease inhibitors), demonstrated a much improved SVR rate in adults. Telaprevir and boceprevir were the first direct-acting antiviral agents approved to combat hepatitis C. Newer medications, including sofosbuvir and simeprevir, have already replaced telaprevir and boceprevir as the treatment of choice for hepatitis C genotype 1. Studies are pending in pediatrics. Combination therapy schemes and staggered therapy is also being explored in adults. Interleukin 28B, a host marker of immune responsiveness, has also been evaluated to predict host response to treatment with standard peginterferon and ribavirin, but will become even less important as IFN free regimens become standard practice. Varying IFN-free regimens are now available for all HCV genotypes allowing even greater likelihood of achieving viral eradication, with completely oral medication regimens, and without the use of IFN and its attendant side effects. With the rapid development of new medications and regimens, frequent review of up-to-date resources, such as www.hcvguidelines.org, will be vital to provide optimal care.

Prevention
No vaccine is yet available to prevent HCV, although ongoing research suggests this will be possible in the future. Current Ig preparations are not beneficial, likely because Ig preparations produced in the United States do not contain antibodies to HCV because blood and plasma donors are screened for anti-HCV and excluded from the donor pool. Broad neutralizing antibodies to HCV were found to be protective and might pave the road for vaccine development.

Once HCV infection is identified, patients should be screened yearly with a liver ultrasound and serum α-fetoprotein for HCC, as well as for any clinical evidence of liver disease. Vaccinating the affected patient against HAV and HBV will prevent superinfection with these viruses and the increased risk of developing severe liver failure.

Prognosis
Viral titers should be checked yearly to document spontaneous remission. Most patients develop chronic hepatitis. Progressive liver damage is higher in those with additional comorbid factors such as alcohol consumption, viral genotypic variations, obesity, and underlying genetic predispositions. Referral to a pediatric gastroenterologist is strongly advised to take advantage of up-to-date monitoring regimens and to optimize their enrollment in treatment protocols when available.

HEPATITIS D
Etiology
Hepadnavirus, the smallest known animal virus, is considered defective because it cannot produce infection without concurrent HBV infection. The 36 nm diameter virus is incapable of making its own coat protein; its outer coat is composed of excess HBsAg from HBV. The inner core of the virus is single-stranded circular RNA that expresses the HDV antigen.

Epidemiology
HDV can cause an infection at the same time as the initial HBV infection (coinfection), or HDV can infect a person who is already infected with HBV (superinfection). Transmission usually occurs by intrafamilial or intimate contact in areas of high prevalence, which are primarily developing countries (see Table 358-1). In areas of low prevalence, such as the United States, the parenteral route is far more common. HDV infections are uncommon in children in the United States but must be considered when ALF occurs. The incubation period for HDV superinfection is approximately 2-8 wk; with coinfection, the incubation period is similar to that of HBV infection.

Pathogenesis
Liver pathology in HDV hepatitis has no distinguishing features except that damage is usually quite severe. In contrast to HBV, HDV causes injury directly by cytopathic mechanisms. The most severe cases of HBV infection appear to result from coinfection of HBV and HDV.

Clinical Manifestations
The symptoms of hepatitis D infection are similar to, but usually more severe than those of the other hepatotropic viruses. The clinical outcome for HDV infection depends on the mechanism of infection. In coinfection, acute hepatitis, which is much more severe than for HBV alone, is common, but the risk of developing chronic hepatitis is low. In superinfection, acute illness is rare and chronic hepatitis is common. The risk of ALF is highest in superinfection. Hepatitis D should be considered in any child who experiences ALF.

Diagnosis
HDV has not been isolated and no circulating antigen has been identified. The diagnosis is made by detecting IgM antibody to HDV; the antibodies to HDV develop approximately 2-4 wk after coinfection and approximately 10 wk after a superinfection. A test for anti-HDV antibody is commercially available. PCR assays for viral RNA are available as research tools (see Table 358-2).

Complications
HDV must be considered in all cases of ALF. Coinfection with HBV can also result in a more severe chronic disease.

Treatment
The treatment is based on supportive measures once an infection is identified. There are no specific HDV-targeted treatments to date. The treatment is mostly based on controlling and treating HBV infection, without which HDV cannot induce hepatitis. Small research studies suggest that IFN is the preferred treatment regimen, but ongoing studies still seek the ideal management strategy and the regimen should be personalized for each patient.

Prevention
There is no vaccine for hepatitis D. Because HBV replication cannot occur without hepatitis B coinfection, immunization against HBV also prevents HDV infection. Hepatitis B vaccines and HBIG are used for the same indications as for hepatitis B alone.

HEPATITIS E
Etiology
HEV has been cloned using molecular techniques. This RNA virus has a nonenveloped sphere shape with spikes and is similar in structure to the caliciviruses.

Epidemiology
Hepatitis E is the epidemic form of what was formerly called non-A, non-B hepatitis. Transmission is fecal–oral (often waterborne) and is associated with shedding of 27-34 nm particles in the stool (see Table 358-1). The highest prevalence of HEV infection has been reported in the Indian subcontinent, the Middle East, Southeast Asia, and Mexico, especially in areas with poor sanitation. The prevalence, however, appears to be increasing in the United States and other developed
HEV is associated with a high risk of death in pregnant women. No other complications are recognized in association with this virus.

Diagnosis
Recombinant DNA technology has resulted in development of antibodies to HEV particles, and IgM and IgG assays are available to distinguish between acute and resolved infections (see Table 358-3). IgM antibody to viral antigen becomes positive after approximately 1 wk of illness. Viral RNA can be detected in stool and serum by PCR.

Prevention
A recombinant hepatitis E vaccine is highly effective in adults. No evidence suggests that Ig is effective in preventing HEV infections. Ig pooled from patients in endemic areas might prove to be effective.

Pathogenesis
HEV appears to act as a cytopathic virus. The pathologic findings are similar to those of the other hepatitis viruses.

Clinical Manifestations
The clinical illness associated with HEV infection is similar to that of HAV but is often more severe. As with HAV, chronic illness does not occur. In addition to often causing a more severe episode than HAV, HEV tends to affect older patients, with a peak age between 15 and 34 yr. HEV is a major pathogen in pregnant women, in whom it causes ALF with a high fatality incidence. HEV could also lead to decompensation of pre-existing chronic liver disease.
**APPROACH TO ACUTE OR CHRONIC HEPATITIS**

Although new treatment modalities for chronic viral hepatitis are continuously being developed and treatment outcomes have improved, the major medical breakthrough in regard to the pediatric population is prevention, with the availability of effective and safe vaccines for the HAV and HBV infections. The availability of more sensitive and reliable diagnostic tools may lead to improved care for affected patients. The primary care physician is at the forefront of the care and control of patients exposed to these viruses. Aggressive perinatal, childhood, and adolescent immunization strategies have already had a major impact in endemic HAV and HBV areas.

Identifying deterioration of the patient with acute hepatitis and the development of ALF is a major contribution of the primary pediatrician (Fig. 358-6). If ALF is identified, the clinician should immediately refer the patient to a transplantation center; this can be lifesaving.

Once chronic infection is identified, close follow-up and referral to a pediatric gastroenterologist is recommended to enroll the patient in appropriate treatment trials. Treatment of chronic HBV and HCV in children should preferably be delivered within, or using data from pediatric controlled trials as indications, timing, regimen, and outcomes remain to be defined and cannot simply be extrapolated from adult data. All patients with chronic viral hepatitis should avoid, as much as possible, further insult to the liver: HAV vaccine is recommended; patients must avoid alcohol consumption and obesity, and they should exercise care when taking new medications, including nonprescription drugs and herbal medications.

International adoption and ease of travel continue to change the epidemiology of hepatitis viruses. In the United States, chronic HBV and HCV have a high prevalence among international adoptee patients; vigilance is required to establish early diagnosis in order to offer appropriate treatment as well as prophylactic measures to limit viral spread.

Chronic hepatitis can be a stigmatizing disease for children and their families. The pediatrician should offer, with proactive advocacy, appropriate support for them as well as needed education for their social circle. Scientific data and information about support groups are available for families on the websites for the American Liver Foundation (www.liverfoundation.org) and the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (www.naspghan.org), as well as through pediatric gastroenterology centers.

*Bibliography is available at Expert Consult.*
Bibliography

Hepatitis A


Hepatitis B


Hepatitis C


Hepatitis C


Chapter 359
Liver Abscess
Robert M. Kliegman

Pyogenic liver abscesses are rare in children, with an incidence of 10/100,000 hospitalizations. Pyogenic hepatic abscesses can be caused by bacteria entering the liver via the portal circulation in cases of omphalitis, portal vein pylephlebitis, intraabdominal infection, or abscess secondary to appendicitis or inflammatory bowel disease; a primary bacteremia (sepsis, endocarditis); ascending cholangitis associated with biliary tract obstruction caused by gallstones or sclerosing cholangitis, after a Kasai procedure, or secondary to choledochal cysts; contiguous infection (subphrenic abscess) or penetrating trauma; and cryptogenic biliary tract infections. Very rarely, liver abscesses occur after percutaneous liver biopsy. Hepatic abscesses can also occur in neonates in association with sepsis, umbilical vein associated infection, or cannulation; 50% are seen in children younger than 6 yr old. In adults with pyogenic liver abscesses, liver transplantation is a significant risk factor; it is not known if pediatric liver transplant patients are also at increased risk. Children with chronic granulomatous disease, Job syndrome, or cancer are also at increased risk for a hepatic abscess.

In children with pyogenic liver abscesses, the most common pathogenic organisms include *Staphylococcus aureus*, *Streptococcus* spp.; *Escherichia coli*, *Klebsiella pneumoniae*, *Salmonella*, and anaerobic organisms; *Entamoeba histolytica* or *Toxocara canis*-associated liver abscesses have also been reported in developing countries or in highly endemic areas.

Amebic disease is rare in the United States and is associated with immigrants from or travel to highly endemic areas. Recovery of *E. histolytica* from the stool is pathogenic and highly suggestive of an amebic abscess, but this must be distinguished from *Entamoeba dispar*, which looks similar but is nonpathogenic; antiamebic antibodies help identify *E. histolytica*. Multiple microabscesses can be seen secondary to bacteremia, candidemia, or cat scratch disease. Polymicrobial involvement is seen in approximately 50%; cryptogenic abscesses are often monomicrobial with *S. aureus* as the lead single agent in children without underlying liver or intestinal tract disease.

Signs and symptoms are nonspecific and can include fever, chills, night sweats, malaise, fatigue, nausea, abdominal pain with right upper quadrant tenderness, and hepatomegaly; jaundice is uncommon. Diagnosis can be challenging and is often delayed; a high index of suspicion is necessary in children with risk factors. Serum aminotransferase and more often the alkaline phosphatase levels are elevated. The erythrocyte sedimentation rate is high, and leukocytosis is common. The results of blood cultures are positive in 50% of patients. Chest x-rays might show elevation of the right hemidiaphragm with decreased mobility or a right pleural effusion. Ultrasound or CT can confirm diagnosis (Figs. 359-1 to 359-3). Solitary liver abscesses (70% of cases) in the right lobe of the liver (75% of cases) are more common than multiple abscesses or solitary left lobe abscesses. Enzyme-linked immunosorbent assay testing for *E. histolytica* Gal/GalNAc (galactose/N-acetyl-d-galactosamine) lectin in serum is usually positive with amebiasis.

Figure 359-1 Liver abscess. A, Contrast-enhanced CT scan demonstrates a multiloculated septated mass of decreased attenuation in the right lobe of the liver. There is increased attenuation of the septa. There is also faintly visible edema between the abscess and the enhanced normal liver. B, Injection of contrast material after percutaneous drainage of this documented streptococcal abscess demonstrates the multilocular nature of the lesion and its irregularly margined wall. (From Kuhn JP, Slovis TL, Haller JO: Caffrey’s pediatric diagnostic imaging, vol 2, ed 10, Philadelphia, 2004, Mosby, p. 1470.)
Hepatic candidiasis. Transverse sonogram (A) and CT scan (B) of the upper abdomen demonstrate “bull’s-eye” lesions in the right lobe of the liver in an immunocompromised patient. The calcifications seen on the CT scan are presumed to represent sequelae of prior infection. Liver biopsy demonstrated candidiasis. (From Kuhn JP, Slovis TL, Haller JO: Caffrey’s pediatric diagnostic imaging, vol 2, ed 10, Philadelphia, 2004, Mosby, p. 1472.)


Treatment requires percutaneous ultrasound- or CT-guided needle aspiration and less often open surgical drainage, particularly if multiple or large abscesses are present. Some place a drain and leave it in until the abscess wall collapses, others just do single or repeated aspirations. Aerobic and anaerobic cultures should be obtained. Some treat empirically without aspiration or drainage. If amebic disease is present, most do not attempt aspiration.

Antibiotic therapy should initially be broad spectrum but then narrowed, based on the culture results of the abscess fluid. Empirical initial antibiotic regimens include ampicillin/sulbactam, ticarcillin/clavulanic acid, or piperacillin/tazobactam. Others recommend a combination of a third-generation cephalosporin plus metronidazole. Amebic abscesses are treated with metronidazole or tinidazole plus paromomycin (oral nonabsorbable to treat the associated intestinal amebic infection). Antibiotic therapy for pyogenic abscess is intravenous for 2-3 wk followed by oral therapy to complete a 4-6 wk course. Mortality has decreased significantly since the 1980s with early diagnosis and initiation of appropriate therapy.

Bibliography is available at Expert Consult.
Bibliography
Liver disease is found in a wide variety of systemic illnesses, both as a result of the primary pathologic process and as a secondary complication of the disease or associated therapy.

**INFLAMMATORY BOWEL DISEASE**

Ulcerative colitis and Crohn disease are associated with hepatobiliary disease that includes autoimmune and inflammatory processes related to inflammatory bowel disease (IBD) (sclerosing cholangitis, autoimmune hepatitis), drug toxicity (thiopurines, methotrexate, 5-ASA, biologics), malnutrition and disordered physiology (fatty liver, cholelithiasis), bacterial translocation and systemic infections (hepatic abscess, portal vein thrombosis), hypercoagulability (infarction, Budd-Chiari), and long-term complications of these liver diseases, such as ascending cholangitis, cirrhosis, portal hypertension, and biliary carcinoma. Hepatobiliary manifestations may continue to progress even when intestinal symptoms are well-controlled and are unrelated to either the severity or duration of intestinal disease.

**Sclerosing cholangitis** is the most common hepatobiliary disease associated with IBD, occurring in 2-8% of adult patients with ulcerative colitis and less often in Crohn disease. Conversely, 70-90% of patients with sclerosing cholangitis have ulcerative colitis. In pediatric patients with IBD, the diagnosis typically occurs in the 2nd decade of life with a median age of 14 yr. Sclerosing cholangitis is characterized by progressive inflammation and fibrosis of segments of the intra- and extrahepatic bile ducts and can progress to complete obliteration. Genetic susceptibility, with associations with the cystic fibrosis transmembrane conductance regulator (CFTR) and several human leukocyte antigens, has been demonstrated. Many patients are asymptomatic and the disease is initially diagnosed by routine liver function testing that reveals elevated serum alkaline phosphatase (AP), 5'-nucleotidase, or
γ-glutamyl transpeptidase activities. Antinuclear or anti-smooth muscle antibodies might also be present in the serum. Ten percent to 15% of adult patients present with symptoms including anorexia, weight loss, pruritus, fatigue, right upper quadrant pain, and jaundice; intermittent acute cholangitis accompanied by fever, jaundice, and right upper quadrant pain can also occur. Portal hypertension can develop with progressive disease. These symptoms are less common in children, in whom hepatobiliary disease is often recognized by routine screening of liver function tests. In children with sclerosing cholangitis, approximately 11% present initially with hepatic manifestations and the associated asymptomatic IBD is discovered only on subsequent endoscopy.

Magnetic resonance cholangiography is an established first-line diagnostic test for sclerosing cholangitis. Characteristic findings include beading and irregularity of the intrahepatic and extrahepatic bile ducts. Liver biopsy typically reveals periductal fibrosis and inflammation, fibroobliterative cholangitis, and portal fibrosis, but it is not required for the diagnosis in patients with radiologic evidence of sclerosing cholangitis.

Sclerosing cholangitis is strongly associated with hepatobiliary malignancies (cholangiocarcinoma, hepatocellular carcinoma, gallbladder carcinoma) with a reported incidence varying between 9% and 14%. In one large series, patients with IBD and sclerosing cholangitis had a 10-fold increased risk of colorectal carcinoma and a 14-fold increased risk of pancreatic cancer compared to the general population. Tumor serology (CA 19-9) and cross-sectional liver imaging may be a useful screening strategy to identify patients with sclerosing cholangitis at increased risk for cholangiocarcinoma.

There is no definitive medical treatment for sclerosing cholangitis; liver transplantation is the only long-term option for progressive cirrhosis, and autoimmune disease can recur in the allograft in 20–25% of patients. Short-term therapy aims at improving biliary drainage and attempting to slow the obliteratoric process. Ursodeoxycholic acid, at a dose of 15–30 mg/kg/24 hr, improves bile flow and laboratory parameters but has not shown to improve clinical outcome. Dominant extrabiliary biliary strictures may be dilated or endoscopically stented. Immunosuppressive therapy with corticosteroids and/or azathioprine improves biochemical parameters but has been disappointing in halting long-term histologic progression. Symptomatic therapy should be initiated for pruritus (rifampin, ursodeoxycholic acid, diphenhydramine), malnutrition (enteral supplementation), and ascending cholangitis (antibiotics) as indicated. Total colectomy may not be beneficial in preventing or managing hepatobiliary complications in patients with ulcerative colitis.

IBD-associated autoimmune hepatitis (AIH) can closely resemble IBD-associated sclerosing cholangitis, a condition often referred to as overlap syndrome or autoimmune sclerosing cholangitis (ASC). These patients typically exhibit hypergubulinemia (marked increase in serum immunoglobulin G levels). In some children, the disease is initially diagnosed as AIH and later is found to be sclerosing cholangitis after cholangiography; in other cases, AIH manifests years after diagnosis of IBD-associated sclerosing cholangitis. Liver biopsy in patients with ASC shows interface hepatitis, in addition to the bile duct injury associated with sclerosing cholangitis. Immunosuppressive medication (corticosteroids and/or azathioprine) is the mainstay of therapy for ASC; long-term response does not appear to be as favorable as in AIH alone. Long-term survival in children with ASC appears to be similar to those with sclerosing cholangitis, with an overall median (50%) survival free of liver transplantation of 12.7 yr.

Fatty liver disease might also be more prevalent in adult patients with IBD, ranging from 25–40% in 1 large series and often correlates with severity of IBD. Gallstones are more prevalent in those with Crohn disease (11%) than in those with ulcerative colitis (7.5%) and in normal subjects (5%). The true prevalence of these IBD-associated liver diseases in pediatric patients is unknown, however.

**BACTERIAL SEPSIS**

Sepsis can mimic liver disease and should be excluded in any critically ill patient who develops cholestasis in the absence of markedly elevated serum aminotransferase or AP levels, even when other signs of infection are not evident. Gram-negative organisms are most often isolated from blood cultures, in particular *Escherichia coli*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*. Lipopolysaccharides and other bacterial endotoxins are thought to interfere with bile secretion by directly altering the structure or function of bile canalicular membrane transport proteins. The serum bilirubin level, predominantly the conjugated fraction, is elevated. Serum AP and aminotransferase activities may also be elevated. Liver biopsy shows intrahepatic cholestasis with little or no hepatocyte necrosis. Kupffer cell hyperplasia and an increase in inflammatory cells are also common. Similar findings can occur with urosepsis.

**CELIAC DISEASE**

Celiac disease (see Chapter 338.2) may present with laboratory abnormalities, including aminotransferase elevation and prolonged prothrombin time, as well as histologic changes, such as mild periportal and lobular inflammation. These abnormalities typically all improve on a gluten-free diet. Gastrointestinal symptoms may not be present. Other autoimmune liver diseases (AIH, primary sclerosing cholangitis) are also associated with celiac disease although they do not respond as well to a gluten-free diet.

**CARDIAC DISEASE**

Hepatic injury can occur as a complication of severe acute or chronic congestive heart failure (see Chapter 442), cyanotic congenital heart disease (see Chapters 430 and 431), and acute ischemic shock. In all conditions, passive congestion and reduced cardiac output can contribute to liver damage. Elevated central venous pressure is transmitted to the hepatic veins, smaller venules, and, ultimately, the surrounding hepatocytes, resulting in hepatocellular atrophy in the centrilobular zone of the liver. Owing to decreased cardiac output, there is decreased hepatic arterial blood flow, and centrilobular hypoxia results. Hepatic necrosis leads to lactic acidosis, elevated aminotransferase levels, cholestasis, prolonged partial thromboplastin time, cirrhosis, and possibly hypoglycemia as a result of impaired hepatocellular metabolism. Jaundice, tender hepatomegaly, and, in some cases, ascites and splenomegaly can occur. However, aminotransferases are often minimally elevated with slowly progressive fibrosis since there is minimal inflammation or cell death.

After acute hypovolemic shock, serum aminotransferase levels can rise dramatically but rapidly return to normal when perfusion and cardiac function improve. Hepatic necrosis or acute liver failure can occur in infants with hypoplastic left heart syndrome and coarctation of the aorta. High systemic venous pressures after Fontan procedures can also lead to hepatic dysfunction, marked by prolonged prothrombin time and cardiac cirrhosis. The aim of therapy in all causes of cardiac-associated liver diseases is to improve cardiac output, reduce systemic venous pressures, and monitor for other signs of hypoperfusion. Even mild liver disease can have an impact on mortality after cardiac surgery, with poorer outcomes with progressively worse liver disease. In adults with cirrhosis undergoing cardiac surgery, overall mortality was 17% but varied significantly from 5% with mild disease to 70% with advanced liver disease.

**CHELATION ASSOCIATED WITH TOTAL PARENTERAL NUTRITION**

Total parenteral nutrition (TPN) can cause a variety of liver diseases, including hepatic steatosis, gallbladder and bile duct damage, and cholestasis. Cholestasis is the most severe complication and can lead to progressive fibrosis and cirrhosis. It is the major factor limiting effective long-term use of TPN in children and adults. Risk factors for TPN-associated cholestasis include prolonged duration of TPN, prematurity, low birthweight, sepsis, necrotizing enterocolitis, and short bowel syndrome.

The pathogenesis of TPN-associated cholestasis is multifactorial. Sepsis; excess caloric intake; high amounts of protein, fat, or carbohydrate; specific amino acid toxicities; nutrient deficiencies; and toxicities related to components such as manganese, aluminum, and copper can
all contribute to hepatic injury. Recent data implicate both the type and volume of lipid administered. Prolonged enteral fasting compromises mucosal integrity and increases bacterial mucosal translocation. Fasting also decreases release of cholecystokinin, which promotes bile flow. This leads to biliary stasis, cholestasis, and formation of biliary sludge and gallstones, which exacerbates hepatic dysfunction. Sepsis, particularly that caused by Gram-negative bacteria, and associated endotoxins, can also exacerbate liver damage.

Early histologic findings include macrovesicular steatosis, canalicular cholestasis, and periportal inflammation. These changes can regress after cessation of short-term TPN. Prolonged duration of TPN is marked by bile duct proliferation or ductopenia, portal fibrosis, and expansion of portal triads and it can progress to cirrhosis and end-stage liver disease.

Clinical onset is typically marked by gradual onset of cholestasis, developing after more than 2 wk of TPN. In low birthweight infants, the onset of jaundice can overlap the phase of physiologic (unconjugated) hyperbilirubinemia. Any icteric infant who has received TPN for more than 1 wk should have bilirubin fractionated. With prolonged duration, hepatic enlargement or splenomegaly can develop. Serum bile acid concentrations can increase. Rises in serum aminotransferase activities may be a late finding. An elevation in serum AP activity may be caused by rickets, a common complication of TPN in low birthweight infants.

In addition to cholestasis, biliary complications of intravenous nutrition include cholelithiasis and the development of biliary sludge, associated with thick, inspissated gallbladder contents. These may be asymptomatic. Hepatic steatosis or elevated serum aminotransferase levels can also occur in the absence of cholestasis, particularly in older children. This is generally mild and resolves after TPN is discontinued. Serum bilirubin and bile acid levels remain within the normal range. Other causes of liver disease should also be considered, especially if evidence of hepatic dysfunction persists despite weaning from TPN and initiating enteral feeds. If serum AP or aminotransferase levels remain elevated, liver biopsy may be necessary for accurate diagnosis.

Treatment of TPN-associated cholestasis is focused on avoiding progressive liver injury by limiting duration whenever possible. Enteral feeding should be initiated as soon as tolerated and prolonged fasting should be avoided. Even small volumes of nutrients given by intermittent oral feedings or by continuous nasogastric drip promote bile flow, enterohepatic recirculation of bile acids, and intestinal motility, and they enhance mucosal barrier function, reducing the risk of bacterial translocation. Improved TPN solutions that meet the specific needs of neonates can prevent deficiencies and toxicities. The risk of further hepatic injury should always be considered when weighing the option of continuing TPN indefinitely, and all efforts should be made to try to advance enteral feeds whenever possible. There has been concern that the soy-based emulsions provided with TPN may be a significant contributing factor to TPN-associated cholestasis as a result of proinflammatory omega-6 fatty acids. Several strategies have been employed to minimize exposure to these fatty acids by limiting total lipid and/or introducing alternate sources of lipid including fish oil and olive oil to provide more omega-3 fatty acids. The long-term effects of these strategies on essential fatty acid deficiency or growth are unclear although there is some evidence that TPN-associated cholestasis may improve.

Ursodeoxycholic acid therapy may be beneficial in improving jaundice and hepatosplenomegaly. Other therapies, such as administration of antibiotics to reduce intraluminal bacterial overgrowth or oral administration of taurine or cholecystokinin, remain experimental.

Cystic fibrosis (CF) (see Chapter 403) is caused by mutations in the CFTR gene, which impair chloride transport across the apical membranes of epithelial cells in numerous organs (including cholangioocytes). The majority of patients with CF have some evidence of hepatobiliary disease; however, less than one-third of these patients develop clinically significant liver disease. Hepatobiliary complications account for approximately 2.5% of overall mortality in patients with CF. The onset of liver disease occurs at a median age of 10 yr, and >90% occurs by 20 yr.

Focal biliary cirrhosis is the pathognomonic liver lesion in CF and is postulated to result, in part, from impaired secretory function of the bile duct epithelium. Blockage of biliary ductules secondary to viscid secretions results in periductal inflammation, bile duct proliferation, and increased fibrosis within focal portal tracts. Gradual progression to multilobular cirrhosis can occur and result in portal hypertension and end-stage liver disease in 1-8% of patients. Liver disease tends to occur mainly in males with pancreatic insufficiency and requires 2 CFTR mutations without residual function. One candidate gene modifier for clinical phenotypes of CF-related liver disease that shows a strong association is SERPINA1. However, additional study of mutational analysis is necessary before we are able to predict which patients with CF will develop liver disease. Clinical risk factors that may be associated with liver disease include older age, pancreatic insufficiency, male gender, and possibly a history of meconium ileus.

Treatment with oral ursodeoxycholic acid (10-15 mg/kg/day) may be beneficial in improving liver function, presumably by improving bile flow; further research is necessary to determine whether a true long-term benefit exists. Because it is difficult to predict which patients will develop liver disease, prophylactic therapy is not possible. Progression of liver disease is generally slow. Patients who develop end-stage liver disease might require liver transplantation for survival.

BONE MARROW TRANSPLANTATION

Liver disease is common in patients who have received hematopoietic stem cell transplantation (SCT), whether the cells are harvested from bone marrow or peripheral blood (see Chapters 135-139). The pathogenesis is varied and includes infections (viral, bacterial, or fungal); toxicity from parenteral nutrition, chemotherapy, or radiation; veno-occlusive disease (VOD); graft-versus-host disease (GVHD); or hemosiderosis secondary to iron overload from frequent blood transfusions. GVHD, drug toxicity, and sepsis are the most common causes of liver dysfunction after allogeneic SCT.

Diagnosis is often challenging because of the coexistence of multiple risk factors. Clinical course, symptoms and signs, and biochemical liver function and viral serologic tests must be considered in making the correct diagnosis. Percutaneous liver biopsy may be necessary; histology can show extensive bile duct injury in GVHD, viral inclusions in cytomegalovirus disease, or the characteristic endothelial lesion in VOD. It is important to diagnose the cause accurately, because treatment for GVHD differs markedly from that of other conditions (i.e., initiating small dose immunosuppression for GVHD) and can worsen hepatitis secondary to infections.

GVHD of the liver can be acute or chronic but often occurs with the presence of GVHD in other target organs such as the skin and gut (see Chapter 137). Hepatic GVHD is caused by immunologic reaction to bile duct epithelium, leading to a nonsuppurative cholangitis. Histologic features of GVHD include loss of intralobular bile ducts, endothelial injury of hepatic and portal venules, and hepatocellular necrosis.

Onset typically occurs at the time of donor engraftment (days 14-21 after SCT). In acute hepatic GVHD, serum aminotransferase levels can rise markedly in the absence of elevated bilirubin, AP, and γ-glutamyl transpeptidase levels, mimicking viral hepatitis. Acute hepatic GVHD can manifest both early (days 14-21) and late (after day 70) after allogeneic SCT. In chronic hepatic GVHD, serum aminotransferase levels are not as markedly elevated and cholestasis is more prominent, with marked rises in serum conjugated bilirubin, γ-glutamyl transpeptidase, and AP levels. Other signs and symptoms can include hepatic tenderness, dark urine, acholic stools, itching, and anemia.

VOD of the liver usually develops in the 1st 3 wk after SCT. The incidence ranges from 5-39% in pediatric patients, with reported mortality rates varying from 0-47%. Risk factors include trauma, high-dose
conditioning regimens, coagulopathies, sickle cell anemia, leukemia, polycythemia vera, thalassemia major, hepatic abscesses, irradiation, GVHD, iron overload, preexisting liver disease, and younger age. VOD is caused by fibrous obliteration of the terminal hepatic venules and small lobular veins, with resultant damage to the surrounding hepatocytes and sinusoids. It is not associated with thrombus formation, in contrast with Budd-Chiari syndrome, which involves occlusion of the larger hepatic veins or inferior vena cava by a web, mass, or thrombus.

Pathologic changes in patients with VOD are best demonstrated using special (trichrome) stains to highlight the central veins. The lesions may be patchy. Later in the course, hepatic venules may be completely obliterated.

Symptoms typically include jaundice, painful hepatomegaly, rapid weight gain, and ascites. VOD resolves in the majority of patients but can also lead to multisystem organ failure, hepatic encephalopathy, and fulminating hepatic failure. Less-severe forms may be characterized by jaundice and ascites with a slow resolution; in very mild cases, histologic changes may be the sole manifestation. The diagnosis rests on the exclusion of other diseases, such as GVHD, congestive cardiomyopathy, constrictive pericarditis, and Budd-Chiari syndrome.

Treatment for VOD with defibrotide has been successful in multicenter phase II trials in both adult and pediatric patients; defibrotide, an agent with antithrombotic and thrombolytic properties, is administered at doses of 20–40 mg/kg/day. Complete response rates vary between 36% and 76% and survival of longer than 100 days post-SCT ranges from 32–79%, with better outcomes in pediatric patients. Little toxicity has been noted; however, pediatric patients are at a higher risk of bleeding with treatment compared to adults. Oral ursodeoxycholic acid can decrease the incidence of severe liver disease in patients undergoing SCT and reduces the incidence of VOD and transplant-related mortality in adults. Supportive management includes maintaining intravascular hydration and renal perfusion.

HEMOGLOBINOPATHIES

Patients with sickle cell anemia (see Chapter 462.1) or thalassemia (see Chapter 462.10) can have hepatic dysfunction caused by acute or chronic viral hepatitis, hemosiderosis from frequent transfusion therapy, hepatic crises related to severe intrahepatic cholestasis, sequestration, or ischemic necrosis. Cholelithiasis and hemosiderosis are both common and treatable. Higher volume of transfusions is associated with both higher hepatic iron content and fibrosis. Chelation therapy for iron overload is usually safe and effective.

Hepatic sickle cell crisis or “sickle hepatopathy” occurs in approximately 10% of patients with sickle cell disease. It manifests with intense right upper quadrant pain and tenderness, fever, leukocytosis, and jaundice. Bilirubin levels may be markedly elevated; serum AP levels may be only moderately elevated. It can be difficult to distinguish sickle hepatopathy from viral hepatitis, acute cholecystitis or cholecodocholithiasis; therefore, these conditions should be excluded. Generally, hepatic sickle cell crisis is self-limited and symptoms resolve within 1-3 wk. Sickle cell intrahepatic cholestasis manifests as hepatomegaly, abdominal pain, hyperbilirubinemia, and coagulopathy, and can progress to acute liver failure, leaving transplantation as the only therapeutic option. Transplantation carries a high risk for graft loss from vascular complications.

On occasion, children with sickle cell disease experience a benign elevation of bilirubin levels >20 mg/dL but unaccompanied by severe pain or fever. There is no change in hematocrit or reticuloocyte count nor any association with a hemolytic crisis.

HISTIOCYTIC DISORDERS

Langerhans cell histiocytosis (see Chapter 507.1) is the most common of the histiocytoses and typically affects the bone and skin. However, it can cause infiltration of high-risk organs such as the liver resulting in perportal inflammation and sclerosing cholangitis. Liver involvement often results in worse outcomes. Hemophagocytic lymphohistiocytosis (see Chapter 507.2) is a multiorgan, severe, and potentially fatal inflammatory process associated with activation of macrophages that mimics sepsis. The hepatic manifestation of hemophagocytic lymphohistiocytosis is usually acute liver failure with portal inflammatory infiltrates noted on liver biopsy.

Bibliography is available at Expert Consult.

360.1 Nonalcoholic Fatty Liver Disease

Bernadette E. Vitola and William F. Balistreri

Nonalcoholic fatty liver disease (NAFLD) is part of the spectrum of liver disease strongly associated with obesity and is the most common chronic liver disease in children. NAFLD can range from fatty liver alone to a triad of fatty infiltration, inflammation, and fibrosis, termed nonalcoholic steatohepatitis (NASH), which resembles alcoholic liver disease but occurs with little or no exposure to ethanol. Unlike adults, NASH in children has 2 distinct histologic types. Type 1 NASH resembles adult histologic findings with steatosis and balloon degeneration of hepatocytes and/or periportal fibrosis. Type 2 NASH includes steatosis and portal inflammation. Many patients are asymptomatic. Liver histology from autopsy data suggests that 10% of children and 38% of obese children ages 2-19 yr have NAFLD. The risk is lower in African-American children. Elevated serum aminotransferase levels are not sensitive or specific markers for NAFLD. A normal serum alanine aminotransferase level is present in 21-23% of pediatric patients with NAFLD. No biomarkers are currently a reliable alternative to biopsy. Although ultrasonography detects NAFLD, no current imaging modalities distinguish between steatosis and NASH. A liver biopsy may be required for a delimiting diagnosis. The estimated prevalence in adults is thought to be as high as 15-20% for NAFLD overall and 2-4% for NASH. Risk factors in pediatric cohorts include obesity, male gender, white or Hispanic ethnicity, hypertriglycerideremia, and insulin resistance. Hepatic steatosis alone may be benign, but up to a quarter of patients with NASH can develop progressive fibrosis with resultant cirrhosis. The long-term prognosis of NASH that has developed in childhood is unknown. Children diagnosed with NAFLD should be screened for comorbid conditions associated with the metabolic syndrome, including diabetes, hypertension, dyslipidemia, and obstructive sleep apnea. Obese children and overweight children with other risk factors who are older than 3 yr of age should be screened for NAFLD by checking aminotransferase levels and liver ultrasound, even though neither is highly sensitive or specific.

Although there is no definitive treatment for NAFLD, gradual weight loss is effective in normalizing serum alanine aminotransferase and improving NAFLD. Low glycemic index foods, avoiding fructose, and substituting polysaturated fatty acids for saturated fats may help. Vitamins E and C provide no additional benefit to the efficacy of lifestyle intervention (diet and exercise) in improving steatosis or biochemical abnormalities in pediatric NAFLD. However, vitamin E does improve balloon degeneration in pediatric NASH. Metformin has produced mixed results in the treatment of NAFLD. Thiazolidinediones (pioglitazone, rosiglitazone) improve liver histology in adults with NASH but have not been well studied in children. Ursodeoxycholic acid has not been efficacious. In view of the potential role of the gut microbiome in contributing to the pathogenesis of NAFLD, the role of probiotics as an adjunct to lifestyle changes is under investigation. A preliminary study using docosahexanoic acid in children showed improved insulin sensitivity, alanine aminotransferase, triglycerides, body mass index, and histology in children with NAFLD. Cysteamine bitartrate (slow release), a potential precursor of glutathione, an antioxidant, may reduce liver enzyme levels, as well as serum leptin and adiponectin levels, and is also a potential candidate for the treatment of NAFLD.

Bibliography is available at Expert Consult.
Bibliography


Bibliography

Hepatocytes contain a high density of mitochondria, because the liver, with its biosynthetic and detoxifying functions, is highly dependent on adenosine triphosphate. Defects in mitochondrial function can lead to impaired oxidative phosphorylation, increased generation of reactive oxygen species, impairment of other metabolic pathways, and activation of mechanisms of cellular death. Mitochondrial disorders can be divided into primary, in which the mitochondrial defect is the primary cause of the disorder, and secondary, in which mitochondrial function is affected by exogenous injury or a genetic mutation that affects non-mitochondrial proteins (see Chapter 37). Primary mitochondrial disorders can be caused by mutations affecting mitochondrial DNA (mtDNA) or by nuclear genes that encode mitochondrial proteins or cofactors (Tables 361-1 and 361-2). Secondary mitochondrial disorders include diseases with an uncertain etiology such as Reye syndrome; disorders caused by endogenous or exogenous toxins, drugs, or metals; and other conditions in which mitochondrial oxidative injury may be involved in the pathogenesis of liver injury.

### EPIDEMIOLOGY

Mitochondrial respiratory chain disorders of all types affect 1 in 20,000 children younger than 16 yr of age; liver involvement has been reported in 10-20% of patients with respiratory chain defect. More than 200 pathogenic point mutations, deletions, insertions, and rearrangements that involve mtDNA and nuclear DNA that encode mitochondrial proteins are identified. Mitochondrial genetics are unique because mitochondria are able to replicate, transcribe, and translate their mitochondrial-derived DNA independently. A typical hepatocyte contains approximately 1000 copies of mtDNA. Oxidative phosphorylation (the process of adenosine triphosphate production) occurs in the respiratory chain located in the inner mitochondrial membrane and is divided into 5 multienzyme complexes: reduced nicotinamide adenine dinucleotide coenzyme Q reductase (complex I), succinate–coenzyme Q reductase (complex II), reduced coenzyme Q–cytochrome-c reductase (complex III), cytochrome-c oxidase (complex IV), and adenosine triphosphate synthase (complex V). The respiratory chain peptide components are encoded by both nuclear and mtDNA genes, hence mutations in either genome can result in disorders of oxidative phosphorylation. Thirteen essential polypeptides are synthesized from the small 16.5-kilobase circular double-stranded mtDNA. Mitochondrial DNA also encodes the 24 transfer RNAs required for intramitochondrial protein synthesis, whereas nuclear genes encode more than 70 respiratory chain subunits and an array of enzymes and cofactors required to maintain mtDNA, including DNA polymerase-γ (POLG), thymidine kinase 2, and deoxyguanosine kinase.

Expression of mitochondrial disorders is complex and epidemiologic studies are hampered by technical difficulties collecting and processing tissue specimens needed to make accurate diagnoses, the variability in clinical presentation, and the fact that most disorders display maternal inheritance with variable penetrance (see Chapter 80). mtDNA mutates 10 times more often than nuclear DNA secondary to a lack of introns, protective histones, and an effective repair system in mitochondria. Mitochondrial genetics also display a threshold effect in that the type and severity of mutation required for clinical expression varies among people and organ systems, this is explained by the concept of heteroplasmy, in which cells and tissues harbor both normal and mutant mtDNA in various amounts because of random partitioning during cell division.

### CLINICAL MANIFESTATIONS

Defects in oxidative phosphorylation can affect any tissue to a variable degree, with the most energy-dependent organs being the most vulnerable. One should consider the diagnosis of a mitochondrial disorder in a patient of any age who presents with progressive, multisystem involvement that cannot be explained by a specific diagnosis. Gastrointestinal complaints include vomiting, diarrhea, constipation, failure to thrive, and abdominal pain; certain mitochondrial disorders have characteristic gastrointestinal presentations. Pearson marrow-pancreas syndrome manifests with sideroblastic anemia and exocrine pancreatic insufficiency; whereas mitochondrial neurogastrointestinal encephalomyopathy manifests with chronic intestinal pseudoobstruction and cachexia. Hepatic presentations range from chronic cholestasis, hepatomegaly, cirrhosis, steatosis to fulminant hepatic failure and death.

### PRIMARY MITOCHONDRIAL HEPATOPATHIES

#### Neonatal Liver Failure

A common presentation of respiratory chain defects is severe liver failure manifested as jaundice, hypoglycemia, coagulopathy, renal dysfunction, and hyperammonemia, with onset within the 1st few wk to mo of life. The key biochemical features include a markedly elevated plasma lactate concentration, an elevated molar ratio of plasma lactate to pyruvate (>25 mol/mol), and a raised ratio of β-hydroxybutyrate to acetoacetate (2.0 mol/mol). Symptoms are nonspecific and include lethargy and vomiting. Most patients additionally have neurologic involvement manifested as a weak suck, recurrent apnea, or myoclonic epilepsy. Liver biopsy shows predominantly microvesicular steatosis, cholestasis, bile duct proliferation, glycogen depletion, and iron overload. With standard therapy, the prognosis is very poor, and most patients die from liver failure or infection in the 1st few mo of life. **Cytochrome-c oxidase** (complex IV) is the most common deficiency in these infants, although complexes I and III and mtDNA depletion syndromes also are implicated (see Table 361-1).

<table>
<thead>
<tr>
<th>Table 361-1</th>
<th>Classification of Primary Mitochondrial Hepatopathies</th>
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<tbody>
<tr>
<td>Respiratory chain (electron transport) defects (oxidative phosphorylation)</td>
<td>Neonatal liver failure</td>
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<tr>
<td>Neonatal liver failure</td>
<td>Complex I deficiency</td>
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<tr>
<td>Complex IV deficiency (SCO1 mutations)</td>
<td>Complex III deficiency (BCS1L mutations)</td>
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<tr>
<td>Complex IV deficiency</td>
<td>Coenzyme Q deficiency</td>
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<tr>
<td>Multiple complex deficiencies (transfer and elongation factor mutations)</td>
<td>mtDNA depletion syndrome (DUGOK, MPV17, POLG, SUCLG1, C10orf2/Twinkle mutations)</td>
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<tr>
<td>Later-onset liver dysfunction or failure</td>
<td>Alpers-Huttenlocher disease (POLG mutations)</td>
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<td>Pearson marrow-pancreas syndrome (mtDNA deletion)</td>
<td>Mitochondrial neurogastrointestinal encephalopathy (TYMP mutations)</td>
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<td>Navajo neurohepatopathy (MPV17 mutations)</td>
<td>Fatty acid oxidation defects</td>
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<td>Long-chain 3-hydroxyacyl-coenzyme A dehydrogenase</td>
<td>Carnitine palmitoyltransferases I and II deficiencies</td>
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<td>Carnitine–acylcaritine translocase deficiency</td>
<td>Urea cycle enzyme deficiencies</td>
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<td>Electron transfer flavoprotein and electron transfer flavoprotein dehydrogenase deficiencies</td>
<td>Phosphoenolpyruvate carboxykinase (mitochondrial) deficiency; nonketotic hyperglycemia</td>
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<tr>
<td>Citrin deficiency; neonatal intrahepatic cholestasis caused by citrin deficiency (SLC25A13 mutations)</td>
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</tbody>
</table>

Nystagmus, hypotonia, renal Fanconi syndrome, I, III, IV
Infantile liver failure with subsequent recovery
CNS, muscle, I, III, IV
Steatosis
I, III, IV
CNS, muscle
Steatosis
I, III, IV
-<
CLINICAL FEATURES
IV
CNS, muscle
Steatosis
Kidneys, CNS, muscle
Steatosis, fibrosis
Kidneys, CNS, muscle
Nystagmus, hypotonia, renal Fanconi syndrome, acidosis
I, III, IV
MPV17
I, III, IV
Steatosis, fibrosis
CNS, PNS
Hypotonia
SUCLG1
I, III, IV
Steatosis
CNS, muscle
Myopathy, sensorineural hearing loss, respiratory failure
POLG1
I, III, IV
Steatosis, fibrosis
CNS, muscle
Liver failure preceded by neurologic symptoms, intractable seizures, ataxia, psychomotor regression
C10orf2/Twinkle
I, III, IV
Steatosis
CNS, muscle
Infantile-onset spinocerebellar ataxia, loss of skills
BCS1L
III (GRACLE)
CNS ±, muscle ±, kidneys
Fanconi-type renal tubulopathy
SCO1
IV
Steatosis, fibrosis
Muscle
TRMU
I, III, IV
Steatosis, fibrosis
Infantile liver failure with subsequent recovery
EF1
I, III, IV
Steatosis
CNS
Severe, rapidly progressive encephalopathy
EFTu
I, III, IV
Unknown
CNS
Severe lactic acidosis, rapidly fatal encephalopathy
CNS, central nervous system; GRACLE, growth restriction, aminoaciduria, cholestasis, iron overload, lactic acidosis, and early death; PNS, peripheral nervous system.


Alpers Syndrome (Alpers-Huttenlocher Syndrome or Alpers Hepatopathic Poliodystrophy)
Diagnostic criteria include refractory, mixed-type seizures that include a focal component; psychomotor regression that is episodic and triggered by intercurrent infections; and hepatopathy with or without acute liver failure. Alpers syndrome manifests from infancy up to 8 yr of age with seizures, hypotonia, feeding difficulties, psychomotor regression, and ataxia. Patients develop hepatomegaly and jaundice and have a slower progression to liver failure than those with cytochrome-c oxidase deficiency. Elevated blood or cerebrospinal fluid lactate and pyruvate levels are supportive for the diagnosis, in addition to characteristic electroencephalogram findings (high-amplitude slow activity with polyspikes), asymmetric abnormal visual evoked responses, and low-density areas or atrophy in the occipital or temporal lobes on computed tomography scanning of the brain. In some patients, complex I deficiency has been found in liver or muscle mitochondria. The disease is inherited in an autosomal recessive fashion; mutations in the catalytic subunit of the nuclear gene mtDNA POLG have been identified in multiple families with Alpers syndrome, leading to the advent of molecular diagnosis for Alpers syndrome. Patients with POLG mutations are susceptible to valproate-induced liver dysfunction.

Mitochondrial DNA Depletion Syndrome
Mitochondrial DNA depletion syndrome (MDS) is characterized by a tissue-specific reduction in mtDNA copy number, leading to deficiencies in complexes I, III, and IV. MDS manifests with phenotypic heterogeneity; multisystem and localized disease forms include myopathic, hepatocerebral, and liver-restricted presentations. Infants with the hepatocerebral form present in the neonatal period. The first symptoms are metabolic and rapidly progress to hepatic failure with hypoglycemia and vomiting. This stage is followed by neurologic involvement affecting the central and peripheral systems. Laboratory studies are characterized by lactic acidosis, hypoglycemia and markedly elevated α-fetoprotein in plasma. In some patients iron overload has been found with elevated transferrin saturation, high ferritin levels, and iron accumulation in hepatocytes and Kupffer cells. Death usually occurs by 1 yr of age. Spontaneous recovery has been reported in a patient with liver-restricted disease. Inheritance is autosomal recessive and mutations in the nuclear gene deoxyguanosine kinase gene (DGUK) have been identified in many patients with hepatocerebral MDS. Thymidine kinase 2 has been implicated in the myopathic form; no known genetic defect has been identified in liver-restricted MDS. Multiple other nuclear genes including POLG, MPV17, Twinkle helicase gene, and SUCLG1, have been implicated in hepatocerebral MDS. Liver biopsies of patients with MDS show microvesicular steatosis, cholestasis, focal cytoplasmic biliary necrosis, and cytoidosiderosis in hepatocytes and sinusoidal cells. Ultrastructural changes are characteristic of oncogenic transformation of mitochondria, which is characterized by mitochondria with sparse cristae, granular matrix, and dense or vesicular inclusions. If the native DNA-encoded complex II is normal and the activities of the other complexes are decreased, one should investigate mtDNA copy numbers for a MDS. Diagnosis is established by demonstration of a low ratio of mtDNA (<10%) to nuclear DNA in affected tissues and/or genetic testing. Importantly, the sequence of the mitochondrial genome is normal.

Navajo Neurohepatopathy
Navajo neurohepatopathy (NNH) is an autosomal recessive sensorimotor neuropathy with progressive liver disease found only in Navajo Indians of the southwestern United States. The incidence is 1 in 1,600 live births. Diagnostic criteria include sensory neuropathy; motor neuropathy; corneal anesthesia; liver disease; metabolic or infectious complications including failure to thrive, short stature, delayed puberty, or systemic infection; and evidence of central nervous system demyelination on radiographic imaging and peripheral nerves biopsies. MPV17 gene mutation is implicated in the pathogenesis of NNH. Interestingly, this is the same gene implicated in MDS (see earlier), demonstrating that NNH may be a specific type of MDS found only in Navajo Indians. NNH is divided into 3 phenotypic variations based on age of presentation and clinical findings.

First, classic NNH appears in infancy with severe progressive neurologic deterioration manifesting clinically as weakness, hypotonia, loss of sensation with accompanying acral mutilation, corneal ulcerations, and poor growth. Liver disease, present in the majority of patients, is secondary and variable and includes asymptomatic elevations of liver function tests, Reye syndrome–like episodes,
hepatocellular carcinoma, or cirrhosis. γ-Glutamyl transpeptidase levels tend to be higher than in other forms of NNH. Liver biopsy might show chronic portal tract inflammation and cirrhosis, but it shows less cholestasis, hepatocyte ballooning, and giant cell transformation than other forms of NNH.

Infantile NNH manifests between the ages of 1 and 6 mo with jaundice and failure to thrive, and progresses to liver failure and death by 2 yr of age. Patients have hepatomegaly with moderate elevations in aspartate aminotransferase, alanine aminotransferase, and γ-glutamyl transpeptidase. Liver biopsy demonstrates pseudocoincinar formation, multinucleate giant cells, portal and lobular inflammation, canalicular cholestasis, and microvesicular steatosis. Progressive neurologic symptoms are not usually noticed at presentation but do develop later.

Childhood NNH manifests from age 1-5 yr with the acute onset of fulminant hepatic failure that leads to death within months. Most patients also have evidence of neuropathy at presentation. Liver biopsies are similar to those in infantile NNH, except significant hepatocyte ballooning and necrosis, bile duct proliferation, and cirrhosis are also seen.

There is no effective treatment for any of the forms of NNH, and neurologic symptoms often preclude liver transplantation. The identical MPV17 mutation is seen in patients with both the infantile and classic form of NNH highlighting the clinical heterogeneity of NNH.

Pearson Syndrome
Pearson marrow-pancreas syndrome has a neonatal-onset with severe macrocytic anemia, variable neutropenia and thrombocytopenia, and ringed sideroblasts in the bone marrow. Diarrhea and fat malabsorption develop in early childhood secondary to extensive pancreatic fibrosis, acinar atrophy and partial villous atrophy of the small intestine. The liver involvement includes hepatomegaly, steatosis, and cirrhosis. Liver failure and death have been reported before the age of 4 yr. Other features of the syndrome include renal tubular disease, photosensitivity, diabetes mellitus, hydrops fetalis, and the late development of visual impairment, tremor, ataxia, proximal muscle weakness, external ophthalmoplegia, and a pigmentary retinopathy. Methylglutaconic aciduria is a useful diagnostic marker. Large deletions of mtDNA are reported in most patients resulting in complexes I and III deficiency. mtDNA deletions can be detected in patients' cultured fibroblasts as well as in peripheral blood lymphocytes.

Villous Atrophy Syndrome
Children with this disease present with severe anorexia, vomiting, chronic diarrhea, and villous atrophy in the 1st yr of life. Hepatic involvement includes mild elevation of aminotransferase levels, hepatomegaly, and steatosis. Lactic acidosis is worsened with high-dextrose intravenous infusions or enteral nutrition. Diarrhea improved by 5 yr of age in association with the normalization of intestinal biopsies. Subsequently, patients develop retinitis pigmentosa, cerebellar ataxia, sensorineural deafness, and proximal muscle weakness, with eventual death late in the 1st decade of life. The disease is attributed to a mtDNA rearrangement defect. A complex III deficiency was found in the muscle of affected patients.

GRACILE Syndrome
The acronym GRACILE sums the most important clinical features, namely fetal growth restriction (birth weight about ~4 SD), aminoaciduria (caused by Fanconi-type tubulopathy), cholestasis (with steatosis and cirrhosis), iron overload, severe lactic acidosis, and early death. The syndrome is associated with mutations of the complex I assembly factor BCS1L. The liver histology shows microvesicular steatosis and cholestasis with abundant iron accumulation in hepatocytes and Kupffer cells. The liver iron content slightly decreases with age, concomitantly with increasing fibrosis and cirrhosis. Abnormal transaminases and coagulation are noted, but the cause of death seems to be related to energy depletion than to liver failure. About half of the cases die within the 1st 2 wk; the oldest infant lived to 4 mo of age.

Mutations in Nuclear Translation and Elongation Factor Genes
Mutations in nuclear translation factor genes (TRMU) of the respiratory chain enzyme complexes have been identified as the etiology for acute liver failure manifesting at ages 1 day to 6 mo. The respiratory chain deficit was similar to MDS, where the activity of the native DNA encoded complex II was normal, whereas complexes I, III, and IV were decreased. The elongation factor EFG1 (gene GFM1) mutation was associated with fetal growth restriction, lactic acidosis, liver dysfunction that progresses into liver failure and death. The mutation in the elongation factor EFTu manifests as severe lactacidosis and lethalencephalopathy with mild hepatic involvement.

SECONDARY MITOCHONDRIAL HEPATOPATHIES
Secondary mitochondrial hepatopathies are caused by a hepatotoxic metal, drug, toxin, or endogenous metabolite. In the past, the most common secondary mitochondrial hepatopathy was Reye syndrome, the prevalence of which peaked in the 1970s and had a mortality rate of >40%. Even though mortality has not changed, the prevalence has decreased from >500 cases in 1980 to approximately 35 cases per year since. As to the decline of Reye syndrome, recent literature data reveal that this is related to more accurate modern diagnosis of infectious, metabolic, or toxic disease, reducing the percentage of idiopathic or true cases of Reye syndrome. Reye syndrome is precipitated in a genetically susceptible person by the interaction of a viral infection (influenza, varicella) and salicylate and or antiemetic use. Clinically, it is characterized by a preceding viral illness that appears to be resolving and the acute onset of vomiting and encephalopathy (Table 361-3).

Neurologic symptoms can rapidly progress to seizures, coma, and death. Liver dysfunction is invariably present when vomiting develops, with coagulopathy and elevated serum levels of aspartate aminotransferase, alanine aminotransferase, and ammonia. Importantly, patients remain anicteric and serum bilirubin levels are normal. Liver biopsies show microvesicular steatosis without evidence of liver inflammation or necrosis. Death is usually secondary to increased intracranial pressures and herniation. Patients who survive have full recovery of liver function but should be carefully screened for fatty-acid oxidation and fatty-acid transport defects (Table 361-4).

Acquired abnormalities of mitochondrial function can be caused by several drugs and toxins, including valproic acid, cyanide, amiodarone, chloramphenicol, iron, antimycin A, the emetic toxin of Bacillus cereus, and nucleoside analogs. Valproic acid is a branched fatty acid that can be metabolized into the mitochondrial toxin 4-envalproic acid. Children with underlying respiratory chain defects appear more sensitive to the toxic effects of this drug and valproic acid is reported to precipitate liver failure in patients with Alpers syndrome and cytochrome-c oxidase deficiency. Nucleoside analogs directly inhibit mitochondrial respiratory chain complexes. The reverse transcriptase inhibitors zidovudine, didanosine, stavudine, and zalcitabine used to treat HIV-infected patients inhibit DNA polymerase-γ of mitochondria and can block elongation of mtDNA, leading to mtDNA

<table>
<thead>
<tr>
<th>Symptoms at the time of admission:</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. Usually quiet, lethargic and sleepy, vomiting, laboratory evidence of liver dysfunction</td>
</tr>
<tr>
<td>II. Deep lethargy, confusion, delirium, combative ness, hyperpnoea, hyperreflexia</td>
</tr>
<tr>
<td>III. Obtunded, light coma ± seizures, decorticate rigidity, intact pupillary light reaction</td>
</tr>
<tr>
<td>IV. Seizures, deepening coma, decerebrate rigidity, loss of oculocephalic reflexes, fixed pupils</td>
</tr>
<tr>
<td>V. Coma, loss of deep tendon reflexes, respiratory arrest, fixed dilated pupils, flaccidity/decerebration (intermittent); isoelectric electroencephalogram</td>
</tr>
</tbody>
</table>

Table 361-3 | Clinical Staging of Reye Syndrome and Reye-Like Diseases
depletion. Other conditions that can lead to mitochondrial oxidative stress include cholestasis, nonalcoholic steatohepatitis, α₁-antitrypsin deficiency, and Wilson disease.

**TREATMENT OF MITOCHONDRIAL HEPATOPATHIES**
There is no effective therapy for most patients with mitochondrial hepatopathies; neurologic involvement often precludes orthotropic liver transplantation. Several drug mixtures that include antioxidants, vitamins, cofactors, and electron acceptors have been proposed, but no randomized, controlled trials have been completed to evaluate these drug combinations. Current treatment strategies are supportive and include the infusion of sodium bicarbonate for acute metabolic acidosis, low carbohydrate diet may decrease the lactic acidosis, transfusions for anemia and thrombocytopenia, and exogenous pancreatic enzymes for pancreatic insufficiency.

*Bibliography is available at Expert Consult.*

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**Table 361-4**

<table>
<thead>
<tr>
<th>Diseases That Present a Clinical or Pathologic Picture Resembling Reye Syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolic disease</td>
</tr>
<tr>
<td>• Organic aciduria</td>
</tr>
<tr>
<td>• Disorders of oxidative phosphorylation</td>
</tr>
<tr>
<td>• Urea cycle defects (carbamoyl phosphate synthetase, ornithine transcarbamylase)</td>
</tr>
<tr>
<td>• Defects in fatty acid oxidation metabolism</td>
</tr>
<tr>
<td>• Acyl–coenzyme A dehydrogenase deficiencies</td>
</tr>
<tr>
<td>• Systemic carnitine deficiency</td>
</tr>
<tr>
<td>• Hepatic carnitine palmitoyltransferase deficiency</td>
</tr>
<tr>
<td>• 3-OH, 3-methylglutaryl-coenzyme A lyase deficiency</td>
</tr>
<tr>
<td>• Fructosemia</td>
</tr>
<tr>
<td>Central nervous system infections or intoxications (meningitis), encephalitis, toxic encephalopathy</td>
</tr>
<tr>
<td>Hemorrhagic shock with encephalopathy</td>
</tr>
<tr>
<td>Drug or toxin ingestion (salicylate, valproate)</td>
</tr>
</tbody>
</table>
Bibliography
Autoimmune hepatitis is a chronic hepatic inflammatory process manifested by elevated serum aminotransaminase concentrations, liver-associated serum autoantibodies, and/or hypergammaglobulinemia. The target of the inflammatory process can include hepatocytes and to a lesser extent bile duct epithelium. Chronicity is determined either by duration of liver disease (typically >3-6 mo) or by evidence of chronic hepatic decompensation (hypoalbuminemia, thrombocytopenia) or physical stigmata of chronic liver disease (clubbing, spider telangiectasia, splenomegaly, ascites). The severity is variable; the affected child might have only biochemical evidence of liver dysfunction, might have stigmata of chronic liver disease, or can present in hepatic failure.

Chronic hepatitis can also be caused by persistent viral infection (see Chapter 358), drugs (see Chapter 363), metabolic diseases (see Chapter 361), or unknown and autoimmune disorders (Table 362-1). Approximately 5% or less of chronic cases in the United States are associated with hepatitis B infection; unusually severe disease may be caused by superimposed infection with hepatitis D (a defective RNA virus that is dependent on replicating hepatitis B virus). More than 90% of hepatitis B infections in the 1st yr of life become chronic, compared with 5-10% among older children and adults. Chronic hepatitis develops in >50% of acute hepatitis C virus infections. Patients receiving blood products or who have had massive transfusions are at increased risk. Hepatitis A does not lead to chronic liver disease. Hepatitis E can become chronic in immunosuppressed patients. Drugs commonly used in children that can cause chronic liver injury include isoniazid, methyldopa, pemoline, nitrofurantoin, dantrolene, minocycline, pemoline, and the sulfonamides. Metabolic diseases can lead to chronic hepatitis, including α₁-antitrypsin deficiency, inborn errors of bile acid biosynthesis, and Wilson disease. Nonalcoholic steatohepatitis, usually associated with obesity and insulin resistance, is another common cause of chronic hepatitis. It can progress to cirrhosis, but responds to weight reduction. In many cases, the cause of chronic hepatitis is unknown; in some, an autoimmune mechanism is suggested by the finding of serum antinuclear and anti-smooth muscle antibodies and by multisystem involvement (arthropathy, thyroiditis, rashes, Coombs-positive hemolytic anemia).

Autoimmune hepatitis is a clinical constellation that suggests an immune-mediated process; it is responsive to immunosuppressive therapy (Table 362-2). Autoimmune hepatitis typically refers to a primarily hepatocyte-specific process, whereas autoimmune cholangiopathy and sclerosing cholangitis are predominated by intra- and extrahepatic bile duct injury. Overlap of the process involving both hepatocyte and bile duct directed injury may be more common in children. De novo hepatitis can be seen in a subset of liver transplant recipients whose initial disease was not autoimmune.

**ETIOLOGY**

In autoimmune hepatitis a dense portal mononuclear cell infiltrate invades the surrounding parenchyma and comprises T and B lymphocytes, macrophages, and plasma cells. The immunopathogenic mechanisms underlying autoimmune hepatitis are unsettled. Triggering factors can include molecular mimicry, infections, drugs, and the environment (toxins) in a genetically susceptible host. Several human leukocyte antigen class II molecules, particularly DR3, DR4, and DR7 isoforms, confer susceptibility to autoimmune hepatitis. Self-antigenic

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**Table 362-1** Disorders Producing Chronic Hepatitis

<table>
<thead>
<tr>
<th>Chronic viral hepatitis</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Hepatitis B</em></td>
</tr>
<tr>
<td><em>Hepatitis C</em></td>
</tr>
<tr>
<td><em>Hepatitis D</em></td>
</tr>
</tbody>
</table>

Autoimmune hepatitis

| Anti-actin antibody positive |
| Anti-liver-kidney microsomal antibody positive |
| Anti-soluble liver antigen antibody-positive |
| Others (includes antibodies to liver-specific lipoproteins or asialoglycoprotein) |
| Overlap syndrome with sclerosing cholangitis and autoantibodies |
| Systemic lupus erythematosus |
| Celiac disease |

Drug-induced hepatitis

| Wilson disease |
| Nonalcoholic steatohepatitis |
| α₁-Antitrypsin deficiency |
| Tyrosinemia |
| Niemann-Pick disease type 2 |
| Glycogen storage disease type iv |
| Cystic fibrosis |
| Galactosemia |
| Bile acid biosynthetic abnormalities |

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peptides are processed by populations of antigen presenting cells and presented to CD4 and CD8 effector T-cells. CD4+ T lymphocytes recognizing a self-antigenic liver peptide orchestrate liver injury. Cell-mediated injury by cytokines released by CD8+ cytotoxic T cells and/ or antibody-mediated cytotoxicity can be operative. There is also evidence that regulatory T-cells from autoimmune hepatitis patients are impaired in their ability to control the proliferation of CD4 and CD8 effector cells. Cytochrome P450 2D6 is the main autoantigen in type 2 autoimmune hepatitis.

Antibody-coated hepatocytes may be lysed by complement or Fc-bearing natural killer lymphocytes. Heterozygous mutations in the autoimmune regulator gene (AIRE), which encodes a transcription factor controlling the negative selection of autoreactive thymocytes, can be found in some children with autoimmune hepatitis types 1 and 2. AIRE mutations also cause autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (also called autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy syndrome) in which autoimmune hepatitis occurs in approximately 20% of patients.

**PATHOLOGY**

The histologic features common to untreated cases include inflammatory infiltrates, consisting of lymphocytes and plasma cells that expand portal areas and often penetrate the lobule (interface hepatitis); moderate to severe piecemeal necrosis of hepatocytes extending outward from the limiting plate; variable necrosis, fibrosis, and zones of parenchymal collapse spanning neighboring portal triads or between a portal triad and central vein (bridging necrosis); and variable degrees of bile duct epithelial injury. Distortion of hepatic architecture can be severe; cirrhosis may be present in children at the time of diagnosis. Histologic features in acute liver failure may be obscured by massive necrosis and multilobular collapse. Other histologic features may suggest an alternative diagnosis: characteristic periodic acid–Schiff-positive, diastase-resistant granules are seen in α1-antitrypsin deficiency, and macrovesicular and microvesicular steatosis is found in Nonalcoholic steatohepatitis and often in Wilson disease. Bile duct injury can suggest an autoimmune cholangiopathy. Ultrastructural analysis might suggest distinct types of storage disorders.

**LABORATORY FINDINGS**

The findings are related to the severity of presentation. In many asymptomatic cases, serum aminotransferase ranges between 100 and 300 IU/L, whereas levels in excess of 1,000 IU/L can be seen in symptomatic young patients. Serum bilirubin concentrations may be normal in mild cases but are commonly 2-10 mg/dL in more severe cases. Serum alkaline phosphatase and γ-glutamyl transpeptidase activities are normal to slightly increased but may be more significantly elevated in autoimmune cholangiopathy or in the setting of overlap with sclerosing cholangitis. Serum γ-globulin levels can show marked polyclonal elevations. Hypoalbuninemia is common. The prothrombin time is prolonged, most often as a result of vitamin K deficiency but also as a reflection of impaired hepatocellular function. A normochromic normocytic anemia, leukopenia, and thrombocytopenia are present and become more severe with the development of portal hypertension and hypersplenism.

### Table 362-2 Classification of Autoimmune Hepatitis

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>TYPE 1 AUTOIMMUNE HEPATITIS</th>
<th>TYPE 2 AUTOIMMUNE HEPATITIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Characteristic autoantibodies</td>
<td>Antinuclear antibody*</td>
<td>Antibody against liver-kidney microsome type 1*</td>
</tr>
<tr>
<td></td>
<td>Smooth-muscle antibody*</td>
<td>Antibody against liver cytosol type 1*</td>
</tr>
<tr>
<td></td>
<td>Antictin antibody†</td>
<td>Antibody against liver-kidney microsomal type 3</td>
</tr>
<tr>
<td></td>
<td>Autoantibodies against soluble liver antigen and liver-pancreas antigen†</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Atypical perinuclear antineutrophil cytoplasmic antibody</td>
<td></td>
</tr>
<tr>
<td>Geographic variation</td>
<td>Worldwide</td>
<td>Worldwide; rare in North America</td>
</tr>
<tr>
<td>Age at presentation</td>
<td>Any age</td>
<td>Predominantly childhood and young adulthood</td>
</tr>
<tr>
<td>Gender of patients</td>
<td>Female in ~75% of cases</td>
<td>Female in ~95% of cases</td>
</tr>
<tr>
<td>Association with other autoimmune diseases</td>
<td>Common</td>
<td>Common§</td>
</tr>
<tr>
<td>Clinical severity</td>
<td>Broad range, variable</td>
<td>Generally severe</td>
</tr>
<tr>
<td>Histopathologic features at presentation</td>
<td>Broad range, mild disease to cirrhosis</td>
<td>Generally advanced</td>
</tr>
<tr>
<td>Treatment failure</td>
<td>Infrequent</td>
<td>Frequent</td>
</tr>
<tr>
<td>Relapse after drug withdrawal</td>
<td>Variable</td>
<td>Common</td>
</tr>
<tr>
<td>Need for long-term maintenance</td>
<td>Variable</td>
<td>~100%</td>
</tr>
</tbody>
</table>

*The conventional method of detection is immunofluorescence. †Tests for this antibody are rarely available in commercial laboratories. ‡This antibody is detected by enzyme-linked immunosorbent assay. §Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy is seen only in patients with type 2 disease.

Most patients with autoimmune hepatitis have hypergammaglobulinemia. Serum immunoglobulin G levels usually exceed 16 g/L. Characteristic patterns of serum autoantibodies define distinct subgroups of autoimmune hepatitis (see Table 362-2). The most common pattern (type 1) is associated with the formation of non–organ-specific antibodies, such as antinuclear (smooth muscle) and antinuclear antibodies. Approximately 50% of these patients are 10-20 yr of age. High titers of a liver-kidney microsomal antibody are detected in another form (type 2) that usually affects children 2-14 yr of age. A subgroup of primarily young women may demonstrate autoantibodies against a soluble liver antigen but not against nuclear or microsomal proteins. Antineutrophil cytoplasmic antibodies may be seen more commonly in autoimmune cholangiopathy. Autoantibodies are rare in healthy children so that titers as low as 1:40 may be significant, although nonspecific elevation in autoantibodies can be observed in a variety of liver diseases. Up to 20% of patients with apparent autoimmune hepatitis might not have autoantibodies at presentation. Antibodies to a cytochrome P450 component of liver-kidney microsomal can be found in adult patients with chronic hepatitis C infection. Homologies in antigenic peptide epitopes between the hepatitis C virus and cytochrome P450 might explain this. Other, less-common autoantibodies include rheumatoid factor, antiparietal cell antibodies, and antithyroid antibodies. A Coombs-positive hemolytic anemia may be present.

**DIAGNOSIS**

Autoimmune hepatitis is a clinical diagnosis based on certain diagnostic criteria; no single test will make this diagnosis. Diagnostic criteria with scoring systems have been developed for adults and modified slightly for children, although these scoring systems were developed as research and not diagnostic tools. Important positive features include female gender, primary elevation in transaminases and not alkaline phosphatase, elevated γ-globulin levels, the presence of autoantibodies (most commonly antinuclear, smooth muscle, or liver-kidney microsome), and characteristic histologic findings (Fig. 362-1). Important negative features include the absence of viral markers (hepatitides B, C, D) of infection, absence of a history of drug or blood product exposure, and negligible alcohol consumption.

Common conditions that might lead to chronic hepatitis should be excluded (see Table 362-1). The differential diagnosis includes α1-antitrypsin deficiency (see Chapter 357) and Wilson disease (see Chapter 357.2). The former disorder must be excluded by performing α1-antitrypsin phenotyping and the latter by measuring serum ceruloplasmin and 24 hr urinary copper excretion and/or hepatic copper levels. Chronic hepatitis may occur in patients with inflammatory bowel disease, but liver dysfunction in such patients is more commonly caused by pericholangitis or sclerosing cholangitis. Celiac disease (see Chapter 338.2) is associated with liver disease that is akin to autoimmune hepatitis, and appropriate serologic testing should be performed, including assays for antitissue transglutaminase antibodies or antineutrophil cytoplasmic antibodies. An ultrasonogram should be done to identify a choledochal cyst or other structural disorders of the biliary system. MR cholangiography may be very useful for screening for evidence of sclerosing cholangitis. An overlap syndrome with features of primary sclerosing cholangitis and autoimmune hepatitis is being increasingly recognized with wider application of MR cholangiography. Dilated or obliterated veins on ultrasonography suggest the possibility of the Budd-Chiari syndrome.

**TREATMENT**

Prednisone, with or without azathioprine or 6-mercaptopurine, improves the clinical, biochemical, and histologic features in most patients with autoimmune hepatitis and prolongs survival in most patients with severe disease. The goal is to suppress or eliminate hepatic inflammation with minimal side effects. Prednisone at an initial dose of 1-2 mg/kg/24 hr is continued until aminotransferase values return to less than twice the upper limit of normal. The dose should then be lowered in 5 mg decrements over 2-4 mo until a maintenance dose of 0.1-0.3 mg/kg/24 hr is achieved. In patients who respond poorly, who experience severe side effects, or who cannot be maintained on low-dose steroids, azathioprine (1.5-2.0 mg/kg/24 hr, up to 100 mg/24 hr) can be added, with frequent monitoring for bone marrow suppression. Measurement of thiopurine methyltransferase activity should be done prior to beginning treatment with the thiopurine drugs azathioprine and 6-mercaptopurine. Patients with low activity (10% prevalence) or absent activity (prevalence 0.3%) are at risk for developing severe drug-induced myelotoxicity from accumulation of the unmetabolized drug. Measurement of the drug metabolites, 6-thioguanine nucleotide and 6-methylmercaptopurine, is useful in determining why a patient is not responding to a standard dose of a thiopurine drug and may help in avoiding myelosuppression and hepatotoxicity. Single-agent therapy with alternate-day corticosteroids should be used with great caution, although addition of azathioprine to alternate-day steroids can be an effective approach that minimizes corticosteroid-related toxicity. In patients with a mild and relatively asymptomatic presentation, some favor a lower starting dose of prednisone (10-20 mg) coupled with the simultaneous early administration of either 6-mercaptopurine (1.0-1.5 mg/kg/24 hr) or azathioprine (1.5-2.0 mg/kg/24 hr). Patients with primary sclerosing cholangitis/autoimmune hepatitis overlap syndrome respond similarly to immunosuppressive therapy. Precise diagnostic criteria for autoimmune disease in the setting of sclerosing cholangitis do not exist. Autoimmune markers and immunoglobulin levels are often elevated in children with sclerosing cholangitis and do not necessarily indicate a diagnosis of coincident autoimmune hepatitis. The cholesteric agent, ursodeoxycholic acid, is often used in biliary tract disease, but trials in adults with primary sclerosing cholangitis have not shown efficacy, and patients have experienced toxicity at higher doses. There is a potential role for budesonide combined with azathioprine in treatment of noncirrhotic patients. Budesonide is a corticosteroid with high first-pass clearance by the liver and fewer systemic side effects including suppression of hypothalamic–pituitary axis. Cyclosporine, tacrolimus, mycophenolate mofetil, and sirolimus have been used in the management of cases refractory to standard therapy. Use of these agents should be reserved for practitioners with extensive experience in their administration, because the agents have a more restricted therapeutic to toxic ratio.

Histologic progress does not necessarily need to be assessed by sequential liver biopsies, although biochemical remission does not ensure histologic resolution. Follow-up liver biopsy is an important consideration in patients for whom consideration is given to discontinuing corticosteroid therapy. In patients with disappearance of symptoms and biochemical abnormalities and resolution of the necroinflammatory process on biopsy, an attempt at gradual discontinuation of medication is justified. There is a high rate of relapse after discontinuation of therapy. Relapse can require reinstitution of induction dosing of immunosuppression to control disease relapse.

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**Figure 362-1** Autoimmune hepatitis. Liver biopsy showing fibrous expansion of the portal tracts with moderate portal lymphocytic infiltrates rich in plasma cells (arrowhead). There is extensive interface hepatitis (arrows). Original magnification ×20. (Courtesy of Margret Magid, Mount Sinai School of Medicine.)
PROGNOSIS

The initial response to therapy in autoimmune hepatitis is generally prompt, with a >75% rate of remission. Transaminases and bilirubin fall to near-normal levels, often in the 1st 1-3 mo. When present, abnormalities in serum albumin and prothrombin time respond over a longer period (3-9 mo). In patients meeting the criteria for tapering and then withdrawal of treatment (25-40% of children), 50% are weaned from all medication; in the other 50%, relapse occurs after a variable period. Relapse usually responds to retreatment. Many children will not meet the criteria for an attempt at discontinuation of immunosuppression and should be maintained on the smallest dose of prednisone that minimizes biochemical activity of the disease. A careful balance of the risks of continued immunosuppression and ongoing hepatitis must be continually evaluated. This requires continual screening for complications of medical therapy (monitoring of linear growth velocity, ophthalmologic examination, bone density measurement, blood pressure monitoring). Intermittent flares of hepatitis can occur and can necessitate recycling of prednisone therapy.

Some children have a relatively steroid-resistant form of hepatitis. More extensive evaluations of the etiology of their hepatitis should be undertaken, directed particularly at reassessing for the presence of either sclerosing cholangitis or Wilson disease. Nonadherence to medical therapy is one of the most common causes of “resistance” to medical therapy. Progression to cirrhosis can occur in autoimmune hepatitis despite a good response to drug therapy and prolongation of life. Corticosteroid therapy in fulminant autoimmune disease may be useful, although it should be administered with caution, given the predisposition of these patients to systemic bacterial and fungal infections.

Liver transplantation has been successful in patients with end-stage or fulminant liver disease associated with autoimmune hepatitis (see Chapter 368). Disease recurs after transplantation in approximately 30% of patients and is associated with increased concentrations of serum autoantibodies and interface hepatitis on liver biopsy.

Bibliography is available at Expert Consult.
Bibliography


The liver is the main site of drug metabolism and is particularly susceptible to structural and functional injury after ingestion, parenteral administration, or inhalation of chemical agents, drugs, plant derivatives (home remedies), or environmental toxins. The possibility of drug use or toxin exposure at home or in the parents’ workplace should be explored for every child with liver dysfunction. The clinical spectrum of illness can vary from asymptomatic biochemical abnormalities of liver function to fulminant failure. Liver injury may be the only clinical feature of an adverse drug reaction or may be accompanied by systemic manifestations and damage to other organs. In hospitalized patients, clinical and laboratory findings may be confused with the underlying illness. In a recent series after acetaminophen, antimicrobial (50%) and central nervous system agents (40%) were the most commonly implicated drug classes causing liver injury in children.

There is growing concern about environmental hepatotoxins that are insidious in their effects. Many environmental toxins including the plasticizers, biphenyl A and the phthalates, are ligands for nuclear receptors that transcriptionally activate the promoters of many genes involved in xenobiotic and lipid metabolism and may contribute to obesity and nonalcoholic fatty liver disease. Nonalcoholic fatty liver disease now affects 5-10% of all children in the United States and has the potential to evolve to cirrhosis and liver failure.

Hepatic metabolism of drugs and toxins is mediated by a sequence of enzymatic reactions that in large part transform hydrophobic, less-soluble molecules into more nontoxic, hydrophilic compounds that can be readily excreted in urine or bile (see Chapter 59). Relative liver size, liver blood flow, and extent of protein binding also influence drug metabolism. Phase 1 of the process involves enzymatic activation of the substrate to reactive intermediates containing a carboxyl, phenol, epoxide, or hydroxyl group. Mixed-function monooxygenase, cytochrome-c reductase, various hydrolases, and the cytochrome P450 (CYP) system are involved in this process. Nonspecific induction of these enzymatic pathways, which can occur during intercurrent viral infection, with starvation, and with administration of certain drugs such as anticonvulsants, can alter drug metabolism and increase the potential for hepatotoxicity. A single agent can be metabolized by >1 biochemical reaction. The reactive intermediates that are potentially damaging to the cell are enzymatically conjugated in phase 2 reactions with glucuronic acid, sulfate, acetate, glycine, or glutathione. Some drugs may be directly metabolized by these conjugating reactions without first undergoing phase 1 activation. Phase 3 is the energy-dependent excretion of drug metabolites and their conjugates by an array of membrane transporters in the liver and kidney such as the multidrug resistant protein 1.

Pathways for biotransformation are expressed early in the fetus and infant, but many phase 1 and phase 2 enzymes are immature, particularly in the 1st yr of life. CYP3A4 is the primary hepatic CYP expressed postnatally and metabolizes more than 75 commonly used therapeutic drugs and several environmental pollutants and procarcinogens. Hepatic CYP3A4 activity is poorly expressed in the fetus but increases after birth to reach 30% of adult values by 1 mo and 50% of adult values between 6 and 12 mo of age. CYP3A4 can be induced by a number of drugs, including phenytoin, phenobarbital, and rifampin. Enhanced production of toxic metabolites can overwhelm the capacity of phase 2 reactions. Conversely, numerous inhibitors of CYP3A4 from several different drug classes, such as erythromycin and cimetidine, can lead to toxic accumulations of CYP3A4 substrates. By contrast, although CYP2D6 is also developmentally regulated (maturation by 10 yr of age), its activity depends more on genetic polymorphisms than on sensitivity to inducers and inhibitors because more than 70 allelic variants of CYP2D6 significantly influence the metabolism of many drugs. Uridine diphosphateglucuronosyltransferase 1A6, a phase 2 enzyme that glucurononidates acetaminophen, is also absent in the human fetus, increases slightly in the neonate, but does not reach adult levels until sometime after 10 yr of age. Mechanisms for the uptake and excretion of organic ions can also be deficient early in life. Impaired drug metabolism via phase 1 and phase 2 reactions present in the 1st few mo of life is followed by a period of enhanced metabolism of many drugs in children through 10 yr of age compared with adults.

Genetic polymorphisms in genes encoding enzymes and transporters mediating phases 1, 2, and 3 reactions can also be associated with impaired drug metabolism and an increased risk of hepatotoxicity. Some cases of idiosyncratic hepatotoxicity can occur as a result of aberrations (polymorphisms) in phase 1 drug metabolism, producing intermediates of unusual hepatotoxic potential combined with developmental, acquired, or relative inefficiency of phase 2 conjugating reactions. Children may be more or less susceptible than adults to hepatotoxic reactions; liver injury after the use of the anesthetic halothane is rare in children, and acetaminophen toxicity is less common in infants than in adolescents, whereas most cases of fatal hepatotoxicity associated with sodium valproate use have been reported in children. Excessive or prolonged therapeutic administration of acetaminophen combined with reductions in caloric or protein intake can produce hepatotoxicity in children. In this setting, acetaminophen metabolism may be impaired by reduced synthesis of sulfated and glucuronated metabolites and reduced stores of glutathione. Immaturity of hepatic drug metabolic pathways can prevent degradation of a
toxic agent; under other circumstances, the same immaturity might limit the formation of toxic metabolites. Severe sodium valproate hepatotoxicity is often associated with an underlying inherited mitochondrial disorder.

Chemical hepatotoxicity can be predictable or idiosyncratic. Predictable hepatotoxicity implies a high incidence of hepatic injury in exposed persons, with dose dependence. It is understandable that only a few drugs in clinical use fall into this category. These agents might damage the hepatocyte directly through alteration of membrane lipids (peroxidation) or through denaturation of proteins; such agents include carbon tetrachloride and trichloroethylene. Indirect injury can occur through interference with metabolic pathways essential for cell integrity or through distortion of cellular constituents by covalent binding of a reactive metabolite; examples include the liver injury produced by acetaminophen or by antimetabolites such as methotrexate or 6-mercaptopurine.

Idiosyncratic hepatotoxicity is uncommon and unpredictable but accounts for the majority of adverse reactions. In contrast to previous dogma that idiosyncratic reactions are independent of dose, there is new information that higher doses of drugs metabolized in the liver have a greater risk for hepatotoxicity.

Idiosyncratic drug reactions in certain patients can reflect aberrant pathways for drug metabolism, possibly related to genetic polymorphisms, with production of toxic intermediates (isoniazid and sodium valproate can cause liver damage through this mechanism). Duration of drug use before liver injury varies (weeks to ≥1 yr) and the response to reexposure may be delayed.

An idiosyncratic reaction can also be immunologically mediated as a result of prior sensitization (hypersensitivity); extrahaematogenous manifestations of hypersensitivity can include fever, rash, arthralgia, and eosinophilia. Duration of exposure before reaction is generally 1–4 wk, with prompt recurrence of injury on re-exposure. Studies indicate that arene oxides, generated through oxidative (CYP) metabolism of aromatic anticonvulsants (phenytoin, phenobarbital, carbamazepine), can initiate the pathogenesis of some hypersensitivity reactions. Arogen oxides, formed in vivo, can bind to cellular macromolecules, thus perturbing cell function and possibly initiating immunologic mechanisms of liver injury.

Although the generation of chemically reactive metabolites has received great attention in the pathogenesis of hepatotoxicity, increasing evidence now exists for the multifactorial nature of the process, in particular the role played by the host immune system. Activation of liver nonparenchymal Kupffer cells and infiltration by neutrophils perpetuates toxic injury by many drugs by release of reactive oxygen and nitrogen species as well as cytokines. Stellate cells can also be activated, potentially leading to hepatic fibrosis and cirrhosis.

The pathologic spectrum of drug-induced liver disease is extremely variable. Hepatocyte damage can lead to elevations of serum aminotransferase activities and serum bilirubin levels and to impaired liver test abnormalities often from intercurrent infection.

| Table 363.1 Patterns of Hepatic Drug Injury |
|-----------------|-----------------|
| DISEASE                  | DRUG             |
| Centrilobular necrosis  | Acetaminophen    |
| Microvesicular steatosis| Valproic acid    |
| Acute hepatitis         | Isoniazid        |
| General hypersensitivity| Sulphonamides    |
| Fibrosis                | Methotrexate     |
| Cholestasis             | Chlorpromazine   |
| Sinusoidal obstruction syndrome | Irradiation plus busulfan |
| Portal and hepatic vein thrombosis | Estrogens |
| Biliary sludge          | Ceftriaxone      |

<table>
<thead>
<tr>
<th>Table 363.2 Potentially Hepatotoxic Herbal or Dietary Supplements</th>
</tr>
</thead>
<tbody>
<tr>
<td>Celandine (creosote bush, greasewood, Larrea tridentata)</td>
</tr>
<tr>
<td>Chinese herbs</td>
</tr>
<tr>
<td>Comfrey leaves (pyrrolizidine alkaloids)</td>
</tr>
<tr>
<td>Germander extracts (Teucrium chamaedrys)</td>
</tr>
<tr>
<td>Kava (Kava kava, awa, kew)</td>
</tr>
<tr>
<td>LipoKinetix (phenylpropanolamine, sodium usinate, diiodothyronine, yohimbine, caffeine)</td>
</tr>
<tr>
<td>Ma huang (Ephedra)</td>
</tr>
<tr>
<td>Mushroom (Amanita phalloides, Galerina)</td>
</tr>
<tr>
<td>Senecio</td>
</tr>
<tr>
<td>Valerian with skullcap</td>
</tr>
</tbody>
</table>

hepatitis, biliary tract disease, septicemia, ischemic and hypoxic liver injury, malignant infiltration, and inherited metabolic liver disease.

The laboratory features of drug- or toxin-related liver disease are extremely variable. Hepatocyte damage can lead to elevations of serum aminotransferase activities and serum bilirubin levels and to impaired synthetic function as evidenced by decreased serum coagulation factors and albumin. Hyperammonemia can occur with liver failure or with selective inhibition of the urea cycle (sodium valproate). Toxicologic screening of blood and urine specimens can aid in the detecting drug or toxin exposure. Percutaneous liver biopsy may be necessary to distinguish drug injury from complications of an underlying disorder or from intercurrent infection.

Slight elevation of serum aminotransferase activities (generally <2–3 times normal) can occur during therapy with drugs, particularly anticonvulsants, capable of inducing microsomal pathways for drug metabolism. Liver biopsy reveals proliferation of smooth endoplasmic reticulum but no significant liver injury. Liver test abnormalities often resolve with continued drug therapy.

**TREATMENT**

**Treatment of drug- or toxin-related liver injury is mainly supportive.** Contact with the offending agent should be avoided. Corticosteroids might have a role in immune-mediated disease. N-Acetylcysteine therapy, by stimulating glutathione synthesis, is effective in preventing or attenuating hepatotoxicity when administered within 16 hr after an acute overdose of acetaminophen and appears to improve survival in
patients with severe liver injury even up to 36 hr after ingestion (see Chapter 63). Intravenous L-carnitine may be of value in treating valproic acid–induced hepatotoxicity. Orthotopic liver transplantation may be required for treatment of drug- or toxin-induced hepatic failure.

PROGNOSIS
The prognosis of drug- or toxin-induced liver injury depends on its type and severity. Injury is usually completely reversible when the hepatotoxic factor is withdrawn. The mortality of submassive hepatic necrosis with fulminant liver failure can, however, exceed 50%. Hyperbilirubinemia, coagulopathy, and elevated serum creatinine are associated with an increased risk of death or need for liver transplantation. With continued use of certain drugs, such as methotrexate, effects of hepatotoxicity can proceed insidiously to cirrhosis, even with normal or near normal liver tests. Neoplasia can follow long-term androgen therapy. Rechallenge with a drug suspected of having caused previous liver injury is rarely justified and can result in fatal hepatic necrosis.

PREVENTION
The prevention of drug-induced liver injury remains a challenge. Monitoring of liver biochemical tests may be useful in some cases, but it can prove difficult to sustain for agents used for many years. Such testing may be particularly important in patients with pre-existing liver disease. For drugs with particular hepatotoxic potential, even if episodes are infrequent in children, such as with the use of isoniazid, patients should be advised to immediately stop the medication with onset of nausea, vomiting, abdominal pain, and fatigue until liver damage is excluded. Obvious symptoms of liver disease such as jaundice and dark urine can lag behind severe hepatocellular injury. Monitoring for toxic metabolites and genotyping can be effective in preventing severe toxicity with the use of azathioprine. Advances in pharmacogenomics, such as the use of gene chips to detect variants in some of the CYP enzymes, hold promise of a personalized approach to prevent hepatotoxicity.

Bibliography is available at Expert Consult.
Bibliography


Fulminant hepatic failure (acute liver failure) is a clinical syndrome resulting from massive necrosis of hepatocytes or from severe functional impairment of hepatocytes. Synthetic, excretory, and detoxifying functions of the liver are all severely impaired. In adults, hepatic encephalopathy has been an essential diagnostic feature. This narrow definition may be problematic because early hepatic encephalopathy can be difficult to detect in infants and children. The currently accepted definition in children includes biochemical evidence of acute liver injury (usually <8 wk duration); no evidence of chronic liver disease; and hepatic-based coagulopathy defined as a prothrombin time (PT) >15 sec or international normalized ratio (INR) >1.5 not corrected by vitamin K in the presence of clinical hepatic encephalopathy, or a PT >20 sec or INR >2 regardless of the presence of clinical hepatic encephalopathy. Liver failure in the perinatal period can be associated with prenatal liver injury and even cirrhosis. Examples include neonatal iron storage (hemochromatosis) disease, tyrosinemia, and some cases of congenital viral infection. Liver disease may be noticed at birth or after several days of apparent well-being. Fulminant Wilson disease also occurs in older children who were previously asymptomatic but, by definition, have preexisting liver disease. In some cases of liver failure, particularly in the idiopathic form of acute hepatic failure, the onset of encephalopathy occurs later, from 8-28 wk after the onset of jaundice.

ETIOLOGY

Fulminant hepatic failure can be a complication of viral hepatitis (A, B, D, E). An unusually high risk of fulminant hepatic failure occurs in young people who have combined infections with the hepatitis B virus (HBV) and hepatitis D. Mutations in the precore and/or promoter region of HBV DNA are associated with fulminant and severe hepatitis. HBV is also responsible for some cases of fulminant liver failure in the absence of serologic markers of HBV infection but with HBV DNA found in the liver. Hepatitis C and E viruses are uncommon causes of fulminant hepatic failure in the United States. Patients with chronic hepatitis C are at risk if they have superinfection with hepatitis A virus. Epstein-Barr virus, herpes simplex virus, adenovirus, enteroviruses, cytomegalovirus, parvovirus B19, human herpesvirus-6, and varicella-zoster infections can also produce fulminant hepatitis in children.

Fulminant hepatic failure can also be caused by autoimmune hepatitis in approximately 5% of cases. Patients have a positive autoimmune marker (e.g., antinuclear antibody, anti-smooth muscle antibody, liver-kidney microsomal antibody, or soluble liver antigen) and possibly an elevated serum immunoglobulin G level. Liver histology, if a biopsy can be safely done, might support the diagnosis.

Acute liver failure is a common feature of hemophagocytic lymphohistiocytosis caused by several gene defects, infections by mostly viruses of the herpes group, and a variety of other conditions including organ transplantation and malignancies. Impaired function of natural killer cells and cytokotoxic T-lymphocyte cells with uncontrolled hemophagocytosis and cytokine overproduction is characteristic for genetic and acquired forms of hemophagocytic lymphohistiocytosis. Biochemical markers include elevated ferritin and triglycerides and low fibrinogen.

An idiopathic form of fulminant hepatic failure accounts for 40-50% of cases in children. The disease occurs sporadically and usually without the risk factors for common causes of viral hepatitis. It is likely that the etiology of these cases is heterogeneous, including unidentified or variant viruses, excessive immune activation, and undiagnosed metabolic disorders.

Various hepatotoxic drugs and chemicals can also cause fulminant hepatic failure. Predictable liver injury can occur after exposure to carbon tetrachloride or Amanita phalloides mushroom or after acetaminophen overdose. Acetaminophen is the most common etiology of acute hepatic failure in children and adolescents in the United States and England. In addition to the acute intentional ingestion of a massive dose, a therapeutic misadventure leading to severe liver injury can also occur in ill children given doses of acetaminophen exceeding weight-based recommendations for many days. Such patients can have reduced stores of glutathione after a prolonged illness and a period of poor nutrition. Idiosyncratic damage can follow the use of drugs such as halothane, isoniazid, or sodium valproate. Herbal supplements are additional causes of hepatic failure (see Table 363-2).

Ischemia and hypoxia resulting from hepatic vascular occlusion, severe heart failure, cyanotic congenital heart disease, or circulatory shock can produce liver failure. Metabolic disorders associated with hepatic failure include Wilson disease, acute fatty liver of pregnancy, galactosemia, hereditary tyrosinemia, hereditary fructose intolerance, neonatal iron storage disease, defects in β-oxidation of fatty acids, and deficiencies of mitochondrial electron transport particularly mitochondrial DNA depletion disorders.

PATHOLOGY

Liver biopsy usually reveals patchy or confluent massive necrosis of hepatocytes. Multilobular or bridging necrosis can be associated with collapse of the reticulin framework of the liver. There may be little or no regeneration of hepatocytes. A zonal pattern of necrosis may be observed with certain insults. (Centrilobular damage is associated with acetaminophen hepatotoxicity or with circulatory shock.) Evidence of severe hepatocyte dysfunction rather than cell necrosis is occasionally
the predominant histologic finding (microvesicular fatty infiltrate of hepatocytes is observed in Reye syndrome, $\beta$-oxidation defects, and tetracycline toxicity).

**PATHOGENESIS**

The mechanisms that lead to fulminant hepatic failure are poorly understood. It is unknown why only approximately 1-2% of patients with viral hepatitis experience liver failure. Massive destruction of hepatocytes might represent both a direct cytotoxic effect of the virus and an immune response to the viral antigens. One-third to one-half of patients with HBV-induced liver failure become negative for serum hepatitis B surface antigen within a few days of presentation and often have no detectable HBV antigen or HBV DNA in serum. These findings suggest a hyperimmune response to the virus that underlies the massive liver necrosis. Formation of hepatotoxic metabolites that bind covalently to macromolecular cell constituents is involved in the liver injury produced by drugs such as acetaminophen and isoniazid; fulminant hepatic failure can follow depletion of intracellular substrates involved in detoxification, particularly glutathione. Whatever the initial cause of hepatocyte injury, various factors can contribute to the pathogenesis of liver failure, including impaired hepatoocyte regeneration, altered parenchymal perfusion, endotoxemia, and decreased hepatic reticuloendothelial function.

The pathogenesis of hepatic encephalopathy can relate to increased serum levels of ammonia, false neurotransmitters, amines, increased $\gamma$-aminobutyric acid receptor activity, or increased circulating levels of endogenous benzodiazepine-like compounds. Decreased hepatic clearance of these substances can produce marked central nervous system dysfunction.

**CLINICAL MANIFESTATIONS**

Fulminant hepatic failure can be the presenting feature of liver disease or it can complicate previously known liver disease (acute-on-chronic liver failure). A history of developmental delay and/or neuromuscular dysfunction can indicate an underlying mitochondrial or $\beta$-oxidation defect. A child with fulminant hepatic failure has usually been previously healthy and most often has no risk factors for liver disease such as exposure to toxins or blood products. Progressive jaundice, fetor hepaticus, fever, anorexia, vomiting, and abdominal pain are common. A rapid decrease in liver size without clinical improvement is an ominous sign. A hemorrhagic diathesis and ascites can develop.

Patients should be closely observed for hepatic encephalopathy, which is initially characterized by minor disturbances of consciousness or motor function. Irritability, poor feeding, and a change in sleep rhythm may be the only findings in infants; asterixis may be demonstrable in older children. Patients are often somnolent, confused, or combative on arousal and can eventually become responsive only to painful stimuli. Patients can rapidly progress to deeper stages of coma, in which extensor responses and decerebrate and decorticate posturing appear. Respirations are usually increased early, but respiratory failure can occur in stage IV coma (Table 364-1).

**LABORATORY FINDINGS**

Serum direct and indirect bilirubin levels and serum aminotransferase activities may be markedly elevated. Serum aminotransferase activities do not correlate well with the severity of the illness and can actually decrease as a patient deteriorates. The blood ammonia concentration is usually increased, but hepatic coma can occur in patients with a normal blood ammonia level. PT and the INR are prolonged and often do not improve after parenteral administration of vitamin K. Hypoglycemia can occur, particularly in infants. Hypokalemia, hyponatremia, metabolic acidosis, or respiratory alkalosis can develop.

**TREATMENT**

Specific therapies for identifiable causes of acute liver failure include N-acetylcysteine (acetaminophen), acyclovir (herpes simplex virus), penicillin (Amanita mushrooms), nucleos(t)ide analogs such as entecavir or lamivudine (HBV), and prednisone (autoimmune hepatitis). Management of other types of fulminant hepatic failure is supportive. No therapy is known to reverse hepatocyte injury or to promote hepatic regeneration.

An infant or child with acute hepatic failure should be cared for in an institution able to perform a liver transplantation if necessary and managed in an intensive care unit with continuous monitoring of vital functions. Endotracheal intubation may be required to prevent aspiration, to reduce cerebral edema by hyperventilation, and to facilitate pulmonary toilet. Mechanical ventilation and supplemental oxygen are often necessary in advanced coma. Sedatives should be avoided unless needed in the intubated patient because these agents can aggravate or precipitate encephalopathy. Opiates may be better tolerated than benzodiazepines. Prophylactic use of proton pump inhibitors should be considered because of the high risk of gastrointestinal bleeding. Hypovolemia should be avoided and treated with cautious infusions of isotonic fluids and blood products. Renal dysfunction can result from dehydration, acute tubular necrosis, or functional renal failure (hepatorenal syndrome). Electrolyte and glucose solutions should be administered intravenously to maintain urine output, to correct or prevent hypoglycemia, and to maintain normal serum potassium concentrations. Hyponatremia is common and should be avoided, but it is usually dilutional and not a result of sodium depletion. Parenteral supplementation with calcium, phosphorus, and magnesium may be required. Hypophosphatemia, probably a reflection of liver regeneration, and early phosphorus administration are associated with a better prognosis in acute liver failure, whereas hyperphosphatemia predicts a failure of spontaneous recovery.

Coagulopathy should be treated with parenteral administration of vitamin K and can require infusion of fresh-frozen plasma, cryoprecipitate, and platelets to treat clinically significant bleeding; disseminated intravascular coagulation can also occur. Plasmapheresis can permit temporary correction of the bleeding diathesis without resulting in volume overload. Recombinant factor VIIa has been used for transient correction of coagulopathy refractory to fresh frozen plasma infusions and can facilitate the performance of invasive procedures.

<table>
<thead>
<tr>
<th>Table 364-1</th>
<th>Stages of Hepatic Encephalopathy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>STAGES</strong></td>
<td>I II III IV</td>
</tr>
<tr>
<td><strong>Symptoms</strong></td>
<td>Periods of lethargy, euphoria; reversal of day–night sleeping; may be alert</td>
</tr>
<tr>
<td><strong>Signs</strong></td>
<td>Trouble drawing figures, performing mental tasks</td>
</tr>
<tr>
<td><strong>Electroencephalogram</strong></td>
<td>Normal</td>
</tr>
</tbody>
</table>

**Chapter 364 † Fulminant Hepatic Failure 1967**
such as placement of a central line or an intracranial pressure monitor. Continuous hemofiltration is useful for managing fluid overload and acute renal failure.

Patients should be monitored closely for infection, including sepsis, pneumonia, peritonitis, and urinary tract infections. At least 50% of patients experience serious infection. Gram-positive organisms (*Staphylococcus aureus, Staphylococcus epidermidis*) are the most common pathogens, but Gram-negative and fungal infections are also observed.

Gastrointestinal hemorrhage, infection, constipation, sedatives, electrolyte imbalance, and hypovolemia can precipitate encephalopathy and should be identified and corrected. Protein intake should be initially restricted or eliminated, depending on the degree of encephalopathy. The gut should be purged with several enemas. Lactulose should be given every 2-4 hr orally or by nasogastric tube in doses (10-50 mL) sufficient to cause diarrhea. The dose is then adjusted to produce several acidic, loose bowel movements daily. Lactulose syrup diluted with 1-3 volumes of water can also be given as a retention enema every 6 hr. Lactulose, a nonabsorbable disaccharide, is metabolized to organic acids by colonic bacteria; it probably lowers blood ammonia levels through decreasing microbial ammonia production and through trapping of ammonia in acidic intestinal contents. Oral or rectal administration of a nonabsorbable antibiotic such as rifaximin or neomycin can reduce enteric bacteria responsible for ammonia production. Oral antibiotics may be more effective than lactulose in lowering serum ammonia levels. In a recent clinical trial, N-acetylcysteine was not effective in improving the outcome of patients with acute liver failure not associated with acetaminophen.

Cerebral edema is an extremely serious complication of hepatic encephalopathy that responds poorly to measures such as corticosteroid administration and osmotic diuresis. Monitoring intracranial pressure can be useful in preventing severe cerebral edema, in maintaining cerebral perfusion pressure, and in establishing the suitability of a patient for liver transplantation. Controlled trials have shown a worsened outcome of fulminant hepatic failure in patients treated with corticosteroids.

Temporary liver support continues to be evaluated as a bridge for the patient with liver failure to liver transplantation or regeneration. Nonbiologic systems, essentially a form of liver dialysis with an albumin-containing dialysate, and biologic liver support devices that involve perfusion of the patient's blood through a cartridge containing liver cell lines or porcine hepatocytes can remove some toxins, improve serum biochemical abnormalities, and, in some cases, improve neurologic function, but there has been little evidence of improved survival, and few children have been treated.

Orthotopic liver transplantation can be lifesaving in patients who reach advanced stages (III, IV) of hepatic coma. Reduced-size allografts and living donor transplantation have been important advances in the treatment of infants with hepatic failure. Partial auxiliary orthotopic or heterotopic liver transplantation is successful in a small number of children, and in some cases it has allowed regeneration of the native liver and eventual withdrawal of immunosuppression. Orthotopic liver transplantation should not be done in patients with liver failure and neuromuscular dysfunction secondary to a mitochondrial disorder because progressive neurologic deterioration is likely to continue after transplantation.

**PROGNOSIS**

Children with acute hepatic failure fare better than adults. Improved survival can be attributed to careful intensive care and if necessary liver transplantation. In the largest prospective study from the Pediatric Acute Liver Failure Study Group, 709 children were assessed at 21 days: 50.3% of patients survived with supportive care alone, 36.2% survived after liver transplantation, and 13.4% died. A scoring system based on peak values of total serum bilirubin, PT, and plasma ammonia concentration predicted transplant-free survival. Prognosis varies considerably with the cause of liver failure and stage of hepatic encephalopathy. Survival rates with supportive care may be as high as 90% in acetaminophen overdose and with fulminant hepatitis A. By contrast, spontaneous recovery can be expected in only approximately 40% of patients with liver failure caused by the idiopathic form of acute liver failure or an acute onset of Wilson disease. In patients who progress to stage IV coma (see Table 364-1), the prognosis is extremely poor. Brainstem herniation is the most common cause of death. Major complications such as sepsis, severe hemorrhage, or renal failure increase the mortality. The prognosis is particularly poor in patients with liver necrosis and multiorgan failure.

Age <1 yr, stage 4 encephalopathy, an INR >4, and the need for dialysis before transplantation are associated with increased mortality. Pretransplantation serum bilirubin concentration or the height of hepatic enzymes is not predictive of posttransplantation survival. A plasma ammonia concentration >200 µmol/L is associated with a 5-fold increased risk of death.

Children with acute hepatic failure are more likely to die while on the waiting list compared to children with other diagnoses. Owing to the severity of their illness, the 6 mo post–liver transplantation survival of approximately 75% in most studies is significantly lower than the 90% achieved in children with chronic liver disease. Patients who recover from fulminant hepatic failure with only supportive care do not usually develop cirrhosis or chronic liver disease. Aplastic anemia occurs in approximately 10% of children with the idiopathic form of fulminant hepatic failure and is often fatal.

Bibliography is available at Expert Consult.
Bibliography


Cystic lesions of liver may be initially recognized during infancy and childhood (Table 365-1). Hepatic fibrosis can also occur as part of an associated developmental defect (Table 365-2). Cystic renal disease is usually associated and often determines the clinical presentation and prognosis. Virtually all proteins encoded by genes mutated in combined cystic diseases of the liver and kidney are at least partially localized to primary cilia in renal tubular cells and cholangiocytes.

**CHOLEDOCHAL CYSTS**

Choledochal cysts are congenital dilatations of the common bile duct that can cause progressive biliary obstruction and biliary cirrhosis. Cylindrical (fusiform) and spherical (saccular) cysts of the extrahepatic ducts are the most common types. Segmental or diffuse dilation can be observed. A diverticulum of the common bile duct or dilation of the intraduodenal portion of the common duct (*choledochocèle*) is a variant. Cystic dilation of the intrahepatic bile ducts may be associated with a choledochal cyst or Caroli disease.

The pathogenesis of choledochal cysts remains uncertain. Some reports suggest that junction of the common bile duct and the pancreatic duct before their entry into the sphincter of Oddi might allow reflux of pancreatic enzymes into the common bile duct, causing inflammation, localized weakness, and dilation of the duct. It also has been proposed that a distal congenital stenotic segment of the biliary tree leads to increased intraluminal pressure and proximal biliary dilation. Other possibilities are that choledochal cysts represent malformations of the common duct or that they occur as part of the spectrum of an infectious disease that includes neonatal hepatitis and biliary
**Table 365-1** Renal Disorders Associated with Fibropolycystic Liver Diseases

<table>
<thead>
<tr>
<th>FIBROPOLYCYSTIC LIVER DISEASE</th>
<th>ASSOCIATED RENAL DISORDER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congenital hepatic fibrosis (CHF)</td>
<td>Autosomal-recessive polycystic kidney disease*</td>
</tr>
<tr>
<td></td>
<td>Autosomal-dominant polycystic kidney disease</td>
</tr>
<tr>
<td></td>
<td>Cystic renal dysplasia</td>
</tr>
<tr>
<td></td>
<td>Nephronophthisis</td>
</tr>
<tr>
<td></td>
<td>None</td>
</tr>
<tr>
<td>Caroli syndrome (CS)</td>
<td>Autosomal-recessive polycystic kidney disease*</td>
</tr>
<tr>
<td></td>
<td>Autosomal-dominant polycystic kidney disease</td>
</tr>
<tr>
<td></td>
<td>None</td>
</tr>
<tr>
<td>Caroli disease</td>
<td>Autosomal-recessive polycystic kidney disease</td>
</tr>
<tr>
<td>von Meyenburg complexes (isolated)</td>
<td>?</td>
</tr>
<tr>
<td>von Meyenburg complexes with CHF or CS</td>
<td>Autosomal-recessive polycystic kidney disease</td>
</tr>
<tr>
<td>von Meyenburg complexes with polycystic liver disease</td>
<td>Autosomal-dominant polycystic kidney disease</td>
</tr>
<tr>
<td>Polycystic liver disease</td>
<td>Autosomal-dominant polycystic kidney disease*</td>
</tr>
<tr>
<td></td>
<td>? None</td>
</tr>
</tbody>
</table>

*Most common associated disorders.


**Table 365-2** Syndromes Associated with Congenital Hepatic Fibrosis

<table>
<thead>
<tr>
<th>SYNDROME</th>
<th>FEATURES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jeune syndrome</td>
<td>Asphyxiating thoracic dystrophy, with cystic renal tubular dysplasia and congenital hepatic fibrosis (15q13)</td>
</tr>
<tr>
<td>Joubert syndrome</td>
<td>Oculo-encephalo-hepato-renal (AH11, HPHP1)</td>
</tr>
<tr>
<td>COACH syndrome</td>
<td>Cerebellar vermis hypoplasia, oligophrenia, congenital ataxia, ocular coloboma, and hepatic fibrosis (MKS3, CC2D2A, RPGRIP1L)</td>
</tr>
<tr>
<td>Meckel syndrome type 1</td>
<td>Cystic renal dysplasia abnormal bile duct development with fibrosis, posterior encephalocele, and polydactyly (13q13, 17a21, 8q24)</td>
</tr>
<tr>
<td>Carbohydrate-deficient glycoprotein syndrome type 1b</td>
<td>Phosphomannomerase isomerase 1 deficiency (PMI)</td>
</tr>
<tr>
<td>Ivemark syndrome type 2</td>
<td>Autosomal-recessive renal-hepatic-pancreatic dysplasia</td>
</tr>
<tr>
<td>Miscellaneous syndromes</td>
<td>Intestinal lymphangiectasia, enterocolitis cystic</td>
</tr>
<tr>
<td></td>
<td>Short rib (Beemer-Langer) syndrome</td>
</tr>
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<td>Osteochondrodysplasia</td>
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Approximately 75% of cases appear during childhood. The infant typically presents with cholestatic jaundice; severe liver dysfunction including ascites and coagulopathy can rapidly evolve if biliary obstruction is not relieved. An abdominal mass is rarely palpable. In an older child, the classic triad of abdominal pain, jaundice, and mass occurs in <33% of patients. Features of acute cholangitis (fever, right upper quadrant tenderness, jaundice, leukocytosis) may be present. The diagnosis is made by ultrasonography; cholelithias of the cystic ducts have been identified prenatally using this technique. Magnetic resonance cholangiography is useful in the preoperative assessment of cholelithiasis.

The treatment of choice is primary excision of the cyst and a Roux-en-Y choledochojejunostomy. Simple drainage into the small bowel is less satisfactory owing to a risk of development of carcinomatous nodules in the residual cystic tissue. The postoperative course can be complicated by recurrent cholangitis or stricture at the anastomotic site.

**Autosomal Recessive Polycystic Kidney Disease**

Autosomal recessive polycystic kidney disease (ARPKD) manifests predominantly in childhood (see Chapter 521.2). Bilateral enlargement of the kidneys is caused by a generalized dilation of the collecting tubules. The disorder is invariably associated with congenital hepatic fibrosis and various degrees of biliary ductal ectasia that are discussed in detail later.

The polycystic kidney and hepatic disease 1 (PKHD1) gene, mutated in ARPKD, encodes a protein that is called fibrocytin/polyductin, which is localized to cilia on the apical domain of renal collecting cells and cholangiocytes. The primary defect in ARPKD may be ciliary dysfunction related to the abnormality in this protein. Fibrocytin/polyductin appears to have a role in the regulation of cellular adhesion, repulsion, and proliferation and/or the regulation and maintenance of renal collecting tubules and bile ducts, but its exact role in normal and cystic epithelia remains unknown. Kidney and liver disease are independent and variability in severity and not explainable by type of PKHD1 mutation. Phenotypic variability among affected siblings suggests importance of modifier genes as well as possible environmental influences.

In ARPKD, the cysts arise as ecstatic expansions of the collecting tubules and bile ducts that remain in continuity with their structures of origin. ARPKD normally presents in early life, often shortly after birth, and is generally more severe than autosomal dominant polycystic kidney disease (ADPKD). Fetal ultrasound may visualize large echogenic kidneys, also described as “bright,” with low or absent amniotic fluid (oligohydramnios). However, in many instances the features of ARPKD are not visualized on sonogram until the 3rd trimester or after birth.

Patients with ARPKD can die in the perinatal period owing to renal failure or lung dysgenesis. The kidneys in these patients are usually markedly enlarged and dysfunctional. Respiratory failure can result from compression of the chest by grossly enlarged kidneys, from fluid retention, or from concomitant pulmonary hypoplasia (see Chapter 515.2). The clinical pathologic findings within a family tend to breed true, although there has been some variability in the severity of the disease and the time for presentation within the same family. In patients surviving infancy because of a milder renal phenotype, liver disease may be a prominent part of the disorder. The liver disease in ARPKD is related to congenital malformation of the liver with varying degrees of portal fibrosis, bile ductular hyperplasia, ectasia, and dysgenesis. Initial symptoms are liver related in approximately 26% of patients. This can manifest clinically as variable, cystic dilation of the intrahepatic biliary tree with congenital hepatic fibrosis. Congenital hepatic fibrosis and Caroli disease likely result from an abnormality in remodeling of the embryonic ductal plate of the liver. Ductal plate malformation refers to the persistence of excess embryonic bile duct structures in the portal tracts.

Variable abnormalities of bile ducts (irregular dilation, proliferation, cysts) and portal fibrosis can also be associated with Meckel syndrome,
trisomy 17-18, tuberous sclerosis, and asphyxiating thoracic dystrophy (see Table 365-2).

**Cystic Dilation of the Intrahepatic Bile Ducts (Caroli Disease)**

Congenital saccular dilation can affect several segments of the intrahepatic bile ducts; the dilated ducts are lined by cuboidal epithelium and are in continuity with the main duct system, which is usually normal. Choledochal cysts have also been associated with Caroli disease. Bile duct dilation leads to stagnation of bile and formation of biliary sludge and intraductal lithiasis.

There is a marked predisposition to ascending cholangitis which may be exacerbated by calculus formation within the abnormal bile ducts.

Affected patients usually experience symptoms of acute cholangitis as children or young adults. Fever, abdominal pain, mild jaundice, and pruritus occur, and a slightly enlarged, tender liver is palpable. Elevated alkaline phosphatase activity, direct-reacting bilirubin levels, and leukocytosis may be observed during episodes of acute infection. In patients with Caroli disease, clinical features may be the result of a combination of recurring bouts of cholangitis, reflecting the intrahepatic ductal abnormalities and portal hypertensive bleeding resulting from hepatic fibrosis. Ultrasonography shows the dilated intrahepatic ducts, but definitive diagnosis and extent of disease must be determined by percutaneous transhepatic, endoscopic, or magnetic resonance cholangiography.

Cholangitis and sepsis are treated with appropriate antibiotics. Calculi can require surgery. Partial hepatectomy may be curative in rare cases in which cystic disease is confined to a single lobe. The prognosis is otherwise guarded, largely owing to difficulties in controlling cholangitis and biliary lithiasis and to a significant risk for developing cholangiocarcinoma. ARPKD patients with recurrent cholangitis or complications of portal hypertension may require combined liver-kidney transplant.

**Congenital Hepatic Fibrosis**

Congenital hepatic fibrosis is usually associated with ARPKD and is characterized pathologically by diffuse periportal and peribiliary fibrosis in broad bands that contain distorted bile duct–like structures and that often compress or incorporate central or sublobular veins (see Table 365-2). Irregularly shaped islands of liver parenchyma contain normal-appearing hepatocytes. Caroli disease and choledochal cysts are associated. Most patients have renal disease, mostly autosomal recessive polycystic renal disease and rarely nephronophthisis. Congenital hepatic fibrosis also occurs as part of the COACH syndrome (cerebellar vermis hypoplasia, oligophrenia, congenital ataxia, coloboma, and hepatic fibrosis). Congenital hepatic fibrosis has been described in children with a congenital disorder of glycosylation caused by mutations in the gene encoding phosphomannomutase isomerase (see Chapter 87.6).

Several different forms of congenital hepatic fibrosis have been defined clinically: portal hypertensive (most common) cholangitic, mixed, and latent. The disorder usually has its onset in childhood, with hepatosplenomegaly or with bleeding secondary to portal hypertension. In a recent study, splenomegaly, as a marker for portal hypertension, developed early in life and was present in 60% of children younger than 5 yr of age.

Cholangitis can occur in patients, as these patients have abnormal biliary tracts even without Caroli disease. Hepatocellular function is usually well preserved. Serum aminotransferase activities and bilirubin levels are usually normal in the absence of cholangitis and choledocholithiasis; serum alkaline phosphatase activity may be slightly elevated. The serum albumin level and prothrombin time are normal. Liver biopsy is rarely required for diagnosis, particularly in patients with obvious real disease.

**Treatment** of this disorder should focus on control of bleeding from esophageal varices and aggressive antibiotic treatment of cholangitis. Infrequent mild bleeding episodes may be managed by endoscopic sclerotherapy or band ligation of the varices. After more-severe hemor-
Bibliography

**Choledochal Cysts**


**Caroli Disease**


**Congenital Hepatic Fibrosis**


**Polycystic Diseases of the Liver and Kidney**


ANOMALIES

The gallbladder is congenitally absent in approximately 0.1% of the population. Hypoplasia or absence of the gallbladder can be associated with extrahepatic biliary atresia or cystic fibrosis. Duplication of the gallbladder occurs rarely. Gallbladder ectopia may occur with a transverse, intrahepatic, left-sided, or retroplaced location. Multiseptate gallbladder, characterized by the presence of multiple septa dividing the gallbladder lumen, is another rare congenital anomaly of the gallbladder.

ACUTE HYDROPS

Table 366-1 lists the conditions associated with hydrops of the gallbladder.

Acute noncalculous, noninflammatory distention of the gallbladder can occur in infants and children. It is defined by the absence of calculi, bacterial infection, or congenital anomalies of the biliary system. The disorder may complicate acute infections and Kawasaki disease, but the cause is often not identified. Hydrops of the gallbladder may also develop in patients receiving long-term parenteral nutrition, presumably as a result of gallbladder stasis during the period of enteral fasting. Hydrops is distinguished from acalculous cholecystitis by the absence of a significant inflammatory process and a generally benign prognosis.

Affected patients usually have right upper quadrant pain with a palpable mass. Fever, vomiting, and jaundice may be present and are usually associated with a systemic illness such as streptococcal infection. Ultrasonography shows a markedly distended, echo-free gallbladder, without dilation of the biliary tree. Acute hydrops is usually treated conservatively with a focus on supportive care and managing the icteric illness; cholecystostomy and drainage are rarely needed. Spontaneous resolution and return of normal gallbladder function usually occur over a period of several wk. If a laparotomy is required, a large, edematous gallbladder is found to contain white, yellow, or green bile. Obstruction of the cystic duct by mesenteric adenopathy is occasionally observed. Cholecystectomy is required if the gallbladder is gangrenous. Pathologic examination of the gallbladder wall shows edema and mild inflammation. Cultures of bile are usually sterile.

CHOLECYSTITIS AND CHOLELITHIASIS

Acute acalculous cholecystitis is uncommon in children and is usually caused by infection. Pathogens include streptococci (groups A and B), Gram-negative organisms, particularly Salmonella and Leptospira interrogans. Parasitic infestation with Ascaris or Giardia lamblia may be found. Calculus cholecystitis may rarely follow abdominal trauma or burn injury or is associated with a systemic vasculitis, such as periarteritis nodosa.

Clinical features include right upper quadrant or epigastric pain, nausea, vomiting, fever, and jaundice. Right upper quadrant guarding and tenderness are present. Ultrasonography discloses an enlarged, thick-walled gallbladder, without calculi. Serum alkaline phosphatase activity and direct-reacting bilirubin levels are elevated. Leukocytosis is usual.

Patients may recover with treatment of systemic and biliary infection. Because the gallbladder can become gangrenous, daily ultrasonography is useful in monitoring gallbladder distention and wall thickness. Cholecystectomy is required in patients who fail to improve with conservative management. Cholecystostomy drainage is an alternative approach in a critically ill patient.

Cholelithiasis is relatively rare in otherwise healthy children, occurring more commonly in patients with various predisposing disorders (Table 366-2). In an ultrasonographic survey of 1570 children (ages 6-19 yr) the overall prevalence of gallstone disease was 0.13% (0.27% in female subjects). In children, >70% of gallstones are the pigment type, 15-20% are cholesterol stones, and the remainder are composed of a mixture of cholesterol, organic matrix, and calcium bilirubinate. Black pigment gallstones, composed mostly of calcium bilirubinate and glycoprotein matrix, are a frequent complication of chronic hemolytic anemias. Brown pigment stones form mostly in infants as a result of biliary tract infection. Unconjugated bilirubin is the predominant component, formed by the high β-glucuronidase activity of infected bile. Cholesterol gallstones are composed purely of cholesterol or contain >50% cholesterol along with a mucin glycoprotein matrix and calcium bilirubinate. Calcium carbonate stones have also been described in children.

Patients with hemolytic disease (including sickle cell anemia, the thalassemias, and red blood cell enzymopathies) and Wilson disease are at increased risk for black pigment cholelithiasis. In sickle cell disease, pigment gallstones can develop before age 4 yr and have been reported in 17-33% of patients 2-18 yr of age. Genetic variation in the promoter of uridine diphosphate-glucuronosyltransferase 1A1 (the [TA]7/[TA]7 and [TA]7/[TA]8 genotypes) underlies Gilbert syndrome, a relatively common, chronic form of unconjugated hyperbilirubinemia, and is a risk factor for pigment gallstone formation in sickle cell disease.

Table 366-2

<table>
<thead>
<tr>
<th>Conditions Associated with Cholelithiasis</th>
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<tr>
<td>Biliary dyskinesia</td>
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<tr>
<td>Chronic hemolytic disease (sickle cell anemia, spherocytosis, thalassemia, Gilbert disease)</td>
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<tr>
<td>Ileal resection or disease</td>
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<td>Cystic fibrosis</td>
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<td>Cirrhosis</td>
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<td>Cholestasis</td>
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<td>Crohn disease</td>
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<td>Obesity</td>
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<td>Insulin resistance</td>
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<td>Prolonged parenteral nutrition</td>
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<td>Prematurity with complicated medical or surgical course</td>
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<td>Prolonged fasting or rapid weight reduction</td>
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<td>Treatment of childhood cancer</td>
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<td>Abdominal surgery</td>
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<td>Pregnancy</td>
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<td>Sepsis</td>
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<tr>
<td>Genetic (ABCB4, ABCG5/G8) progressive familial intrahepatic cholestasis</td>
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<td>Cephalosporins</td>
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Cirrhosis and chronic cholestasis also increase the risk for pigment gallstones. Sick premature infants may also have gallstones; their treatment is often complicated by such factors as bowel resection, necrotizing enterocolitis, prolonged parenteral nutrition without enteral feeding, cholestasis, frequent blood transfusions, and use of diuretics. Cholelithiasis in premature infants is often asymptomatic and may resolve spontaneously. Brown pigment stones are found in infants with obstructive jaundice and infected intra- and extraportal bile ducts. These stones are usually radiolucent, owing to a lower content of calcium phosphate and carbonate and a higher amount of cholesterol than in black pigment stones. MDR3 deficiency caused by ABCB4 mutations is a cholestatic syndrome related to impaired biliary phospholipid excretion. It is associated with symptomatic and recurring cholelithiasis. Patients may show intrahepatic lithiasis, sludge, or microlithiasis along the biliary tree.

Obesity has assumed an increasingly important role as a risk factor for cholesterol cholelithiasis in children, particularly in adolescent girls. Cholesterol gallstones are also found in children with disturbances of the enterohepatic circulation of bile acids, including patients with ileal disease and bile acid malabsorption, such as those with ileal resection, ileal Crohn disease, and cystic fibrosis. Pigment stones can also occur in these patients.

Cholesterol gallstone formation seems to result from an excess of cholesterol in relation to the cholesterol-carrying capacity of micelles in bile. Supersaturation of bile with cholesterol, leading to crystal and stone formation, could result from decreased bile acid or from an increased cholesterol concentration in bile. Other initiating factors that may be important in stone formation include gallbladder stasis or the presence in bile of abnormal mucoproteins or bile pigments that may serve as a nidus for cholesterol crystallization.

Prolonged use of high-dose ceftriaxone, a third-generation cephalosporin, has been associated with the formation of calcium-ceftriaxone salt precipitates (biliary pseudolithiasis) in the gallbladder. Biliary sludge or cholelithiasis can be detected in >40% of children who are treated with ceftriaxone for at least 10 days. In rare cases, children become jaundiced and develop abdominal pain; precipitates usually resolve spontaneously within several months after discontinuation of the drug.

Acute or chronic cholecystitis is often associated with gallstones. The acute form may be precipitated by impaction of a stone in the cystic duct. Proliferation of bacteria within the obstructed gallbladder lumen can contribute to the process and lead to biliary sepsis. Chronic calculous cholecystitis is more common. It can develop insidiously or follow several attacks of acute cholecystitis. The gallbladder epithelium commonly becomes ulcerated and scarred.

More than 50% of patients with gallstones have symptoms, and 18% present with a complication as the first indication of cholelithiasis, such as pancreatitis, choledocholithiasis or acute calculous cholecystitis. The most important clinical feature of cholelithiasis is recurrent abdominal pain, which is often colicky and localized to the right upper quadrant. An older child may have intolerance for fatty foods. Acute cholecystitis is characterized by fever, pain in the right upper quadrant, and often a palpable mass. Jaundice occurs more commonly in children than adults. Pain may radiate to an area just below the right scapula. A plain x-ray of the abdomen may reveal opaque calculi, but radiolucent (cholesterol) stones are not visualized. Accordingly, ultrasonography is the method of choice for gallstone detection. Hepatobiliary scintography is a valuable adjunct in that failure to visualize the gallbladder provides evidence of cholecystitis.

Cholecystectomy is curative. Laparoscopic cholecystectomy is routinely performed in symptomatic infants and children with cholelithiasis. Common bile duct stones are unusual in children, occurring in 2-6% of cases with cholelithiasis, often in association with obstructive jaundice and pancreatitis. Operative cholangiography should be done at the time of surgery, however, to detect unsuspected common duct calculi. Endoscopic retrograde cholangiography with extraction of common duct stones is an option before laparoscopic cholecystectomy in older children and adolescents.

Asymptomatic patients with cholelithiasis pose a more difficult management problem. Studies in adults indicate a lag time of more than a decade between initial formation of a gallstone and development of symptoms. Spontaneous resolution of cholelithiasis has been reported in infants and children. If surgery is deferred for any patient, however, parents should be counseled about signs and symptoms consistent with cholecystitis or obstruction of the common bile duct by a gallstone. In patients with chronic hemolysis or ileal disease, cholecystectomy can be carried out at the same time as another surgical procedure. Because laparoscopic surgery can safely be performed in children with sickle cell disease, elective cholecystectomy is being done more frequently at the time of gallstone diagnosis, before symptoms or complications develop. In cases associated with liver disease, severe obesity, or cystic fibrosis, the surgical risk of cholecystectomy may be substantial so that the risks and benefits of the operation need to be carefully considered.

**BILIARY DYSKINESIA**

Biliary dyskinesia is a motility disorder of the biliary tract that may cause acalculous biliary colic in children, often in association with nausea and fatty food intolerance. There are usually no gallstones on imaging. Sphincter of Oddi dysfunction may be a variant that can present with chronic abdominal pain and recurrent pancreatitis. The diagnosis is based on a cholecystokinin–disopropyl iminodiacetic acid scan demonstrating a gallbladder ejection fraction of less than 35%. Reproduction of pain on cholecystokinin administration may also be seen, as well as the absence of gallbladder filling on an otherwise normal ultrasound examination. In several recent reports, laparoscopic cholecystectomy was effective in providing both short-term and long-term improvement of symptoms in most children with biliary dyskinesia.

Bibliography is available at Expert Consult.
Bibliography


Portal hypertension, defined as an elevation of portal pressure >10-12 mm Hg, is a major cause of morbidity and mortality in children with liver disease. The normal portal venous pressure is approximately 7 mm Hg. The clinical features of the various forms of portal hypertension may be similar, but the associated complications, management, and prognosis can vary significantly and depend on whether the process is complicated by hepatic insufficiency.

ETIOLOGY
Portal hypertension can result from obstruction to portal blood flow anywhere along the course of the portal venous system. Table 367-1 outlines the various disorders associated with portal hypertension. Portal hypertension can occur as a result of prehepatic, intrahepatic, or posthepatic obstruction to the flow of portal blood.

Extrahepatic portal vein obstruction is an important cause of portal hypertension in childhood. The obstruction can occur at any level of the portal vein. Umbilical infection (omphalitis) with or without a history of catheterization of the umbilical vein may be causal in neonates. The infection can potentially spread from the umbilical vein to the left branch of the portal vein and eventually to the main portal venous channel. Intraabdominal infections, including acute
Causes of Portal Hypertension

Intrahepatic Portal Hypertension
- Hepatocellular disease
- Acute and chronic viral hepatitis
- Cirrhosis
- Congenital hepatic fibrosis
- Wilson disease
- α1-Antitrypsin deficiency
- Glycogen storage disease type IV
- Hepatotoxicity
- Methotrexate
- Parenteral nutrition
- Biliary tract disease
- Extrahepatic biliary atresia
- Cystic fibrosis
- Choledochal cyst
- Sclerosing cholangitis
- Intrahepatic bile duct paucity
- Idiopathic portal hypertension
- Postsinusoidal obstruction
- Budd-Chiari syndrome
- Venocclusive disease

Extrahepatic Portal Hypertension
- Portal vein agenesis, atresia, stenosis
- Portal vein thrombosis or cavernous transformation
- Splenic vein thrombosis
- Increased portal flow
- Arteriovenous fistula

Table 367-1 Causes of Portal Hypertension

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<tr>
<td>Budd-Chiari syndrome</td>
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<td>Venocclusive disease</td>
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appendicitis and primary peritonitis, can be causal in older children. Portal vein thrombosis is also associated with neonatal dehydration and systemic infection. In older children, inflammatory bowel disease can be associated with a hypercoagulable state and portal venous obstruction. Thrombosis of the portal vein has also occurred in association with biliary tract infections and primary sclerosing cholangitis.

Portal vein thrombosis is associated with hypercoagulable states, such as deficiencies of factor V Leiden, protein C, or protein S. The portal vein can be replaced by a fibrous remnant or contain an organized thrombus. Rare developmental anomalies producing extrahepatic portal hypertension include agenesis, atresia, or stenosis of the portal vein. Obstruction by a web or diaphragm can also occur. At least half of reported cases have no defined cause.

Uncommonly, presinusoidal hypertension can be caused by increased flow through the portal system as a result of a congenital or acquired arteriovenous fistula.

The intrahepatic causes of portal hypertension are numerous. Obstruction to flow can occur on the basis of a presinusoidal process, including acute and chronic hepatitis, congenital hepatic fibrosis, and schistosomiasis. Portal infiltration with malignant cells or granulomas can also contribute. An idiopathic form of portal hypertension characterized by splenomegaly, hypersplenism, and portal hypertension without occlusion of portal or splenic veins and with no obvious disease in the liver has been described. In some patients, noncirrhotic portal fibrosis has been observed.

Cirrhosis is the predominant cause of portal hypertension and is related to obstruction of blood flow through the portal vein. The numerous causes of cirrhosis include recognized disorders such as biliary atresia, autoimmune hepatitis, chronic viral hepatitis, and metabolic liver disease such as α1-antitrypsin deficiency, Wilson disease, glycogen storage disease type IV, hereditary fructose intolerance, and cystic fibrosis.

Postsinusoidal causes of portal hypertension are also observed in childhood. The Budd-Chiari syndrome occurs with obstruction to hepatic veins anywhere between the efferent hepatic veins and the entry of the inferior vena cava into the right atrium. In most cases, no specific cause can be found, but thrombosis can occur from inherited and acquired hypercoagulable states (antithrombin III deficiency, protein C or S deficiency, factor V Leiden or prothrombin mutations, paroxysmal nocturnal hemoglobinemia, pregnancy, oral contraceptives) and can complicate hepatic or metastatic neoplasms, collagen vascular disease, infection, and trauma. Additional causes of the Budd-Chiari syndrome include Behcet syndrome, inflammatory bowel disease, aspergillosis, dacarbazine therapy, and inferior vena cava webs.

Sinusoidal obstruction syndrome (venoocclusive disease) is the most common cause of hepatic vein obstruction in children. In this disorder, occlusion of the centrilobular venules or sublobular hepatic veins occurs. The disorder occurs after total body irradiation with or without cytotoxic drug therapy that is commonly used before bone marrow transplantation. The disease has also occurred after ingestion of herbal remedies containing the pyrrolizidine alkaloids, which are sometimes taken as medicinal teas.

Pathophysiology

The primary hemodynamic abnormality in portal hypertension is increased resistance to portal blood flow. This is the case whether the resistance to portal flow has an intrahepatic cause such as cirrhosis or is due to portal vein obstruction. Portosystemic shunting should decompress the portal system and thus significantly lower portal pressures. Despite the development of significant collaterals deviating portal blood into systemic veins, portal hypertension is maintained by an overall increase in portal venous flow and thus maintenance of portal hypertension. A hyperdynamic circulation is achieved by tachycardia, an increase in cardiac output, and decreased systemic vascular resistance. Splanchnic dilation also occurs. Overall, the increase in portal flow likely contributes to an increase in variceal transmural pressure. The increase in portal blood flow is related to the contribution of hepatic and collateral flow; the actual portal blood flow reaching the liver is reduced. It is also likely that hepatocellular dysfunction and portosystemic shunting lead to the generation of various humoral factors that cause vasodilation and an increase in plasma volume.

Many complications of the portal hypertension can be accounted for by the development of a remarkable collateral circulation. Collateral vessels can form prominently in areas in which absorptive epithelium joins stratified epithelium, particularly in the esophagus or anorectal region. The superficial submucosal collaterals, especially those in the esophagus and stomach and, to a lesser extent, those in the duodenum, colon, or rectum, are prone to rupture and bleeding under increased pressure. In portal hypertension, the vascularity of the stomach is also abnormal and demonstrates prominent submucosal arteriovenous communications between the muscularis mucosa and dilated precapillaries and veins. The resulting lesion, a vascular ectasia, has been called congestive gastropathy and contributes to a significant risk of bleeding from the stomach.

Clinical Manifestations

Bleeding from esophageal varices is the most common presentation. Less commonly, patients bleed from varices around a stoma or from anorectal varices. In patients with underlying hepatic disease, physical examination might show jaundice and stigmata of cirrhosis such as palmar erythema and vascular telangiectasias. Growth retardation can occur in patients with cirrhosis and, to a lesser extent, in children with isolated extrahepatic portal vein obstruction. Ascites may be present in patients with intrahepatic causes of portal hypertension and can transiently occur with portal vein obstruction. Dilated cutaneous collateral vessels carrying blood from the portal to systemic circulation may be apparent in the periumbilical region. In the absence of clinical or biochemical features of liver disease and with a liver of normal size, portal vein obstruction is most likely. Well-compensated cirrhosis cannot be completely ruled out under these conditions. Cholestasis and liver dysfunction with elevated serum bilirubin and aminotransferases occur uncommonly in portal vein obstruction as a result of external compression of bile ducts by cavernous transformation of the portal vein. This complication is called portal hypertensive biliopathy.

An enlarged, hard liver with minimal disturbance of hepatic function suggests the possibility of congenital hepatic fibrosis.
Hemorrhage, particularly in children with portal vein obstruction, can be precipitated by minor febrile, intercurrent illness. The mechanism is often unclear; aspirin or other nonsteroidal antiinflammatory drugs may be a contributing factor by damaging the integrity of a congested gastric mucosa or interfering with platelet function. Coughing during a respiratory illness can also increase intravascular pressure. The bleeding may become apparent with hematemesis or with melena. Gastrointestinal hemorrhage can also originate from portal hypertensive gastropathy or from gastric, duodenal, peristomal, or rectal varices.

Splenomegaly, sometimes with hypersplenism, is the next most common presenting feature in portal vein obstruction and may be discovered first on routine physical examination. Because more than half of patients in many series with portal vein obstruction do not experience bleeding until after age 6 yr, the diagnosis should be suggested in a child without hepatocellular disease who had a complicated neonatal course and in whom asymptomatic splenomegaly later developed. Long-term follow-up of patients with portal vein obstruction has revealed a variety of complications including variceal hemorrhage, hypersplenism, biliary obstruction, growth and development retardation, and neuropsychiatric dysfunction.

Children with portal hypertension, regardless of the underlying cause, may have recurrent bouts of life-threatening hemorrhage. In patients with portal vein obstruction and normal hepatic function, the bleeding usually stops spontaneously. In patients with intrahepatic disease, the combination of portal hypertension and poor liver synthetic ability (coagulopathy) can make bleeding much more difficult to control. Moreover, esophageal hemorrhage and cirrhosis can have injurious effects on the liver, further impairing hepatic function and sometimes precipitating jaundice, ascites, and encephalopathy. Blood in the intestinal lumen can promote bacterial translocation, leading to peritonitis. Another serious complication is the hepatopulmonary syndrome, which develops in ≥10% of patients with portal hypertension. It is defined as an arterial oxygenation defect induced by intrapulmonary microvascular dilation, resulting from release of a number of endogenous vasoactive molecules, including endothelin-1 and nitric oxide into the venous circulation.

DIAGNOSIS
In patients with established chronic liver disease or in those in whom portal vein obstruction is suspected, an experienced ultrasonographer should be able to demonstrate the patency of the portal vein, and Doppler flow ultrasonography can demonstrate the direction of flow within the portal system. The pattern of flow correlates with the severity of cirrhosis and encephalopathy. Reversal of portal vein blood flow (hepatofugal flow) is more likely to be associated with variceal bleeding. Ultrasonography is also effective in detecting the presence of esophageal varices. Another important feature of extrahepatic portal vein obstruction is cavernous transformation of the portal vein, in which an extensive complex of small collateral vessels form. Portal hypertension is cavernous transformation of the portal vein obstruction.

Although bleeding from esophageal or gastric varices is most common in children with portal hypertension, up to one third of patients, particularly those with cirrhosis, have bleeding from some other source such as portal hypertensive gastropathy or gastric or duodenal ulcerations. There is a strong correlation between variceal size as assessed endoscopically and the probability of hemorrhage. Red spots apparent over varices at the time of endoscopy are a strong predictor of imminent hemorrhage.

TREATMENT
The therapy of portal hypertension can be divided into emergency treatment of potentially life-threatening hemorrhage and prophylaxis directed at prevention of initial or subsequent bleeding. It must be emphasized that the use of many therapies is based on experience in adults with portal hypertension. There is a lack of rigorous studies on the ability of endoscopy screening, endoscopic treatment of varices, and use of nonselective β-blockers to alter the outcome of portal hypertension in children.

Treatment of patients with variceal hemorrhage must focus on fluid resuscitation, initially in the form of crystalloid infusion, followed by the replacement of red blood cells. Correction of coagulopathy by administration of vitamin K and/or infusion of platelets or fresh-frozen plasma may be required. A nasogastric tube should be placed to document the presence of blood within the stomach and to monitor for ongoing bleeding. An H₂-receptor blocker or proton pump inhibitor should be given intravenously to reduce the risk of bleeding from gastric erosions. In most patients, particularly those with extrahepatic portal hypertension and with normal hepatic synthetic function, bleeding usually stops spontaneously. Care should be taken in fluid resuscitation of children after bleeding to avoid producing an excessively high venous pressure and increasing risk for further bleeding.

Pharmacologic therapy to decrease portal pressure may be considered in patients with continued bleeding. Vasopressin or one of its analogs is commonly used and is thought to act by increasing splanchnic vascular tone and thus decreasing portal blood flow. Vasopressin is administered initially with a bolus of 0.33 units/kg over 20 min, followed by a continued infusion of the same dose on an hourly basis or a continuous infusion of 0.2 units/1.73 m²/min. The drug has a half-life of approximately 30 min. Its use may be limited by the side effects of vasoconstriction, which can impair cardiac function and perfusion to the heart, bowel, and kidneys and can also, as a result, exacerbate fluid retention. Nitroglycerin, usually given as a portion of a skin patch, has also been used to decrease portal pressure and, when used in conjunction with vasopressin, can ameliorate some of its untoward effects. The somatostatin analog octreotide is more commonly used, and it decreases splanchnic blood flow with fewer side effects. It may be administered by continuous intravenous infusion of 1.0-5.0 µg/kg/hr. However, the use of octreotide in adults with variceal hemorrhage has not been associated with a reduction in rates of rebleeding or mortality. Its use and efficacy in children have not been rigorously evaluated.

After an episode of variceal hemorrhage or in patients in whom bleeding cannot be controlled, endoscopic sclerosis or elastic band ligation of esophageal varices are important options. In endoscopic sclerosis, sclerosants are injected either intravascularly or paravascularly until bleeding has stopped. Although bleeding can be controlled acutely in most cases, further sessions of sclerotherapy are required to achieve temporary obliteration of the varices. Treatments may be associated with further bleeding, bacteremia, esophageal ulceration, and stricture formation. Most centers do not perform endoscopic sclerotherapy of varices prophylactically but use the procedure as a bridge to the time of liver transplantation or a surgical shunting procedure. Endoscopic elastic band ligation of varices has been shown in adult and pediatric studies to be more effective and associated with fewer complications than sclerotherapy.

In patients who continue to bleed despite pharmacologic and endoscopic methods to control hemorrhage, a Sengstaken-Blakemore tube may be placed to stop hemorrhage by mechanically compressing esophageal and gastric varices. The device is rarely used now, but it
may be the only option to control life-threatening hemorrhage. It carries a significant rate of complications and a high rate of bleeding when the device is removed, and it poses a particularly high risk for pulmonary aspiration. The tube is not well tolerated in children without significant sedation.

Various surgical procedures have been devised to divert portal blood flow and to decrease portal pressure. A portacaval shunt diverts nearly all of the portal blood flow into the subhepatic inferior right vena cava. Although portal pressure is significantly reduced, because of the significant diversion of blood from the liver, patients with parenchymal liver disease have a marked risk for hepatic encephalopathy. Even mild hepatic encephalopathy can impair cognitive function, including school performance. More selective shunting procedures, such as mesocaval or distal splenorenal shunt, can effectively decompress the portal system while allowing a greater amount of portal blood flow to the liver. The small size of the vessels makes these operations technically challenging in infants and small children, and there is a significant risk of failure as a result of shunt thrombosis. A shunt may be good option in a child with relatively well-preserved liver function, as sometimes occurs in patients with biliary atresia, congenital hepatic fibrosis, or cystic fibrosis. Portal vein thrombosis has been managed with the Rex shunt (superior mesenteric vein to left portal vein bypass), which restores physiologic portal blood flow and inflow of hepatotropic factors. Growth and cognitive function improve after this procedure.

A transjugular intrahepatic portosystemic shunt, in which a stent is placed by an interventional radiologist between the right hepatic vein and the right or left branch of the portal vein, can aid in the management of portal hypertension in children, especially in those needing temporary relief before liver transplantation. The transjugular intrahepatic portosystemic shunt procedure can precipitate hepatic encephalopathy and is prone to thrombosis.

Orthotopic liver transplantation represents a much better therapy for portal hypertension resulting from intrahepatic disease and cirrhosis. A prior portosystemic shunting operation does not preclude a successful liver transplantation but makes the operation technically more difficult.

Long-term treatment with nonspecific β-blockers, such as propranolol, has been used extensively in adults with portal hypertension. These agents might act by lowering cardiac output and portal perfusion. Evidence in adult patients shows that β-blockers can reduce the incidence of variceal hemorrhage and improve long-term survival. A therapeutic effect is thought to result when the pulse rate is reduced by ≥25%. There is limited published experience with the use of this therapy in children.

**PROGNOSIS**

Portal hypertension secondary to intrahepatic disease has a poor prognosis. Portal hypertension is usually progressive in these patients and is often associated with deteriorating liver function. Efforts should be directed toward prompt treatment of acute bleeding and prevention of recurrent hemorrhage with available methods. Patients with progressive liver disease and significant esophageal varices ultimately require orthotopic liver transplantation. Liver transplantation is the only effective therapy for hepatopulmonary syndrome and should also be considered for patients with portal hypertension secondary to hepatic vein obstruction or resulting from severe venoocclusive disease.

In patients with portal vein obstruction, episodes of bleeding can become less frequent and severe with age as a collateral circulation develops, >50% experience bleeding during adolescence. Neurocognitive defects diagnosed by careful psychologic testing indicate portosystemic encephalopathy caused by naturally occurring portosystemic shunts. Progressive liver disease can occur later as a consequence of bile duct compression from dilated collateral venous channels (portal biliopathy). These complications can be treated or prevented by the Rex shunt.

*Bibliography is available at Expert Consult.*
Bibliography


Liver Transplantation
Jorge D. Reyes and Evelyn Hsu

Refinements in the management of hepatic failure, organ procurement and implantation techniques, organ preservation, perioperative care, and the development of effective immunosuppressive management (cyclosporine in 1978 and tacrolimus in 1989) survival rates for liver transplantation is now >90%. Complications inherent in the toxicity/infection profile of immunosuppressive drug therapy have occurred and enhancements in our understanding of the relationship between recipient and host immune systems have resulted in the development of tailored immunotherapy. In addition, the search for “tolerance” enhancing protocols, which could lead to transplantation without the need for long-term immunosuppression. The creation of a national system for matching these donor organs with waiting recipients (the Organ Procurement and Transplantation Network and the United Network for Organ Sharing [UNOS]) provides equitable sharing of this scarce organ resource to the neediest patients with the adoption of the Pediatric End-Stage Liver Disease and Medical End-Stage Liver Disease (for adolescents) scoring systems.

INDICATIONS
The diseases for which liver transplantation is indicated can be categorized into the following groups:

- Obstructive biliary tract disease: biliary atresia, sclerosing cholangitis, traumatic or postsurgical injury
- Metabolic disorders: α1-antitrypsin deficiency, tyrosinemia type I, glycogen storage disease type IV, Wilson disease, neonatal hemochromatosis, Crigler-Najjar type I, familial hypercholesterolemia, primary oxalosis, organic academia, urea cycle defects
- Acute hepatitis: fulminant hepatic failure, viral, toxin, or drug induced
- Chronic hepatitis with cirrhosis: hepatitis B or C, autoimmune
- Intrahepatic cholestasis: idiopathic neonatal hepatitis, Alagille syndrome, progressive familial intrahepatic cholestasis
- Miscellaneous: cryptogenic cirrhosis, congenital hepatic fibrosis, Caroli disease, cystic fibrosis, polycystic kidney and liver disease, cirrhosis induced by total parenteral nutrition
- Primary liver tumors: benign tumors (hamartomas, hemangiendothelioma), unresectable hepatoblastoma, and hepatocellular carcinoma
- Emerging indications: graft-versus-host-disease (a complication of bone marrow transplantation), hemophilia, and portosystemic shunts

Biliary atresia is the most common indication for liver transplantation in children, followed by metabolic and inborn disorders, autoimmune and familial cholestatic disorders, and acute hepatic necrosis.

Biliary atresia may present with 2 clinical patterns: an acquired form for which there may be nonrandom clustering of potential etiologies (80% of cases), and a syndromic/embryonic form that includes other anomalies, such as polysplenia or asplenia, preduodenal portal vein, intestinal malrotation, situs anomalies, and absence of the retrohepatic vena cava. Hepatopportoenterostomy may benefit survival if performed within the 1st 30 days of life, however, some patients with successful drainage later develop cirrhosis with portal hypertension (variceal bleeding and ascites). Children with biliary atresia (or any other obstructive biliary disorder) who do not achieve successful drainage require liver transplantation within the 1st yr of life.
Inborn errors of metabolism result from a single enzyme deficiency that results in alteration of synthesis, breakdown, transport, or function of carbohydrate, fat, or protein. They can be grouped into those diseases which cause structural damage and cirrhosis, and potentially end-stage liver disease, as well as liver cancer (i.e., α1-antitrypsin deficiency, Wilson disease, cystic fibrosis, progressive familial intrahepatic cholestasis), and those inborn errors that manifest principally by their hepatic enzyme deficiency with no hepatocellular injury; complications occur in “satellite” systems such as the brain (hyperammonemic conditions), the kidney (hyperoxaluria type 1), or heart (familial hypercholesterolemia). Some metabolic disorders place patients at risk for decompensation throughout their entire lives, and others (e.g., Crigler-Najjar) manifest principally after adolescence. Liver transplantation replaces the enzyme deficiency; the value and risk benefit of doing so in the absence of cirrhosis has prompted the pursuit of gene therapy and hepatocyte transplantation as possible alternatives, but their therapeutic benefit is yet to be determined.

Although many patients with fulminant hepatic failure will survive without transplant, it accounts for approximately 13% of pediatric liver transplantation and has required the most intense concentration of multimodal management/support, and organ graft options yet devised. It is a diagnosis without clear etiology in more than 50% of cases, and posttransplantation survival varies but is generally poor because of multifactorial issues related to comorbidities and listing/transplantation graft option availability.

Primary hepatic malignancies in children are rare (<2% of all pediatric malignancies), and account for a little less than 10% of transplants. Hepatoblastoma accounts for the majority of cases (75% of primary liver tumors in childhood) and is usually of an advanced stage, yet adjuvant chemotherapy and total hepatectomy with transplantation provide cure and long-term survival for the majority of patients thus treated. Survival of >85% has been reported by the International Society of Pediatric Oncology and several American centers.

Some diseases do not produce life-threatening complications, yet their impact on growth, development, and quality of life can be so devastating that liver transplantation is a valid therapy and cure. The distribution of liver grafts does follow guidelines based on severity of liver disease as reflected in the Pediatric End-Stage Liver Disease scoring system developed by UNOS, which takes into calculation the measurable values of bilirubin, creatinine, and international normalisation ratio.

Contraindications to liver transplantation include uncontrolled infection of extrahepatic origin, uncontrolled extrahepatic malignancies, and severely disabling and uncorrectable disease in other organ systems, principally the heart and lungs. Although combined liver and heart or lung transplantation has been performed in adults and children, such cases require special consideration and centers dedicated to the complexities of posttransplantation management. Also, disabling neurologic disease can preclude liver transplantation if the outcome will not allow the child to develop some measure of independence and quality of life.

TECHNICAL INNOVATIONS

There are no limitations on age or weight for liver transplantation, a consequence to improved posttransplantation outcomes as a result of improvements in perioperative management (recipient selection, care, and timing of transplantation as well as intra- and posttransplantation care), and to the development and successful transplantation of segmental liver grafts.

To enhance the availability of liver grafts to children and optimize the timing of transplantation, the use of reduced-size or segmental grafts (a right or left lobe of liver, or the left lateral segment of the left lobe) were developed; this advancement allows the selection of a liver from a larger donor for implantation into a child, thus correcting the size mismatch. Because liver reduction inherently removes a potential graft for an adult recipient, techniques were developed for the use of segments from living donors (using usually the left lateral segment for small pediatric recipients), and then split-liver grafts from deceased donors where the left lateral segment is transplanted into a child and the leftover segment of right lobe and medial segment of left lobe (essentially a right trisegment graft) are transplanted into an adult. Reduction of a liver graft is performed ex vivo; split-liver grafts can be accomplished either ex vivo or in situ (in the hemodynamically stable brain-dead donor). Donors suitable for aforementioned graft variants should ideally be young (younger than 45 yr of age), healthy, and nonobese; however, variations are guided by the severity of illness and urgency for transplantation of the recipient.

The implantation of a liver (either whole organ or segment) involves removal of the native liver and encompasses 4 anastomoses: the suprahepatic vena cava, the portal vein, the hepatic artery, and the bile duct. Modifications of the procedure generally involve retaining (or not) of the retrohepatic vena cava, the performance (or not) of a temporary portocaval shunt to decompress the splanchic venous system during the anhepatic phase, and the use of vascular homografts of donor iliac vein or artery to replace the native inflow (guided by the presence of recipient anomalies or thrombosis of native vessels). The donor bile duct may be connected to a loop of recipient intestine (Roux-en-Y limb) or the native bile duct.

UNOS reported outcomes analyzing graft types and outcomes have shown improved graft survival in children younger than 3 yr of age for live donor grafts when compared to deceased donor whole, split, and reduced grafts. After the 1st yr, however, patient and allograft survivals were similar regardless of whether the graft was a whole liver, deceased donor segment, or living donor.

IMMUNOSUPPRESSION

The goal of effective clinical immunosuppression after solid-organ transplantation is to inhibit antigen-induced T-lymphocyte activation and cytokine production, interrupt allo–major histocompatibility complex recognition, or block effector responses. To prevent overly weakening the host response to infection, these effects should be accomplished while preserving immunocompetence. A major emphasis is the prevention of acute and chronic rejection and the ability to reverse refractory acute rejection. These efforts have been, for the most part, successful; the current challenge is long-term survival and quality of life, inherently involving strategies to minimize the long-term toxicity of immunosuppressive drug therapy, which can include renal failure, cardiovascular complications, and infections. Studies have led to a better understanding of lymphocyte subsets and function, the discovery that rejection could be reversed with steroids or antilymphocyte globulin, and then the realization that long-lasting donor-specific unresponsiveness could be achieved with less drug therapy, while preserving immunocompetence.

Immediately peri- or posttransplantation therapy may involve antilymphocyte antibody induction with depleting antibodies (monoclonal or polyclonal) such as antithymocyte globulin antibody, or the use of a chimeric mouse–human antibody that blocks the interleukin-2 receptor of the T cell, thus preventing activation and replication of antigen-selected T cells. Corticosteroids act through the suppression of antibody production and cytokine synthesis (interleukin-2, and interferon-γ), decreasing proliferation of T cells (helper, suppressor, and cytotoxic), B cells, and neutrophils. Maintenance immunosuppression is achieved through the use of calcineurin phosphatase inhibitor activity using drugs such as cyclosporine or tacrolimus; these drugs interfere with the production and release of interleukin-2 which plays a critical role in the cytotoxic T-cell response, thus inhibiting T-cell–mediated acute cellular rejection. Tacrolimus has shown to be a more powerful drug, however, the ability to progress or initiate maintenance immunosuppression in the absence of corticosteroids is of particular benefit in the children. Other drugs, such as azathioprine or mycophenolate mofetil, which inhibit the synthesis of purine nucleosides and thus the proliferation of T and B lymphocytes and antibody formation, may be added to enhance the anti-rejection profile, allow for decrease in the calcineurin dosage, or manage chronic rejection. Rapamycin, a macrolide which binds its molecular target of mammalian target of rapamycin receptor, decreases
interleukin-2 production, and thus T- and B-cell activation and proliferation.

**COMPLICATIONS**

Posttransplantation complications can be related to the pretransplantation condition of the recipient and the donor match and type, immunologic responses to the graft and the need for enhanced immunosuppressive drug therapy, and toxicity effects of these drugs or infections from over-immunosuppression. They can occur at varying specific frequencies over a fairly well-defined time course (early, late, remote).

The most predictable complications involve those inherent to the transplantation operation and include primary nonfunction of the graft (rare in pediatric recipients given the selection criteria of potential donors); hepatic artery thrombosis is the most frequent and early vascular complication, occurring in 5-10% of recipients and can have devastating consequences on the graft (acute necrosis and gangrene, and biliary leaks/strictures/bilomas), which may require urgent retransplantation; portal vein or hepatic vein strictures/occlusions are rare and generally occur later posttransplantation. Biliary strictures are the most frequent surgical complication (10-30%) after liver transplantation and should be included in the differential diagnosis of any posttransplantation liver allograft dysfunction. Management of these complications varies and may include interventional radiologic procedures, reoperation, or retransplantation.

Rejection usually occurs after the 1st 2 wk after transplantation, with the highest incidence (30-60%) within the 1st 90 days. Diagnosis is suspected based on abnormal liver function studies, and rarely are there systemic signs such as fever, abdominal pain, new-onset ascites or hydrothorax; the diagnosis requires biopsy confirmation; treatment algorithms include high doses of corticosteroids and antilymphocyte antibodies. Chronic rejection is less frequent (5-10%) and is characterized by progressive damage and loss of bile ductules with consequent cholestasis; treatment involves long-term enhancement of maintenance immunosuppression with corticosteroids and other agents.

The need to treat rejection can place the patient at a higher risk of drug toxicity or infection. The most common transplantation-related infections are cytomegalovirus and Epstein-Barr virus infections, for which there are well-developed algorithms of prophylaxis. Epstein-Barr virus-induced posttransplant lymphoproliferative disease represents a unique complication of over-immunosuppression and infection occurring in approximately 10% of patients, and that has been managed by withdrawal of immunosuppression and antiviral therapy; some patients require chemotherapy.

**OUTCOMES**

The clinical, surgical, and immunosuppressive drug therapy advances since the 1990s have dramatically improved survival of liver transplantation in children. The SPLIT registry data (1092 patients in North America transplanted since 1995) demonstrate 1-yr patient and graft survival of 86.3% and 80.2%, respectively. UNOS data reveal a 1 yr patient and graft survival for biliary atresia of 95% and 87% respectively. Longer-term survival is inherently dependent on adequacy of long term immunosuppression management, adherence to care protocols, and prevention of infection/toxicities/chronic rejection.

With longer survival times, the issues of growth, quality of life, and patient loss with a functioning graft have come to the forefront. The goals have been reset to seek the induction protocols and strategies that can foster minimization of drug therapy and even a drug-free state, the induction of tolerance.

_Bibliography is available at Expert Consult._
Malformations
Melissa Kennedy and Chris A. Liacouras

Congenital peritoneal bands represent anatomically unabsorbed portions of omentum and mesentery and most commonly occur in the regions of the duodenum, duodenojejunal flexure, ileocecal junction, and ascending colon. Although usually benign, they may be responsible for intestinal obstruction or midgut volvulus and resulting intestinal necrosis. Intraabdominal herniations infrequently occur through ring-like formations produced by anomalous peritoneal bands. Numerous other anomalies can occur in the course of the development of the peritoneum but are rarely of clinical importance. Absence of the omentum or its duplication occurs rarely. Omental cysts arise in obstructed lymphatic channels within the omentum. They may be congenital or can result from trauma and are usually asymptomatic. Abdominal pain or partial small bowel obstruction can result from compression or torsion of the small bowel from traction on the omentum.

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Ascites is the pathologic accumulation of fluid within the peritoneal cavity. Multiple causes of ascites have been described (Table 370-1). In children, hepatic and renal disease are the most common causes, but ascites can also be caused by cardiac disease, trauma, infection, or neoplasia.

The clinical hallmark of ascites is abdominal distention. Early satiety and dyspnea can occur with a moderate amount of ascites. Considerable intraperitoneal fluid can accumulate before ascites is detectable by the classic physical signs: bulging flanks, dullness to percussion, shifting dullness, a fluid wave, and the “puddle sign” (percussion of a supine person’s abdomen over the umbilicus becomes dull as the patient is moved to a prone position and ascitic fluid puddles in dependent regions). Umbilical herniation can be associated with tense ascites. Ultrasound examination is useful for detecting small amounts of ascites.

Abdominal paracentesis can provide symptomatic relief and may be diagnostic of the cause of the ascites. Determining the serum-ascites albumin gradient can help to determine the cause of ascites. A gradient greater than 1.1 g/dL (high-gradient ascites) is consistent with ascites caused by portal hypertension, whereas a gradient <1.1 g/dL (low-gradient ascites) indicates ascites of nonportal-hypertensive etiology.

The course, prognosis, and treatment of ascites depend entirely on the cause. For most patients, treatment consists of dietary sodium restriction and diuretic therapy with spironolactone, with the addition of furosemide in more severe cases. Supplemental albumin can also aid in ascitic fluid mobilization. Refractory cases may require large volume paracentesis or transjugular intrahepatic portosystemic shunting.
Chylous ascites refers to peritoneal fluid that contains lymphatic drainage with a characteristic milky appearance that is rich in triglycerides. Chylous ascites can result from congenital anomaly, injury, or obstruction of the intra-abdominal portion of the thoracic duct. Although uncommon, it can occur at any age. In the pediatric population, the most common cause is lymphatic malformation. Other causes include surgical injury to the lymphatics, trauma, cirrhosis, peritoneal bands, generalized lymphangiomatosis, chronic inflammatory processes of the bowel, and mycobacterial infection. Malignancy is a fairly common cause in the adult population but uncommon in pediatrics. Congenital anomalies of the lymphatic system can be associated with Turner, Noonan, yellow nail, and Klippel-Trenaunay-Weber syndromes.

The most common presentation is painless abdominal distention, and it may be accompanied by poor weight gain and loose stools. Peripheral edema is common. Massive chylous ascites can result in scrotal edema, inguinal and umbilical herniation, and respiratory difficulties.

Diagnosis of chylous ascites depends on the demonstration of milky ascitic fluid obtained via paracentesis after a fat-containing feeding. Ascites fluid analysis reveals high protein content, elevated triglycerides, and lymphocytosis. If the patient has had nothing by mouth, the fluid may appear serous. Hypoalbuminemia, hypogammaglobulinemia, and lymphopenia are common in these patients.

Treatment includes a high-protein, low-fat diet supplemented with medium-chain triglycerides that are absorbed directly into the portal circulation and decrease lymph production. Parenteral alimentation may be necessary if nutrition remains impaired on oral feedings. This may also significantly decrease lymph flow and facilitate sealing at the point of lymph leakage. Octreotide, a somatostatin analog, has been used by subcutaneous route in chylous ascites. The mechanism is not clearly understood; however, it decreases intestinal blood flow leading to decreased portal pressure and it also inhibits lymphatic secretion through somatostatin receptors in the intestinal wall. Paracentesis should be repeated only if abdominal distention causes respiratory distress. Laparotomy may be indicated to search for the site of the leakage if a trial of dietary management has been unsuccessful and a lymphangiogram demonstrates site of leakage.

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Bibliography
Bibliography
Peritonitis

Jessica W. Wen and Chris A. Liacouras

Inflammation of the peritoneal lining of the abdominal cavity can result from infectious, autoimmune, neoplastic, and chemical processes. Infectious peritonitis is usually defined as primary (spontaneous) or secondary. In primary peritonitis, the source of infection originates outside the abdomen and seeds the peritoneal cavity via hematogenous, lymphatic, or transmural spread. Secondary peritonitis arises from the abdominal cavity itself through extension from or rupture of an intraabdominal viscus or an abscess within an organ. Tertiary peritonitis refers to recurrent diffuse or localized disease and is associated with poorer outcomes than secondary peritonitis.

Clinically, patients have abdominal pain, abdominal tenderness, and rigidity on exam. Peritonitis can result from rupture of a hollow viscus, such as the appendix or a Meckel diverticulum; disruption of the peritoneum from trauma or peritoneal dialysis catheter; chemical peritonitis from other bodily fluid, including bile and urine; and infection. Meconium peritonitis is described in Chapters 102.1 and 330. Peritonitis is considered a surgical emergency and requires exploration and lavage of the abdomen except in spontaneous bacterial peritonitis.

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371.1 Acute Primary Peritonitis

Jessica W. Wen and Chris A. Liacouras

ETIOLOGY AND EPIDEMIOLOGY

Primary peritonitis usually refers to bacterial infection of the peritoneal cavity without a demonstrable intraabdominal source. Most cases occur in children with ascites resulting from cirrhosis and nephrotic syndrome. Infection can result from translocation of gut bacteria as
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well as immune dysfunction. Rarely, primary peritonitis occurs in previously healthy children. Pneumococci (most common), group A streptococci, enterococci, staphylococci, and Gram-negative enteric bacteria, especially *Escherichia coli* and *Klebsiella pneumoniae*, are most commonly found. *Mycobacterium tuberculosis*, *Neisseria meningitidis*, and *Mycobacterium bovis* are rare causes.

**CLINICAL MANIFESTATIONS**

Onset may be insidious or rapid and is characterized by fever, abdominal pain and a toxic appearance. Vomiting and diarrhea may be present. Hypotension and tachycardia are common along with shallow, rapid respirations because of discomfort associated with breathing. Abdominal palpation might demonstrate rebound tenderness and rigidity. Bowel sounds are hypoactive or absent. However, signs and symptoms may be subtle at times and increase vigilance is needed in cirrhotic patients who have ascites and present with unexplained leukocytosis, azotemia, or metabolic acidosis.

**DIAGNOSIS AND TREATMENT**

Peripheral leukocytosis with a marked predominance of polymorphonuclear cells is common, although the white blood cell (WBC) count can be affected by preexisting hypersplenism in patients with cirrhosis. Patients with nephrotic syndrome generally have proteinuria, and low serum albumin in these patients is associated with increased risk of peritonitis. X-ray examination of the abdomen reveals dilation of the large and small intestines, with increased separation of loops secondary to bowel wall thickening. Distinguishing primary peritonitis from appendicitis may be impossible in patients without a history of nephrotic syndrome or cirrhosis accordingly, the diagnosis of primary peritonitis is made by CT scan, laparoscopy, or laparotomy. In a child with known renal or hepatic disease and ascites, the presence of peritoneal signs should prompt diagnostic paracentesis. Infected fluid usually reveals a WBC count of ≥250 cells/mm³, with >50% polymorphonuclear cells.

Primary peritonitis is usually monomicrobial. The presence of mixed bacterial flora on ascitic fluid examination or free air on abdominal roentgenogram in children with presumed peritonitis mandates laparotomy to localize a perforation as a likely intraabdominal source of the infection. Inoculation of ascitic fluid obtained at paracentesis directly into blood culture bottles increases the yield of positive cultures. Parenteral antibiotic therapy with broad spectrum coverage, such as ceftaxime, should be started promptly, with subsequent changes dependent on sensitivity testing (vancomycin for resistant pneumococci). Therapy should be continued for 10–14 days.

*Culture-negative neutrocytic ascites* is a variant of primary peritonitis with a ascitic fluid WBC count of >500 cells/mm³, a negative culture, no intraabdominal source of infection, and no prior treatment with antibiotics. It should be treated in a similar manner as primary peritonitis.

_Bibliography is available at Expert Consult._

### 371.2 Acute Secondary Peritonitis

_Jessica W. Wen and Chris A. Liacouras_

Acute secondary peritonitis most often results from entry of enteric bacteria into the peritoneal cavity through a necrotic defect in the wall of the intestines or other viscus as a result of obstruction or infarction or after rupture of an intraabdominal visceral abscess. It most commonly follows perforation of the appendix. Other causes include incarcerated hernias, rupture of a Meckel diverticulum, midgut volvulus, intussusception, hemolytic uremic syndrome, peptic ulceration, inflammatory bowel disease, necrotizing cholecystitis, necrotizing enterocolitis, typhlitis, and traumatic perforation.

Peritonitis in the neonatal period most often occurs as a complication of necrotizing enterocolitis but may be associated with meconium ileus or spontaneous (or indomethacin-induced) rupture of the stomach or intestines. In postpubertal girls, bacteria from the genital tract (*Neisseria gonorrhoeae*, *Chlamydia trachomatis*) can gain access to the peritoneal cavity via the fallopian tubes, causing secondary peritonitis. The presence of a foreign body, such as a ventriculoperitoneal catheter or peritoneal dialysis catheter, can predispose to peritonitis, with skin microorganisms, such as *Staphylococcus epidermidis*, *Staphylococcus aureus*, and *Candida albicans*, contaminating the shunt. Secondary peritonitis results from direct toxic effects of bacteria as well as local and systemic release of inflammatory mediators in response to organisms and their products (lipopolysaccharide endotoxin). The development of sepsis depends on various host and disease factors, as well as promptness of antimicrobial and surgical intervention.

**CLINICAL MANIFESTATIONS**

Similar to primary peritonitis, characteristic symptoms include fever, diffuse abdominal pain, nausea, and vomiting. Physical findings of peritoneal inflammation include rebound tenderness, abdominal wall rigidity, a paucity of body motion (lying still), and decreased or absent bowel sounds from paralytic ileus. Massive exudation of fluid into the peritoneal cavity, along with the systemic release of vasodilative substances, can lead to the rapid development of shock. A toxic appearance, irritability, and restlessness are common. Basilar atelectasis as well as intrapulmonary shunting can develop, with progression to acute respiratory distress syndrome.

Laboratory studies reveal a peripheral WBC count >12,000 cells/µm³, with a marked predominance of polymorphonuclear forms. X-rays of the abdomen can reveal free air in the peritoneal cavity, evidence of ileus or obstruction, peritoneal fluid, and obliteration of the psoas shadow. Other peritoneal fluid findings suggestive of secondary peritonitis include elevated total protein (>1 g/dL), low glucose (<50 mg/dL).

**TREATMENT**

Aggressive fluid resuscitation and support of cardiovascular function should begin immediately. Stabilization of the patient before surgical intervention is mandatory. Antibiotic therapy must provide coverage for organisms that predominate at the site of presumed origin of the infection. In contrast to primary peritonitis, secondary peritonitis is typically polymicrobial. For perforation of the lower gastrointestinal tract, a regimen of ampicillin, gentamicin, and clindamycin or metronidazole will adequately address infection by *E. coli*, *Klebsiella*, and *Bacteroides* spp. and enterococci. Alternative therapy could include tetracycline-clavulanic acid and an aminoglycoside or piperacillin/tazobactam. Surgery to repair a perforated viscus should proceed after the patient is stabilized and antibiotic therapy is initiated. Intraoperative peritoneal fluid cultures will indicate whether a change in the antibiotic regimen is warranted. Empirical treatment for peritoneal dialysis catheter-related peritonitis may include intraperitoneal cefepime or cefazolin plus cefazidime. Serious infection from peritoneal dialysis catheters can generally be prevented with good catheter hygiene and prompt removal and replacement with signs of progressive infection.

_Bibliography is available at Expert Consult._

### 371.3 Acute Secondary Localized Peritonitis (Peritoneal Abscess)

_Jessica W. Wen and Chris A. Liacouras_

**ETIOLOGY**

Intraabdominal abscesses occur less commonly in children and infants than in adults, but can develop in visceral intraabdominal organs (hepatic, splenic, renal, pancreatic, tuboovarian abscesses) or in the interintestinal, peripancreatic, subdiaphragmatic, subhepatic, pelvic, or retroperitoneal spaces. Most commonly, peripancreatic and pelvic abscesses arise from a perforation of the appendix. Transmural
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**Bibliography**


inflammation with fistula formation can result in intraabdominal abscess formation in children with inflammatory bowel disease.

**CLINICAL MANIFESTATIONS**

Prolonged fever, anorexia, vomiting, and lassitude suggest the development of an intraabdominal abscess. The peripheral WBC count is elevated, as is the erythrocyte sedimentation rate. With an appendiceal abscess, there is localized tenderness and a palpable mass in the right lower quadrant. A pelvic abscess is suggested by abdominal distention, rectal tenesmus with or without the passage of small-volume mucous stools, and bladder irritability. Rectal examination might reveal a tender mass anteriorly. Subphrenic gas collection, basal atelectasis, elevated hemidiaphragm, and pleural effusion may be present with a subdiaphragmatic abscess. Psoas abscess can develop from extension of infection from a retroperitoneal appendicitis, Crohn disease, perirenal or intrarenal abscess. Abdominal findings may be minimal, and presentation can include a limp, hip pain, and fever. Ultrasound examination, CT scanning, and MRI may be used to localize intraabdominal abscesses; MRI gives the best resolution of disease involvement.

**TREATMENT**

An abscess should be drained and appropriate antibiotic therapy provided. Drainage can be performed under radiologic control (ultrasound or CT guidance) and an indwelling drainage catheter left in place or surgically depending on location of abscess. Initial broad-spectrum antibiotic coverage such as a combination of ampicillin, gentamicin, and clindamycin or ciprofloxacin and metronidazole should be started and can be modified depending on the results of sensitivity testing. The treatment of appendiceal rupture complicated by abscess formation may be problematic because intestinal phlegmon formation can make surgical resection more difficult. Intensive antibiotic therapy for 4-6 wk followed by an interval appendectomy is often the treatment course followed.

_Bibliography is available at Expert Consult._
Bibliography
Epigastric hernias are ventral hernias in the midline of the abdominal wall between the xiphoid and the umbilicus. Epigastric hernias result from defects in the decussating fibers of the linea alba and are more likely congenital than acquired. Because most epigastric hernias are small and asymptomatic, the true incidence is unknown, but the reported incidence in childhood varies from <1% to as high as 5%. Epigastric hernias may be single or multiple and are 2-3 times more common in males than females. The defect typically contains only preperitoneal fat without a peritoneal sac or abdominal viscera. Epigastric (incisional) hernias can occur in a previous incision site or be associated with ventricular-peritoneal shunts.

**CLINICAL PRESENTATION**

Epigastric hernias typically appear in young children as a visible or palpable mass in the midline, between the umbilicus and the xiphoid, noted by the parents or primary care practitioner. The mass is almost always small (<1 cm) and asymptomatic. The mass is typically present at all times but most apparent at times of irritability or straining. Occasionally, the mass is intermittent and the child relates pain localized to the site of the hernia. Physical examination demonstrates a firm mass, directly in the midline, anywhere between the umbilicus and the xiphoid. Epigastric hernias typically contain only preperitoneal fat and are not reducible because of the small size of the fascial defect.Rarely, a fascial defect is noted without a palpable mass. The mass may be intermittent if the fat reduces with relaxation of the abdominal muscles. Herniation of intestines or abdominal viscera in an epigastric hernia would be exceptionally rare. The mass may be tender to examination, but strangulation of the hernia contents is uncommon. Physical examination is almost always diagnostic and imaging studies are unnecessary.

The natural history of epigastric hernias is for gradual enlargement over time as intermittently more preperitoneal fat is extruded through the defect at times of straining or increased intraabdominal pressure. Left untreated, the defect can enlarge and allow herniation of intraabdominal viscera within a peritoneal sac. Epigastric hernias do not resolve spontaneously, and therefore operative repair is the recommended treatment.

The site should be carefully marked preoperatively because the mass and defect can be difficult to localize after induction of anesthesia. A limited transverse incision is made over the mass and dissection is performed to delineate the edges of the fascial defect. If herniated fat is present, it is dissected free of the subcutaneous tissues and can be reduced or ligated and excised. The defect is closed using absorbable suture. The skin is closed with an absorbable subcuticular suture. Postoperative complications are rare and the recurrence rate is low.

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**372.1 Incisional Hernia**

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Hernia formation at the site of a previous laparotomy is uncommon in childhood. Factors associated with an increased risk of incisional hernia include increased intraabdominal pressure, wound infection, and midline incision. Transverse abdominal incisions are favored because of their increased strength and blood supply, which reduce the likelihood of wound infection and incisional hernia. Although most incisional hernias require repair, operation should be deferred until the child is in optimal medical condition. Some incisional hernias resolve, especially those occurring in infants. Some recommend elastic bandaging to discourage enlargement of the hernia and to promote spontaneous healing. Newborns with abdominal wall defects represent the largest group of children with incisional hernias. Initial management should be conservative, with repair deferred until about 1 yr of age. Incarceration is very uncommon but is an indication for prompt repair.

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